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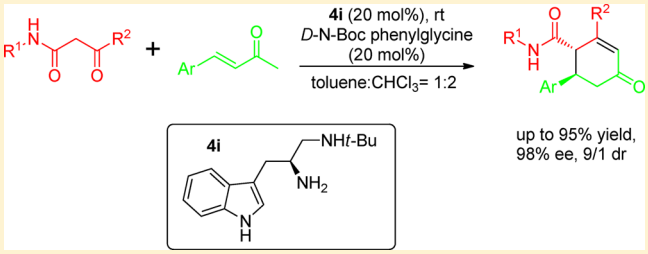
Asymmetric Robinson-Type Annulation Reaction between β-Ketoamides and α,β-Unsaturated Ketones

You-ming Huang, Chang-wu Zheng, and Gang Zhao*

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, China

Supporting Information

ABSTRACT: Enantioselective Robinson-type annulation reaction between β-ketoamide and α,β-unsaturated ketone was developed by utilizing the amino acid derived primary−secondary diamine catalysts. The less reactive acyclic β-ketoamides employed as both electrophile and nucleophile are reported in this asymmetric tandem reaction. A number of chiral cyclohexenone derivatives containing an amide group were obtained in high yields and good selectivities.



INTRODUCTION

Organocatalytic asymmetric reaction is an efficient and powerful tool to construct carbon−carbon and carbon−heteroatom bonds in the syntheses of chiral compounds. Large amounts of enantioselective reactions between varieties of nuclephiles and electrophiles have been developed in the past decades.[1] The activated methylenes as the ideal nucleophiles such as malonates,[2] β-ketoesters,[3] and active thioesters[4] have been commonly used. The β-ketoamide as the analogy of β-ketoester, however, has been rarely explored due to the lower acidity of the α-hydrogen.[5] Among those published papers,[6] the activated amides were typically used as only nucleophiles in asymmetric Michael reactions or Michael addition initiated domino reactions. For example, Dixon, Constantieux, and other groups[6a−g] reported the α-C of activated amides involved Michael reaction (Scheme 1, type 1). On the other hand, there are still other groups[6h−o] focused on two or three nuclephilic centers of activated amides involved tandem reactions (Scheme 1, type 2−4), while the activated amide compounds serving as both nucleophiles and electrophiles in asymmetric domino reactions are still rare. In 2013, Constantieux and co-workers reported an elegant multicomponent reaction with the cyclic β-ketoamides to make the 2,6-diazabicyclo[2.2.2] octanones.[7]

The Robinson-type annulation reaction, introduced almost 80 years ago, is one of the most powerful approaches to construct the cyclohexenone moieties.[8] Organocatalytic asymmetric Robinson annulation sequences have been successfully achieved by both acid and base catalysts such as chiral phosphoric acids, secondary amines, cinchona alkaloids, and phase transfer catalysts.[9] In 2009, we have developed an organocatalytic Robinson annulation reaction between benzoylacetates and α,β-unsaturated ketones by using a novel amine acid derived primary−secondary diamine catalysts developed by our group.[10] This reaction provided the cyclohexenones with excellent enantioselectivities and yields, however, two limitations still need to be addressed. First, the diastereoselectivities are generally moderate (2:1 to 4:1) probably due to the epimerization of the ester.[6a] Second, when the reaction is performed with aliphatic β-ketoester, the yield dropped dramatically. We presume that if the low reactive β-ketoamide is used instead of the β-ketoester, the above-mentioned problems would probably be solved. And as far as we know, β-ketoamides have never been reported in the Robinson-type annulations.

RESULTS AND DISCUSSION

In our initial efforts, the reaction between β-ketoamide (**1a**) and α,β-unsaturated ketone (**2a**) was selected as the model reaction, and a number of amino acid based primary−secondary diamine catalysts were systematically examined in the presence of *D*-*N*-Boc phenylglycine (20 mol %) as the additive.[11] Fortunately, the reactions proceeded smoothly to afford the cyclohexenones with good yields. The catalyst **4a** which provided excellent result in the reaction of ethyl benzoylacetate with benzylideneacetone only gave a disappointing yield and stereoselectivity (Table 1, entry 1). Then the alkyl substituents of secondary amine moiety including the tertiary amine were screened (Table 1, entry 2−7). We found that the steric hindrance of the R group had a great influence on both yield and enantioselectivity and the catalyst **4f** with a bulky *tert*-butyl group provided 95% yield and 90% enantiomeric excess (Table 1, entry 6). It was probably because the basicity of nitrogen atom increased with the increasing steric hindrance of the alkyl substituents of secondary amine moiety and then improved its catalytic activity. Catalysts derived from alternative amino acids (**4h**, **4i**) were also studied (Table 1, entry 8, 9) and the L-tryptophan-derived catalyst **4i** provided the product with excellent yield and enantioselectivity (Table 1, entry 9). It

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Scheme 1. Reaction Patterns of Activated Amides

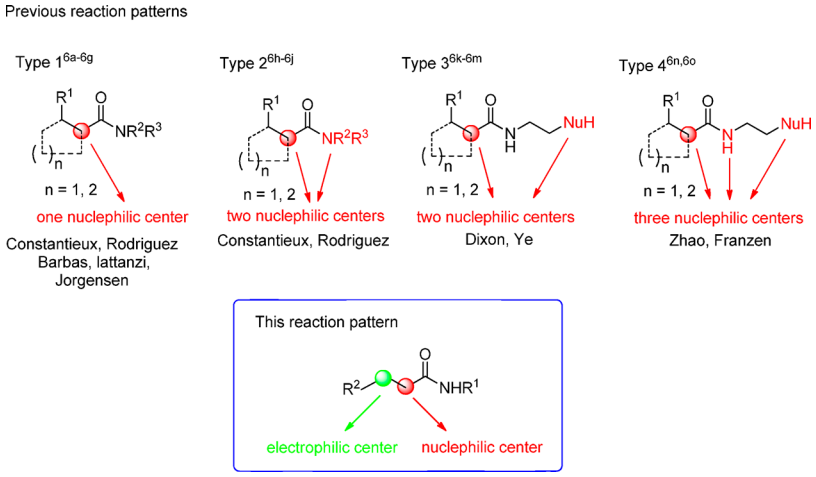
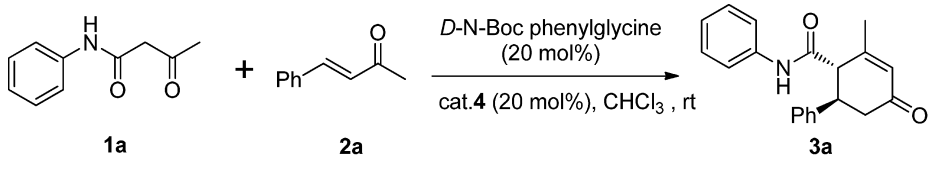
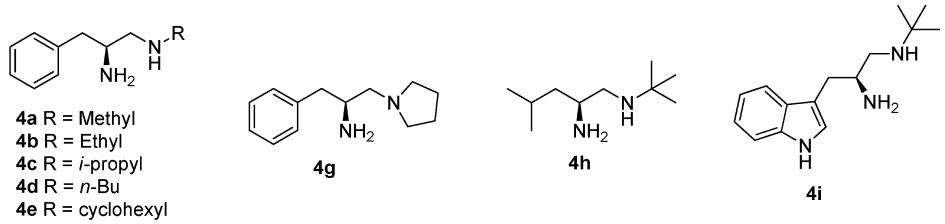


Table 1. Screening of Different Catalysts[a]





entry	catalyst	T (d)	yield (%)[b]	d.r.[c]	ee (%)[d]
1	**4a**	5	28	71/29	76
2	**4b**	5	50	80/20	84
3	**4c**	4	66	79/21	90
4	**4d**	4	92	80/20	81
5	**4e**	3	80	71/29	88
6	**4f**	3	95	71/29	90
7	**4g**	5	28	67/33	72
8	**4h**	3	92	75/25	89
9	**4i**	3	89	67/33	94

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), **4** (20 mol %), solvent (1.0 mL). [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC.

should be noted that with all the catalysts evaluated, the diastereoselectivities of the products were still low and needed to be further optimized.

A variety of common solvents were then screened in order to affect the diastereoselectivity (Table 2). No products were observed with the strong polar dimethyl sulfoxide (DMSO) and low soluble *n*-hexane (Table 2, entries 1−2). When methanol and dimethoxyethane (DME) were used, the reactivity and enantioselectivity in the reaction were decreased (Table 2, entries 3−4). In other solvents such as ethyl acetate (EA), acetonitrile, dichloromethane (DCM), and tetrahydrofuran (THF), the diastereoselectivities were not improved, although the enantioselectivities were preserved (Table 2, entries 5−8). Fortunately, good diastereoselectivity was finally achieved in toluene with marginal drop in the enantioselectivity (86% ee, 88/12 d.r.; Table 2, entry 9). Furthermore, when we used mixed solvents (toluene:$CHCl_3$ = 1:2), the corresponding product could be obtained in excellent enantioselectivity and yield as well as higher diastereoselectivity (Table 2, entry 12). Additionally, lowering the catalyst loading to 10 mol %, the yield dropped seriously, although the stereoselectivity was still excellent (Table 2, entry 13).

Under the optimized reaction conditions, the generality of the Robinson-type reaction was subsequently investigated (Table 3). *β*-ketoamides with various types of substituents on the phenyl rings attached to the nitrogen provided the products with excellent enantioselectivities, good to excellent yields, and moderate to good diastereoselectivities (**1a−1g**), regardless of their electronic nature or positions. And the reactions proceeded efficiently with *β*-ketoamides bearing different *N*-

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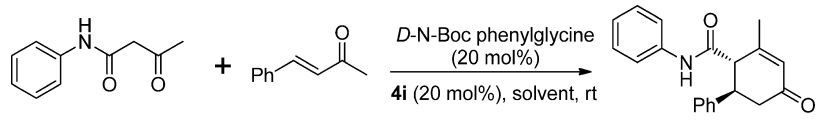
Table 2. Effect of the Solvent on the Reaction[a]

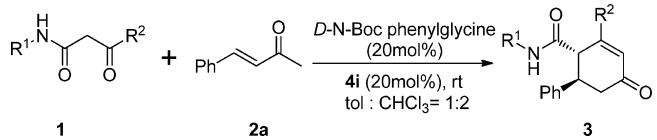


1a 2a 3a

entry	solvent	T (d)	yield (%)[b]	d.r.[c]	ee (%)[d]
1	DMSO	7	trace	–[e]	–[e]
2	*n*-hexane	7	trace	–[e]	–[e]
3	MeOH	6	89	83/17	48
4	DME	6	97	66/33	45
5	EA	3	78	75/25	86
6	CH_3CN	4	99	77/23	90
7	DCM	3	70	60/40	90
8	THF	4	80	60/40	90
9	toluene	3	80	88/12	86
10	toluene:$CHCl_3$ = 2:1	3	77	75/25	80
11	toluene:$CHCl_3$ = 1:1	3	88	87/13	91
12	toluene:$CHCl_3$ = 1:2	3	90	90/10	96
13[f]	toluene:$CHCl_3$ = 1:2	3	42	82/18	91

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), **4i** (20 mol %), solvent (1.0 mL). [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC. [e]Not determined. [f]The reaction was carried out with 10 mol % of **4i** and *D*-*N*-Boc phenylglycine.

Table 3. Scope Study with Different β-Ketoamides[a]



1 2a 3

entry	R^1	R^2	T (d)	product	yield (%)[b]	d.r.[c]	ee (%)[d]
1	C_6H_5(**1a**)	Me	3	**3a**	90	90/10	96
2	*p*-MeO-C_6H_4(**1b**)	Me	4	**3b**	93	82/18	95
3	*p*-Br-C_6H_4(**1c**)	Me	3	**3c**	73	98/2[d]	90
4	*m*−Cl-C_6H_4(**1d**)	Me	3	**3d**	93	72/28	94
5	*o*-MeO-C_6H_4(**1e**)	Me	5	**3e**	69	90/10	96
6	*o*-F-C_6H_4(**1f**)	Me	5	**3f**	92	76/24[d]	84
7	*m*-Me-C_6H_4(**1g**)	Me	4	**3g**	93	75/25	96
8	Bn(**1h**)	Me	4	**3h**	78	88/12	88
9	cyclohexyl(**1i**)	Me	4	**3i**	80	85/15	86
10	*n*-butyl(**1j**)	Me	3	**3j**	75	90/10	92
11	C_6H_5(**1k**)	*n*-propyl	5	**3k**	93	75/25[e]	89

[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), **4i** (20 mol %), solvent (1.0 mL). [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC. [e]Determined by isolated yields of the two diastereoisomers.

alkyl groups (**1h**−**1j**). Notably, the 3-oxo-*N*-phenylhexanamide could also give a very good chemical and optical yield (**1k**).

A variety of α,β-unsaturated ketones were also investigated (Table 4). The reactions seemed unaffected by the electronic nature of the substituents on the aromatic rings either with electron-withdrawing or electron-donating groups (Table 4, **2b**−**2j** and **2m**). The enantioselectivities were only decreased slightly with the substrates bearing *m*-MeO and *o*-naphthyl groups on the phenyl rings (Table 4, **2k**, **2l**).

The absolute configuration of **3o** was unambiguously determined by using a single-crystal X-ray diffraction, and all the other products can therefore be assigned by analogy (Figure 1).

In order to expore the mechanism of this reaction, a control experiment was performed with the tertiary β-ketoamide **1l** and α,β-unsaturated ketone **2a** under the standard conditions (Scheme 2a). As anticipated, no reaction was occurred. The inertness of the tertiary β-ketoamide substrate may be attributed to the decreased acidity resulting from the absence of intramolecular hydrogen bond,[6d,i] which can be regarded as an evidence the amide N−H moiety plays a critical role in activating the β-ketoamide (Scheme 2,b).

On the basis of the above experimental results and previous related studies,[12] we have proposed a plausible catalytic cycle (Scheme 3). First, α,β-unsaturated ketone is activated by the formation of iminium ion with catalyst, and the nucleophilicity of the β-ketoamide is enhanced by the secondary amine of the catalyst. Then the *Si* face of the enone in this intermediate is attacked by the incoming nucleophile, and subsequent intramolecular aldol reaction and dehydration form the chiral cyclohexenone.

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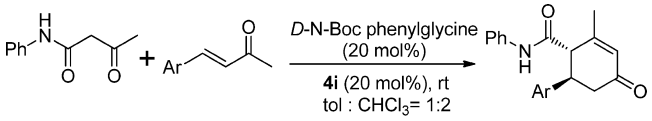
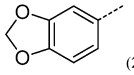
Table 4. Scope Study with Different α,β-Unsaturated Ketones[a]



1a 2 3

Entry	Ar	T [d]	Product	Yield [%][b]	D.r.[c]	Ee [%][d]
1	*p*-NO_2-C_6H_4(**2b**)	3	**3l**	83	75/25	90
2	*p*-F-C_6H_4(**2c**)	3	**3m**	94	88/12	96
3	*p*-Cl-C_6H_4(**2d**)	3	**3n**	70	78/22[e]	98
4	*p*-Br-C_6H_4(**2e**)	4	**3o**	94	88/12[e]	93
5	*p*-Me-C_6H_4(**2f**)	4	**3p**	70	85/15	98
6	*p*-MeO-C_6H_4(**2g**)	3	**3q**	84	75/25	95
7	*p*-BnO-C_6H_4(**2h**)	4	**3r**	92	75/25[e]	87
8	*m*-Me-C_6H_4(**2i**)	3	**3s**	93	75/25	96
9	*m*-Cl-C_6H_4(**2j**)	3	**3t**	83	98/2[d]	95
10	*m*-MeO-C_6H_4(**2k**)	3	**3u**	90	80/20[e]	80
11	2-Naphthyl(**2l**)	4	**3v**	95	78/22[d]	80
12	 (**2m**)	4	**3w**	87	75/25[e]	97

[a]Reaction conditions: **1** (0.4 mmol), **2** (0.2 mmol), **4i** (20 mol %), solvent (1.0 mL). [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC. [e]Determined by isolated yields of the two diastereoisomers.

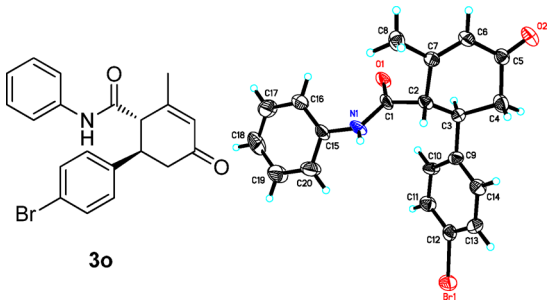
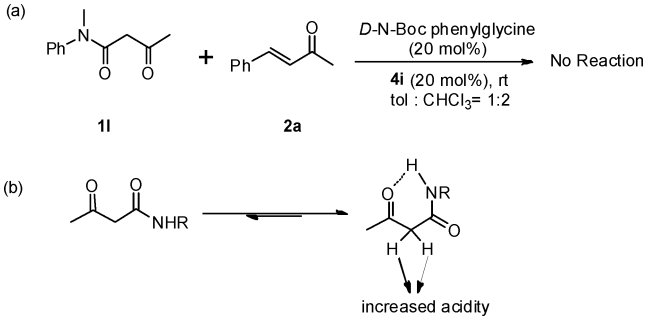


Figure 1. ORTEP structure of compound **3o** (CCDC 1020310).

Scheme 2. Examination of the Role of the N−H of β-Ketoamide[a]

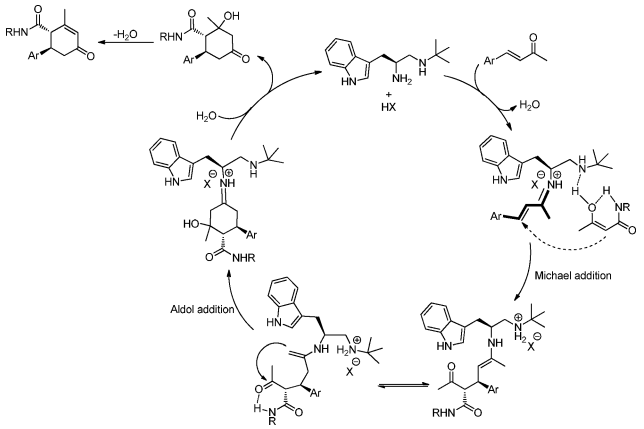


[a](a) Control experiment and (b) conformations of secondary β-ketoamide.

CONCLUSIONS

In summary, we have developed the asymmetric Robinson annulation sequences of β-ketoamides and α,β-unsaturated ketones for the construction of the chiral cyclohexenone derivatives containing an amide group. The acyclic β-ketoamide has been successfully employed as nucleophile and electrophile in the reaction. Excellent yield and enantioselectivity as well as good diastereoselectivity are observed.

Scheme 3. Plausible Catalytic Cycle



EXPERIMENTAL SECTION

The melting points recorded are uncorrected. Nuclear magnetic resonance spectra were recorded at 400 MHz. All chemical shifts (δ) were given in ppm. Data were reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz). Ee values were determined using an HPLC equipped with a PDA detector and a chiral column. Optical rotations were measured for solutions of samples of known concentrations in $CHCl_3$ using a polarimeter equipped with a sodium vapor lamp. High-resolution mass spectra were recorded under TOF conditions. All diamines catalysts were prepared according to procedures reported previously.[10,12] All β-ketoamides were synthesized using reported procedures.[13] All solvents were used after redistillation according to standard procedures.

General Procedure for the Syntheses of 3. To a mixture of α,β-unsaturated ketone **2** (0.2 mmol), catalyst **4** (0.04 mmol), and *D*-N-Boc phenylglycine (0.04 mmol) in toluene/$CHCl_3$ (0.33/0.66 mL) was added β-ketoamide **1** (0.4 mmol) at room temperature. After completion of the reaction, as detected by TLC, the solution was quenched with water (2.0 mL) and extracted with ethyl acteate (3 × 5.0 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide the desired product **3** after flash column chromatography (with hexanes/ethyl acetate = 4/1).

*3-Methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3a**).* Yield 55 mg, 90%; white solid; $[\alpha]_D^{26} = -58.9$ (c = 0.5 in $CHCl_3$); mp = 211−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.73 (d, J = 8 Hz, 2H), 3.38 (d, J = 8 Hz, 1H), 3.71 (q, J = 8 Hz, 1H), 6.13 (s, 1H), 7.09−7.12 (m, 2H), 7.21−7.33 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.4, 44.5, 57.4, 120.6, 125.1, 127.2, 127.3, 127.6, 128.9, 129.0, 129.3, 136.8, 141.2, 157.0, 169.1, 197.4 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3281, 3050, 2960, 1673, 1653, 1593, 1529, 1501, 1446, 1376, 1330, 743, 696 cm^{-1}; d.r.: *trans*/*cis* = 90/10; ESI-MS (m/z): 328.2 ($M + Na^+$); MALDI/DHB calcd for $C_{20}H_{19}NO_2Na^+$: 328.1308, found: 328.1302. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} =27.6 min, t_{minor} = 9.8 min, 96% ee, *cis* diastereoisomer: t_{major} =11.0 min, t_{minor} = 10.5 min, 82% ee.

*N-(4-Methoxyphenyl)-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3b**).* Yield 62 mg, 93%; white solid; $[\alpha]_D^{26}$ = −51.2 (c = 1.0 in $CHCl_3$); mp = 147−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.74 (d, J = 8.4 Hz, 2H), 3.32 (d, J = 9.2 Hz, 1H), 3.70−3.80 (m, 4H), 6.14 (s, 1H), 6.73−6.91 (m, 4H), 7.06 (d, J = 8.8 Hz, 2H), 7.27−7.36 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 42.5, 44.4, 55.5, 57.0, 114.1, 122.0, 122.7, 127.3,

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128.9, 129.9, 141.3, 157.0, 169.1, 197.6 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3303, 2958, 2926, 1651, 1512, 1464, 1414, 1230, 1246, 1171, 1109, 1033, 829, 760, 700 cm^{-1}; d.r.: *trans*/*cis* = 82/18; ESI-MS (*m*/*z*): 358.1 (M + Na^+); MALDI/DHB calcd for $C_{21}H_{22}NO_3^+$ 336.1596, found: 336.1594. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 43.6 min, t_{minor} = 12.8 min, 95% ee, *cis* diastereoisomer: t_{major} =15.2 min, t_{minor} = 14.8 min, 87% ee.

*N-(4-Bromophenyl)-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3c**).* Yield 64 mg, 73%; white solid; $[\alpha]_D^{25}$ = −109.6 (*c* = 1.0 in $CHCl_3$); mp = 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.74 (d, *J* = 9.2 Hz, 2H), 3.34 (d, *J* = 9.2 Hz, 1H), 3.68 (q, *J* = 9.2 Hz, 1H), 6.14 (s, 1H), 6.95 (s, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.24−7.37 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 42.3, 44.7, 57.7, 117.9, 122.0, 127.1, 127.8, 129.1, 129.5, 132.0, 135.7, 141.1, 156.3, 169.0, 197.0 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3309, 3031, 2922, 1660, 1618, 1600, 1590, 1533, 1489, 1396, 1242, 1178, 1072, 1010, 824, 755, 699 cm^{-1}; d.r.: *trans*/*cis* = 98/2; ESI-MS (*m*/*z*): 381.9 (M − H^-); MALDI/DHB calcd for $C_{20}H_{19}NO_2Br^+$ 384.0598, found: 384.0594. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} =19.5 min, t_{minor} = 8.9 min, 90% ee; *cis* diastereoisomer: t_{major} = 28.4 min, t_{minor} = 35.2 min, 88% ee.

*N-(3-Chlorophenyl)-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3d**).* Yield 63 mg, 93% ; white solid; $[\alpha]_D^{26}$ = 7.1 (*c* = 1.0 in $CHCl_3$); mp = 148−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.72 (d, *J* = 7.2 Hz, 2H), 3.29−3.43 (m, 1H), 3.66−3.74 (m, 1H), 6.11 (s, 1H), 7.02−7.15 (m, 3H), 7.16−7.28 (m, 6H), 7.54 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.5, 44.4, 57.1, 118.6, 120.7, 125.1, 127.2, 127.3, 127.7, 129.1, 129.2, 129.94, 134.6, 138.1, 141.0, 157.3, 169.5, 197.7 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3316, 2956, 2925, 2854, 1660, 1592, 1538, 1481, 1456, 1378, 1261, 1181, 1097, 1018, 874, 758, 698 cm^{-1}; d.r.: *trans*/*cis* = 72/28; ESI-MS (*m*/*z*): 338.1 (M − H^-); MALDI/DHB calcd for $C_{20}H_{19}NO_2Cl^+$ 340.1095, found: 340.1094; HPLC (Chiralpak PA-2 column, hexane/*i*-PrOH 55:45, flow rate 0.7 mL/min, λ = 214 nm): *trans* diastereoisomer: t_{major} = 26.5 min, t_{minor} = 7.1 min, 94% ee; *cis* diastereoisomer: t_{major} = 10.7 min, t_{minor} = 18.3 min, 96% ee.

*N-(2-Methoxyphenyl)-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3e**).* Yield 46 mg, 69% ; white solid; $[\alpha]_D^{26}$ = −88.0 (*c* = 0.8 in $CHCl_3$); mp = 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.74−2.77 (m, 2H), 3.45 (d, *J* = 8.4 Hz, 1H), 3.43−3.76 (m, 4H), 6.16 (s, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.03 (dt, *J* = 8.0 Hz, *J* = 2.8 Hz, 1H), 7.20−7.31 (m, 5H), 7.62 (s, 1H), 8.18 (dd, *J* = 2.8 Hz, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 42.2, 44.4, 55.7, 57.7, 110.1, 120.3, 121.1, 124.5, 126.7, 127.2, 127.4, 128.9, 129.3, 141.4, 148.1, 156.8, 168.5, 197.3 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3307, 3031, 2922, 2851, 2838, 1718, 1663, 1600, 1526, 1489, 1436, 1376, 1288, 1177, 1116, 1047, 1027, 751, 700 cm^{-1}; d.r.: *trans*/*cis* = 90/10; ESI-MS (*m*/*z*): 358.2 (M + Na^+); MALDI/DHB calcd for $C_{21}H_{22}NO_3^+$ 336.1593, found: 336.1594; HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} =30.9 min, t_{minor} = 15.2 min, 96% ee; *cis* diastereoisomer: t_{major} = 9.3 min, t_{minor} = 8.4 min, 94% ee.

*N-(2-Fluorophenyl)-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3f**).* Yield 59 mg, 92%; white solid; $[\alpha]_D^{26}$ = −145.2 (*c* = 1.0 in $CHCl_3$); mp = 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.75−2.77 (m, 2H), 3.46 (d, *J* = 9.2 Hz, 1H), 3.73 (q, *J* = 9.2 Hz, 1H), 6.15 (s, 1H), 6.99−7.10 (m, 3H), 7.15 (s, 1H), 7.25−7.33 (m, 6H), 8.03 (t, *J* = 10.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.4, 44.6, 57.4, 115.0 ($^2J_{CF}$ = 19.0 Hz), 122.6, 124.5, 125.1, 125.4 ($^3J_{CF}$ = 8.2 Hz), 127.1, 127.7, 129.1, 129.4, 141.0, 154.4 ($^1J_{CF}$ = 243.3 Hz), 156.5, 169.1, 197.2 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3286, 2955, 2925, 2854, 1666, 1618, 1537, 1504, 1455, 1378, 1366, 1334, 1259, 1170, 1104, 1031, 755, 700 cm^{-1}; d.r: *trans*/*cis* = 76/24; ESI-MS (*m*/*z*): 346.1 (M + Na^+); MALDI/DHB calcd for $C_{20}H_{19}NO_2F^+$ 324.1404, found: 324.1394. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 21.2 min, t_{minor} = 9.6 min, 84% ee; *cis* diastereoisomer: t_{major} = 11.1 min, t_{minor} = 10.5 min, 84% ee.

*3-Methyl-5-oxo-N-(m-tolyl)-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3g**).* Yield 59 mg, 93%; white solid; $[\alpha]_D^{26}$ = −9.84 (*c* = 1.0 in $CHCl_3$); mp = 137−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.27 (s, 3H), 2.71−2.74 (m, 2H), 3.34−3.40 (m, 1H), 3.68−3.72 (m, 1H), 6.12 (s, 1H), 6.90−6.98 (m, 2H), 7.08−7.12 (m, 2H), 7.24−7.32 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 22.4, 42.4, 44.4, 57.3, 117.7, 121.3, 125.9, 127.2, 127.6, 128.8, 129.0, 129.3, 136.8, 139.0, 141.3, 157.1, 169.0, 197.5 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3305, 2930, 2925, 2853, 1660, 1614, 1553, 1490, 1462, 1378, 1258, 1191, 1088, 1019, 759, 698 cm^{-1}; d.r.: *trans*/*cis* = 75/25; ESI-MS (*m*/*z*): 342.1 (M + Na^+); MALDI/DHB calcd for $C_{21}H_{22}NO_2^+$ 320.1643, found: 320.1645. HPLC (Chiralpak PC-2 column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 12.5 min, t_{minor} = 22.6 min, 96% ee; *cis* diastereoisomer: not determined ee.

*N-Benzyl-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3h**).* Yield 50 mg, 78% ; white solid; $[\alpha]_D^{26}$ = −52.8 (*c* = 1.0 in $CHCl_3$); mp = 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (s, 3H), 2.66−2.68 (m, 2H), 3.23 (d, *J* = 10 Hz, 1H), 3.68 (q, *J* = 10 Hz, 1H), 4.18 (dd, *J* = 4.8 Hz, *J* = 14.8 Hz, 1H), 4.37 (dd, *J* = 4.8 Hz, *J* = 14.8 Hz, 1H), 5.65 (s, 1H), 6.08 (s, 1H), 6.80−6.82 (m, 2H), 7.17−7.35 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 42.9, 43.6, 44.4, 56.5, 127.4, 127.46, 127.48, 128.6, 129.0, 137.4, 141.4, 157.5, 170.4, 197.6 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3292, 2953, 2923, 2851, 2360, 2342, 1653, 1558, 1541, 1497, 1456, 1436, 1376, 1222, 1030, 758, 698, cm^{-1}; d.r.: *trans*/*cis* = 88/12; ESI-MS (*m*/*z*): 342.1 (M + Na^+); MALDI/DHB calcd for $C_{21}H_{22}NO_2^+$ 320.1639, found: 320.1645. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 17.8 min, t_{minor} = 9.7 min, 88% ee; *cis* diastereoisomer: t_{major} = 26.7 min, t_{minor} = 16.2 min, 25% ee.

*N-Cyclohexyl-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3i**).* Yield 50 mg, 80%; white solid; $[\alpha]_D^{26}$ = −48.9 (*c* = 0.75 in $CHCl_3$); mp = 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63−0.67 (m, 1H), 1.00−1.16 (m, 2H), 1.17−1.35 (m, 4H), 1.47−1.64 (m, 2H), 1.79−1.84 (m, 1H), 2.00 (s, 3H), 2.67 (d, *J* = 8.4 Hz, 2H), 3.17 (d, *J* = 9.6 Hz, 1H), 3.58−3.66 (m,2H), 5.42 (d, *J* = 8 Hz, 1H), 6.07 (s, 1H), 7.22−7.32 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 24.6, 24.7, 25.3, 32.5, 33.0, 42.7, 44.4, 48.1, 56.9, 127.3, 127.4, 128.8, 129.0, 141.4, 157.7, 169.3, 197.5 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3299, 2931, 2854, 1721, 1642, 1548, 1451, 1378, 1357, 1247, 1194, 890, 757, 699 cm^{-1}; d.r.: *trans*/*cis* = 85/15; ESI-MS (*m*/*z*): 334.2 (M + Na^+); MALDI/DHB calcd for $C_{20}H_{26}NO_2^+$ 312.1968, found: 312.1958. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 12.3 min, t_{minor} = 6.5 min, 86% ee; *cis* diastereoisomer: t_{major} = 10.6 min, t_{minor} = 16.8 min, 72% ee.

*N-Butyl-3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3j**).* Yield 43 mg, 75%; white solid; $[\alpha]_D^{26}$ = −41.3 (*c* = 0.9 in $CHCl_3$); mp = 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 7.2 Hz, 3H), 1.01−1.07 (m, 2H), 1.15−1.22 (m, 2H), 1.99 (s, 3H), 2.67−2.69 (m, 2H), 2.99−3.05 (m, 1H), 3.10−3.19 (m, 2H), 3.65 (q, *J* = 11.2 Hz, 1H), 5.42 (s, 1H), 6.08 (s, 1H), 7.22−7.33 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.7, 22.2, 31.3, 39.3, 42.6, 44.4, 56.7, 127.3, 127.4, 128.9, 129.0, 141.5, 157.6, 170.3, 197.5 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3277, 3088, 2958, 2933, 2872, 1670, 1642, 1575, 1541, 1507, 1456, 1436, 1375, 1264, 1224, 890, 761, 697 cm^{-1}; d.r.: *trans*/*cis* = 90/10; ESI-MS (*m*/*z*): 308.2 (M + Na^+); MALDI/DHB calcd for $C_{18}H_{24}NO_2^+$ 286.1809, found: 286.1802. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7

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mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 8.6 min, t_{minor} = 6.4 min, 92% ee; *cis* diastereoisomer: t_{major} = 7.9 min, t_{minor} = 7.2 min, 94% ee.

*(1R,2S)-5-oxo-N-Phenyl-3-propyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (trans-**3k**).* Yield: 47 mg, 71%; $[\alpha]_D^{26}$ = −131.0 (*c* = 1.0 in $CHCl_3$); mp = 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.6 Hz, 3H), 1.48−1.61 (m, 2H), 2.28−2.34 (m, 2H), 2.76−2.78 (m, 2H), 3.40 (d, *J* = 9.2 Hz, 1H), 3.72 (dd, *J* = 6.4 Hz, *J* = 9.2 Hz, 1H), 6.15 (s, 1H), 7.08−7.13 (m, 2H), 7.21−7.33 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.5, 37.7, 41.9, 44.5, 56.7, 120.6, 125.1, 127.2, 127.6, 128.1, 129.01, 129.03, 136.8, 141.4, 160.4, 169.1, 197.7 ppm. IR (KBr): ν 3245, 3030, 2962, 2922, 1717, 1652, 1522, 1489, 1456, 1376, 1261, 1231, 1094, 1019, 849, 800, 700 cm^{-1}; ESI-MS (*m*/*z*): 356.2 (M + Na$^+$); MALDI/DHB calcd for $C_{22}H_{24}NO_2^+$ 334.1808, found: 334.1802. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): t_{major} = 27.9 min, t_{minor} = 11.0 min, 89% ee

*(1R,2R)-5-oxo-N-Phenyl-3-propyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (cis-**3k**).* Yield: 15 mg, 22%; white solid; $[\alpha]_D^{26}$ = −50.0 (*c* = 0.4 in $CHCl_3$); mp = 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.6 Hz, 3H), 1.59−1.65 (m, 2H), 2.25.2.31 (m, 2H), 2.54 (dd, *J* = 4.0 Hz, *J* = 16.4 Hz, 1H), 3.28 (d, *J* = 5.2 Hz, 1H), 3.37 (t, *J* = 15.2 Hz, 1H), 3.67−3.73 (m, 1H), 6.16 (s, 1H), 6.45 (s, 1H), 7.00−7.08 (m, 3H), 7.21−7.36 (m,7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.2, 37.5, 39.0, 55.8, 120.4, 124.9, 127.3, 127.7, 127.8, 128.8, 129.1, 130.9, 136.8, 140.5, 160.6, 199.2 ppm. IR (neat): ν 3308, 2961, 2927, 1660, 1600, 1539, 1498, 1455, 1443, 1361, 1258, 1182, 1027, 756, 698 cm^{-1}. HPLC (Chiralpak PC-2 column, hexane/*i*-PrOH 80:20, flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 26.8 min, t_{minor} = 17.0 min, 96% ee.

*3-Methyl-4′-nitro-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3l**).* Yield 58 mg, 83%; white solid; $[\alpha]_D^{26}$ = −144.9 (*c* = 0.83 in $CHCl_3$); mp = 153−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.67−2.80 (m, 2H), 3.41 (d, *J* = 9.2 Hz, 1H), 3.88−3.95 (m, 1H), 6.09 (s, 1H), 7.07−7.15 (m, 1H), 7.16−7.30 (m, 3H), 7.39−7.45 (m, 3H), 8.15−8.18 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 41.7, 44.0, 56.7, 120.4, 124.2, 125.5, 128.4, 129.2, 129.3, 136.6, 147.3, 148.5, 156.5, 168.2, 196.1 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3307, 2958, 2925, 2852, 1654, 1601, 1541, 1521, 1444, 1378, 1347, 1262, 1109, 1016, 857, 753, 694 cm^{-1}; d.r.: *trans*/*cis* = 75/25; ESI-MS (*m*/*z*): 373.1 (M + Na$^+$); MALDI/DHB calcd for $C_{20}H_{19}N_2O_4^+$ 351.1339, found: 351.1339. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 46.2 min, t_{minor} = 18.3 min, 90% ee; *cis* diastereoisomer: t_{major} = 44.4 min, t_{minor} = 52.4 min, 78% ee.

*4′-Fluoro-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3m**).* Yield 61 mg, 94%; white solid; $[\alpha]_D^{26}$ = −92.2 (*c* = 0.45 in $CHCl_3$); mp = 235−237 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.71−2.74 (m, 2H), 3.29 (d, *J* = 9.2 Hz, 1H), 3.70−3.77 (m, 1H), 6.15 (s, 1H), 6.91 (s, 1H), 7.01 (t, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.22−7.31 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 42.4, 43.7, 57.7, 115.9 ($^2J_{CF}$ = 21.4 Hz), 120.5, 125.3, 128.7, 128.9 ($^3J_{CF}$ = 6.3 Hz), 129.1, 129.4, 136.7, 156.6, 162.0 ($^1J_{CF}$ = 241.3 Hz), 168.8, 196.9 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3272, 2955, 2924, 2853, 1674, 1599, 1512, 1456, 1378, 1260, 1225, 1018, 802, 746, 691 cm^{-1}; d.r.: *trans*/*cis* = 88/12; ESI-MS (*m*/*z*): 346.0 (M + Na$^+$); MALDI/DHB calcd for $C_{20}H_{19}NO_2F^+$ 324.1396, found: 324.1394. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 34.4 min, t_{minor} = 9.6 min, 96% ee; *cis* diastereoisomer: t_{major} = 23.1 min, t_{minor} = 28.6 min, 89% ee.

*(1R,2S)-4′-Chloro-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (trans-**3n**).* Yield 37 mg, 55%; white solid; $[\alpha]_D^{26}$ = −113.4 (*c* = 1.0 in $CHCl_3$); mp = 200−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.71−2.73 (m, 2H), 3.30 (d, *J* = 10.4 Hz, 1H), 3.68−3.76 (m, 1H), 6.15 (s, 1H), 6.95 (s, 1H), 7.11−7.12 (m, 2H), 7.13−7.16 (m, 2H), 7.20−7.30 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 41.8, 44.0, 56.7, 120.4, 124.1, 124.2, 125.5, 128.4, 129.0, 129.2, 129.4, 136.6, 148.5, 168.2, 196.1 ppm. IR (KBr): ν 3307, 2960, 2924, 2890, 1718, 1655, 1599, 1491, 1444, 1378, 1261, 1091, 1015, 800, 756, 693 cm^{-1}; ESI-MS (*m*/*z*): 362.1 (M + Na$^+$); MALDI/DHB calcd for $C_{20}H_{19}ClNO_2^+$ 340.1109, found: 340.1094. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): t_{major} = 27.0 min, t_{minor} = 9.6 min, 98% ee.

*(1R,2R)-4′-Chloro-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (cis-**3n**).* Yield 10 mg, 15%; white solid; $[\alpha]_D^{26}$ = −34.9 (*c* = 0.67 in $CHCl_3$); mp = 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, 3H), 2.45 (dd, *J* = 6.4 Hz, *J* = 14.4 Hz, 1H), 2.85 (dd, *J* = 4.4 Hz, *J* = 14.4 Hz, 1H), 3.42−3.44 (m, 1H), 3.96−4.01 (m,1H) 6.00 (s, 1H), 7.00−7.36 (m, 9H), 7.81 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 36.6, 40.1, 58.7, 120.0, 124.5, 126.0, 128.8, 128.91, 128.94, 132.8, 137.5, 141.3, 163.4, 164.8, 195.0 ppm. IR (neat): ν 3308, 2963, 1847, 1661, 1652, 1444, 1257, 1090, 1015, 913, 797, 747 cm^{-1}; ESI-MS (*m*/*z*): 362 (M + Na$^+$); DART positive calcd for $C_{20}H_{19}ClNO_2^+$ 340.1099, found: 340.1096. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): t_{major} = 24.4 min, t_{minor} = 17.8 min, 85% ee

*(1R,2S)-4′-Bromo-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (trans-**3o**).* Yield 63 mg, 82% yield; white solid; $[\alpha]_D^{26}$ = −41.8 (*c* = 1.0 in $CHCl_3$); mp = 235 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.70−2.73 (m, 2H), 3.30 (d, *J* = 8.4 Hz, 1H), 3.69−3.76 (m, 1H), 6.14 (s, 1H), 7.02 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 3H), 7.26−7.32 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 43.0, 43.2, 54.9, 120.2, 120.4, 124.3, 128.3, 129.2, 130.3, 131.7, 138.7, 141.8, 158.8, 169.5, 197.1 ppm. IR (KBr): ν 3277, 2935, 2924, 2940, 1680, 1653, 1558, 1541, 1507, 1457, 1445, 1376, 1010, 900, 773, 692 cm^{-1}; ESI-MS (*m*/*z*): 406.0 (M + Na$^+$); MALDI/DHB calcd for $C_{20}H_{19}NO_2Br^+$ 384.0602, found: 384.0594. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): t_{major} = 22.5 min, t_{minor} = 8.5 min, 98% ee.

*(1R,2R)-4′-Bromo-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (cis-**3o**).* Yield 9 mg, 12% yield; white solid; $[\alpha]_D^{26}$ = −93.7 (*c* = 0.15 in $CHCl_3$); mp = 230−232 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 2.52 (d, *J* = 6.8 Hz, *J* = 18.4 Hz, 1H), 2.90 (d, *J* = 4.4 Hz, *J* = 18.4 Hz, 1H), 3.50 (d, *J* = 7.2 Hz, 1H), 4.01−4.03 (m, 1H), 6.06 (s, 1H), 7.06−7.12 (m, 3H), 7.25−7.29 (m, 2H), 7.41−7.43 (m, 4H), 7.94 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 36.5, 40.1, 58.6, 120.0, 120.3, 124.5, 126.0, 128.9, 129.1, 129.4, 131.7, 131.9, 137.5, 139.6, 141.8, 163.4, 194.9 ppm. IR (neat): ν 3320, 2928, 1660, 1599, 1545, 1488, 1443, 1380, 1261, 1073, 1010, 811, 753 cm^{-1}; ESI-MS (*m*/*z*): 406.0 (M + Na$^+$); DART positive calcd for $C_{20}H_{19}NO_2Br^+$ 384.0592, found: 384.0594. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): t_{major} = 25.6 min, t_{minor} = 18.0 min, 95% ee

*3,4′-Dimethyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3p**).* Yield 45 mg, 70%; white solid; $[\alpha]_D^{26}$ = −87.0 (*c* = 0.83 in $CHCl_3$); mp =230−232 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.31 (s, 3H), 2.73 (d, *J* = 8.4 Hz, 2H), 3.33 (d, *J* = 9.6 Hz, 1H), 3.65−3.72 (m, 1H), 6.14 (s, 1H), 6.90 (s, 1H), 7.09−7.16 (m, 5H), 7.22−7.29 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 22.4, 42.5, 44.1, 57.7, 120.5, 125.1, 127.0, 128.9, 129.4, 129.7, 136.8, 137.3, 138.2, 156.7, 169.0, 197.4 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3309, 2900, 2840, 1653, 1600, 1558, 1444, 1339, 1245, 810, 754, 692 cm^{-1}; d.r.: *trans*/*cis* = 85/15; ESI-MS (*m*/*z*): 342.2 (M + Na$^+$); MALDI/DHB calcd for $C_{21}H_{22}NO_2^+$ 320.1641, found: 320.1645. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 16.1 min, t_{minor} = 8.1 min, 98% *ee*; *cis* diastereoisomer: not determined ee.

*4′-Methoxy-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3q**).* Yield 56 mg, 84%; white solid; $[\alpha]_D^{26}$ = −29.7 (*c* = 0.92 in $CHCl_3$); mp = 135−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.45−2.71 (m, 2H), 3.26−3.40 (m, 1H), 3.63−3.69 (m, 1H), 3.75 (s, 3H), 6.09 (s, 1H), 6.79−6.85 (m, 2H), 7.05−7.11 (m, 2H), 7.13−7.17 (m, 2H), 7.19−7.25 (m, 3H), 7.61 (s,

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1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.8, 43.7, 55.3, 57.8, 114.4, 120.6, 125.1, 128.2, 129.0, 129.3, 133.2, 136.9, 157.0, 159.0, 169.1, 197.6 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3150, 3012, 2957, 2931, 1670, 1602, 1543, 1514, 1444, 1251, 1180, 1033, 897, 755, 693 cm^{-1}; d.r.: *trans*/*cis* = 75/25; ESI-MS (*m*/*z*): 358.1 (M + Na$^+$); MALDI/DHB calcd for $C_{21}H_{22}NO_3^+$ 336.1595, found: 336.1594. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 28.5 min, t_{minor} = 12.8 min, 95% ee; *cis* diastereoisomer: t_{major} = 14.5 min, t_{minor} = 16.6 min, 94% ee.

*4′-(Benzyloxy)-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3r**).* Yield 76 mg, 92%; white solid; $[\alpha]_D^{26}$ = −76.1 (*c* = 0.56 in $CHCl_3$); mp = 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.66−2.69 (m, 2H), 3.23−3.36 (m, 1H), 3.62−3.69 (m, 1H), 4.99 (s, 2H), 6.09 (s, 1H), 6.87−7.05 (m, 2H), 7.07−7.45 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.7, 43.7, 57.7, 70.1, 115.4, 120.6, 125.1, 127.3, 127.4, 128.0, 128.2, 128.6, 129.0, 129.3, 133.5, 136.9, 157.1, 158.1, 169.2, 197.6 ppm. IR (KBr): ν 3033, 2958, 2925, 2855, 1660, 1600, 1542, 1512, 1443, 1378, 1304, 1248, 1179, 1024, 897, 833, 754, 695 cm^{-1}; d.r.: *trans*/*cis* = 75/25; ESI-MS (*m*/*z*): 434.3 (M + Na$^+$); MALDI/DHB calcd for $C_{27}H_{26}NO_3^+$ 412.1910, found: 412.1907. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 29.4 min, t_{minor} = 20.8 min, 87% ee; *cis* diastereoisomer: t_{major} = 30.1 min, t_{minor} = 42.0 min, 92% ee.

*3,3′-Dimethyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3s**).* Yield 59 mg, 93% yield; white solid; $[\alpha]_D^{26}$ = −39.1 (*c* = 0.17 in $CHCl_3$); mp = 222−224 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.27 (s, 3H), 2.72 (d, *J* = 8.4 Hz, 2H), 3.24−3.38 (m, 1H), 3.57−3.70 (m, 1H), 6.13 (s, 1H), 6.23−7.12 (m, 5H), 7.18−7.28 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 22.4, 42.4, 44.4, 57.4, 120.7, 123.9, 125.1, 128.2, 128.4, 128.8, 129.0, 136.9, 138.8, 141.2, 157.1, 169.2, 197.5 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3200, 2955, 2925, 2853, 2359, 2342, 1677, 1651, 1548, 1462, 1377, 1088, 1018, 760, 668 cm^{-1}; d.r.: *trans*/*cis* = 75/25; ESI-MS (*m*/*z*): 342.1 (M + Na$^+$); MALDI/DHB calcd for $C_{21}H_{22}NO_2^+$ 320.1649, found: 320.1645. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 19.7 min, t_{minor} = 7.4 min, 96% ee; *cis* diastereoisomer: t_{major} = 7.9 min, t_{minor} = 9.0 min, 78% ee.

*3′-Chloro-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3t**).* Yield 56 mg, 83%; white solid; $[\alpha]_D^{26}$ = −126.0 (*c* = 1.0 in $CHCl_3$); mp = 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.64−2.75 (m, 2H), 3.34−3.69 (m, 1H), 3.71−3.76 (m, 1H), 6.13 (s, 1H), 7.08−7.30 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 42.0, 44.0, 57.1, 120.7, 125.3, 125.8, 127.1, 127.9, 129.1, 129.4, 130.3, 134.8, 136.6, 143.2, 156.6, 168.7, 196.7 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3200, 2956, 2923, 2853, 1667, 1598, 1549, 1463, 1338, 1234, 1087, 1019, 890, 692, 668 cm^{-1}; d.r.: *trans*/*cis* = 98/2; ESI-MS (*m*/*z*): 362.0 (M + Na$^+$); MALDI/DHB calcd for $C_{20}H_{19}NO_2Cl^+$ 340.1101, found: 340.1099. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 36.3 min, t_{minor} = 9.6 min, 95% ee; *cis* diastereoisomer: t_{major} = 11.6 min, t_{minor} = 11.3 min, 92% ee.

*3′-Methoxy-3-methyl-5-oxo-N-phenyl-1,2,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxamide (**3u**).* Yield 60 mg, 90%; white solid; $[\alpha]_D^{26}$ = −75.8 (*c* = 1.0 in $CHCl_3$); mp = 244−246 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.72−2.74 (m, 2H), 3.35 (d, *J* = 9.6 Hz, 1H), 3.66−3.72 (m, 1H), 3.72 (s, 3H), 6.14 (s, 1H), 6.78−6.80 (m, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 7.09−7.12 (m, 1H), 7.22−7.29 (m, 5H), 7.34 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.4, 44.5, 55.2, 57.3, 112.8, 113.3, 119.3, 120.6, 125.1, 129.0, 130.1, 136.9, 142.9, 157.0, 160.0, 169.1, 197.4 ppm (additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3315, 2950, 2924, 2853, 1660, 1660, 1548, 1497, 1463, 1387, 1263, 1233, 1088, 1018, 855, 756, 693 cm^{-1}; d.r.: *trans*/*cis* = 80/20; ESI-MS (*m*/*z*): 358.1 (M + Na$^+$); MALDI/DHB calcd for $C_{21}H_{22}NO_3^+$ 336.1591, found: 336.1594. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 33.9 min, t_{minor} = 9.6 min, 80% ee; *cis* diastereoisomer: t_{major} = 10.6 min, t_{minor} = 11.1 min, 81% ee.

*2-Methyl-6-(naphthalen-2-yl)-4-oxo-N-phenylcyclohex-2-enecarboxamide (**3v**).* Yield 67 mg, 95%; white solid; $[\alpha]_D^{26}$ = −43.4 (*c* = 1.0 in $CHCl_3$); mp = 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 2.81−2.84 (m, 2H), 3.48 (d, *J* = 9.2 Hz, 1H), 3.87−3.92 (m, 1H), 6.16 (s, 1H), 7.05 (t, *J* = 6.8 Hz, 1H), 7.13−7.21 (m, 5H), 7.38−7.48 (m, 3H), 7.67 (s, 1H), 7.34−7.81 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 42.3, 44.4, 57.3, 120.6, 125.0, 126.1, 126.2, 126.5, 127.7, 127.8, 128.9, 129.3, 132.7, 133.5, 136.7, 138.5, 156.9, 169.1, 197.3 ppm(additional peaks and line broadenings are observed due to diastereoisomers). IR (KBr): ν 3247, 2962, 2925, 1673, 1651, 1600, 1548, 1489, 1444, 1377, 1349, 1292, 1262, 1238, 1192, 1091, 1019, 903, 861, 810, 752, 694 cm^{-1}; d.r.: *trans*/*cis* = 78/22; ESI-MS (*m*/*z*): 378.1 (M + Na$^+$); MALDI/DHB calcd for $C_{24}H_{22}NO_2^+$ 356.1652, found: 356.1645. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 46.1 min, t_{minor} = 11.6 min, 80% ee; *cis* diastereoisomer: t_{major} = 13.7 min, t_{minor} = 18.9 min, 88% ee.

*(1S,6R)-6-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-4-oxo-N-phenylcyclohex-2-enecarboxamide (trans-**3w**).* Yield 46 mg, 65%; white solid; $[\alpha]_D^{26}$ = −59.1 (*c* = 1.0 in $CHCl_3$); mp = 218 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.62−2.75 (m, 2H), 3.29 (d, *J* = 9.2 Hz, 1H), 3.62−3.68 (m, 1H), 5.93 (d, *J* = 11.6 Hz, 2H), 6.13 (s, 1H), 6.70−6.76 (m, 3H), 6.98−7.03 (m, 1H), 7.10−7.14 (m, 1H), 7.24−7.30 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 42.9, 44.2, 57.4, 101.2, 107.2, 108.6, 101.2, 107.2, 108.6, 120.7, 125.1, 129.0, 129.2, 135.1, 136.9, 147.0, 148.0, 157.4, 169.2, 197.6 ppm. IR (neat): ν 3280, 2956, 2924, 2853, 1695, 1660, 1634, 1549, 1532, 1520, 1445, 1258, 1039, 800, 680 cm^{-1}; ESI-MS (*m*/*z*): 372.1 (M + Na$^+$); MALDI/DHB calcd for $C_{21}H_{20}NO_4^+$ 350.1388, found: 350.1387. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *trans* diastereoisomer: t_{major} = 31.2 min, t_{minor} = 11.7 min, 97% ee.

*(1R,6R)-6-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-4-oxo-N-phenylcyclohex-2-enecarboxamide (cis-**3w**).* Yield 15 mg, 22%; white solid; $[\alpha]_D^{26}$ = −20.3 (*c* = 0.6 in $CHCl_3$); mp = 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.56 (dd, *J* = 6.8 Hz, *J* = 18.4 Hz, 1H), 2.92 (dd, *J* = 4.8 Hz, *J* = 18.4 Hz, 1H), 3.50−3.51 (m, 1H), 3.98−4.01 (m, 1H), 5.96 (s, 1H), 6.09 (s, 1H), 6.71−6.77 (m, 3H), 7.09−7.13 (m, 1H), 7.10−7.14 (m, 1H), 7.28−7.48 (m, 4H), 7.88 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 37.0, 40.6, 59.4, 101.0, 107.8, 108.4, 120.0, 120.4, 120.5, 124.4, 125.9, 128.8, 128.9, 136.6, 146.5, 147.8, 163.6, 195.2 ppm. IR (neat): ν 3308, 2963, 2923, 1650, 1600, 1548, 1488, 1443, 1260, 1095, 1038, 799 cm^{-1}; ESI-MS (*m*/*z*): 372.1 (M + Na$^+$); DART Positive calcd for $C_{21}H_{20}NO_4^+$ 350.1384, found: 350.1387. HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, λ = 254 nm): *cis* diastereoisomer: t_{major} = 14.6 min, t_{minor} = 17.1 min, 97% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Cif file for **3o** and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhaog@sioc.ac.cn. Tel: 0086-21-54925182. Fax: 0086-21-64166128.

Notes

The authors declare no competing financial interest.

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