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Photochemically Promoted Aza-Diels–Alder-Type Reaction: High Catalytic Activity of the Cr(III)/Bipyridine Complex Enhanced by Visible Light Irradiation

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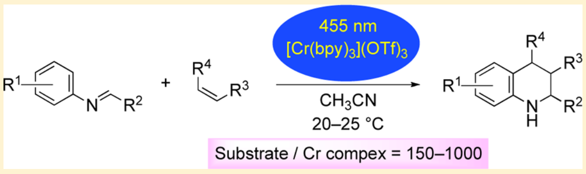
Supporting Information

ABSTRACT: Aza-Diels–Alder-type cycloaddition reactions between a range of *N*-arylimines and functionalized alkenes were effectively catalyzed by the Cr(III)/bipyridine complex under irradiation of blue light, to give the corresponding 1,2,3,4-tetrahydroquinoline derivatives in high yields with excellent diastereoselectivity. Typically, the reaction of benzylideneaniline with 1-vinyl-2-pyrrolidinone proceeded smoothly with a substrate-to-catalyst molar ratio (S/C) of 1000 and completed within 4 h at room temperature (20–25 °C), affording the cycloaddition product in 97% yield.



The tetrahydroquinoline framework is a quite common structural motif found in a number of biologically active natural products and pharmaceuticals.[1] Therefore, the development of new synthetic methodologies for this important class of compounds has attracted much attention among researchers in the fields of drug discovery and medicinal chemistry as well as synthetic chemistry.[2] Among the numerous methods for preparing the tetrahydroquinoline ring system, the aza-Diels–Alder-type reaction between *N*-arylimines and functionalized alkenes is one of the most versatile approaches, because a wide range of diverse products can be readily obtained with this reaction merely by changing the combination of imines and alkenes.[3] It is well-known that the [4+2] cycloaddition reactions between *N*-arylimines and functionalized alkenes are catalyzed by Brønsted acids,[4] or by Lewis acids that include group-3 metal triflates,[5] $Sb_2(SO_4)_3$,[6] $SbCl_3$,[7] $InCl_3$,[8] $FeCl_3$,[9] $Al(OTf)_3$,[10] and others.[11,12] Some of these reactions catalyzed by Lewis acids were extended to the asymmetric reaction by combination with chiral ligands or by using chiral organocatalysts.[13,14] It has also been reported that the cycloaddition reaction is promoted via single electron transfer by using a pyrrilium salt under UV irradiation,[15] cerium(IV) salt,[16] nitrosonium salt,[17] or an aminium cation radical.[18] However, these methods also have some drawbacks from the viewpoint of efficient and practical catalytic reaction, namely, they require expensive rare metals with relatively large catalyst loading (1–10 mol%, in many cases). Guo and co-workers reported that a triphenylmethylium cation catalyzed the aza-Diels–Alder-type reaction with a catalyst loading of 0.5 mol%.[19] However, when the catalyst loading decreased to 0.05 mol%, the yield of the product (60% after 12 h) was not satisfactory. We herein report a new catalytic system for the aza-Diels–Alder-type reaction by using a chromium/bipyridine complex under visible light irradiation. The catalytic efficiency is quite high and the reaction completes within a few hours under a substrate-to-catalyst molar ratio (S/C) of 1000 in the best case.

$[Cr(bpy)_3](OTf)_3$ (**1**) is easily synthesized from $CrCl_3$ according to the method described in the literature.[20] The complex behaves as a strong oxidizing reagent in its excited state, the redox potential of which is calculated as $E°(Cr^{3+}(bpy)_3*/Cr^{2+}(bpy)_3)$ = +1.45 V (vs SCE).[21,22] The absorption maximum of lowest energy transition in the UV–vis spectrum of **1** is reported as 455 nm (blue light region).[21] In spite of this attractive redox property, there have been few reports on the synthetic use of complex **1**. This situation prompted us to investigate the aza-Diels–Alder-type reaction by using **1** as a visible-light photocatalyst. Elegant investigations into the Diels–Alder-type reaction of dienes and alkenes with related photooxidizing Cr/phenanthroline catalysts were previously reported by Rappé and Shores et al.[23]

At an initial attempt, a solution containing *N*-phenylimine **2a** (0.2 mmol), 1-vinyl-2-pyrrolidinone (**3**) (0.55 mmol), and Cr(III)/bpy complex **1** (0.004 mmol, S/C = 50) in CH_3CN (4 mL) was irradiated with 455 nm LED at room temperature for 3 h. To our delight, most of the starting material **2a** was consumed, giving the cycloaddition product *cis*-**4a** in 77% yield accompanied by small amounts of *trans*-**4a** (approximately <3%) (Table 1, entry 1). It should be noted that neither $RuCl_3(bpy)_3$ nor $[Ir(dFCF_3ppy)_2(bpy)]PF_6$, which are very popular photocatalysts available in the blue light region,[24–26] were effective, and the reactions resulted in almost quantitative recovery of the starting materials under the same reaction conditions (entries 2 and 3). No reaction occurred without **1** (entry 4). Unexpectedly, small amounts of **4a** were obtained

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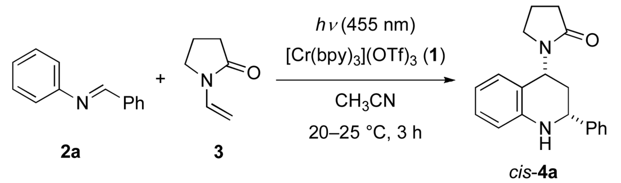
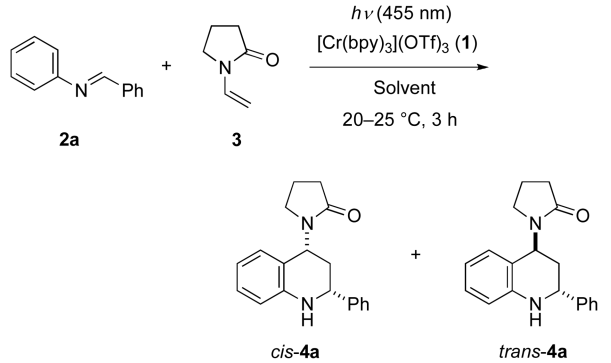
Table 1. Initial Attempts[a]



entry	deviation from standard conditions	yield of *cis*-**4a** (%)[b]
1	none	77
2	$RuCl_3(bpy)_3$, instead of **1**	0[c]
3	$[Ir(dFCF_3ppy)_2(bpy)]PF_6$, instead of **1**	0[c]
4[d]	no **1**	0[c]
5[e]	no light	35
6[e]	no light, with 2,6-di-*tert*-butyl-4-methylpyridine[f]	2

[a]Reactions were conducted at 20−25 °C using 0.2 mmol of **2a**, 0.55 mmol of **3**, and 0.004 mmol of **1** in 4 mL of solvent under irradiation with 455 nm LED. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Only **2a**, **3**, and CH_3CN were observed in ^{1}H NMR analysis of the crude mixture. [d]Carried out with 0.29 mmol of **3** and 2 mL of solvent. [e]Carried out with 0.25 mmol of **3**, 0.002 mmol of **1**, and 2 mL of solvent. [f]15-fold molar amounts of the base were added.

Table 2. Solvent Screen[a]



		yield or recovery (%)[b]		
entry	solvent	*cis*-**4a**	*trans*-**4a**	**2a**
1	CH_3CN	78	3	12
2	CH_3NO_2	45	2	23
3[c]	CH_2Cl_2	35	1	61
4[c]	$PhCF_3$	9	<1	70
5[c]	THF	22	1	61
6[c]	MTBE	5	<1	82
7[c]	AcOEt	8	<1	79
8	CH_3OH	13	<1	52
9	acetone	23	<1	9

[a]Reactions were conducted at 20−25 °C using 0.2 mmol of **2a**, 0.25 mmol of **3**, and 0.002 mmol of **1** in 2 mL of solvent under irradiation with 455 nm LED. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Complex **1** did not completely dissolve in the solvent.

even in the absence of photo irradiation (entry 5). We guessed that the trace of residual acid contained in **1** brought about a relatively slow reaction. In fact, the formation of adduct **4a** was suppressed by the addition of 2,6-di-*tert*-butyl-4-methylpyridine as a Brønsted base (entry 6).[27]

Thus, we found that complex **1** effectively catalyzes the aza-Diels−Alder-type reaction under blue light irradiation, and we next screened a series of solvents to identify a suitable one for this reaction. The reactions were carried out by using **2a** (0.2 mmol), **3** (0.25 mmol), and **1** (0.002 mmol, S/C = 100) in CH_3CN (2 mL), and discontinued in 3 h irrespective of the consumption of the starting material. As can be seen from Table 2, the solvent employed largely affected the result of the reaction. Acetonitrile was the solvent of choice, and gave the adduct *cis*-**4a** in good yield with a small recovery of **2a** (entry 1). The stereoselectivity was comparably high with that reported in the literature for the UV-irradiated cycloaddition reaction between imines and **3**.[15] A moderate yield of **4a** was obtained in nitromethane with messy byproducts (entry 2). The reactions in solvents with medium polarity were rather slow, partially due to the poor solubility of **1** in these solvents (entries 3−7). Adduct **4a** was also obtained in methanol and acetone, but the yield was low and was accompanied by unidentified byproducts in both cases (entries 8 and 9).

With the most suitable solvent for the reaction settled, we next applied this cycloaddition reaction to a series of *N*-arylimines **2**. In these studies, 2-fold molar amounts of **3** with respect to **2** were employed, and the reaction was continued until the imine was consumed except when the reaction was very slow. The results are listed in Table 3. The reaction with imine **2a** proceeded well under the condition of S/C = 500 to afford the addition product **4a** in 95% isolated yield (entry 1). Notably, the same reaction was completed even under the condition of S/C = 1000 with slightly prolonged reaction time, giving **4a** in high yield (entry 2). The reaction under more diluted conditions (initial substrate concentration = 0.1 M) gave comparable yield and stereoselectivity (entry 3). We presumed that the slight decrease of the yield in entry 3 was caused by competitive hydrolysis of imine **2a**, though commercial dehydrated grade solvent was used. The reaction was applicable to a range of imines that were derived from *para*-substituted anilines, **2b**−**2e**, as well as unsubstituted **2a** to give the corresponding tetrahydroquinoline derivatives in excellent yields and diastereoselectivities (entries 4−7). In contrast, an imine with a nitro group, **2f**, was slow to react, and gave the product **4f** in low yield and medium *cis*-selectivity with a recovery of **2f** (33%) (entry 8). Fortunately, when the 4-acetamide-substituted imine **2g** was employed instead of **2f**, the reaction proceeded nicely, giving the product **4g** in 95% yield and 98% *cis*-selectivity (entry 9). This result allowed us to obtain tetrahydroquinoline derivatives having nitrogen functionality at the 6-position. When the reaction was conducted with imine **2h**, which had bromine at the *meta*-position, the 7-bromotetrahyroquinoline derivative **4h** was obtained in moderate yield (entry 10). In this case, a hardly separable mixture that might contain regio isomer of **4h** was also obtained but the mixture was not fully characterized. In contrast, the reaction with *N*-arylimine from *m*-anisidine **2o** gave 5-methoxytetrahydroquinoline **4o′** as major product accompanied by a comparable amount of 7-isomer **4o** (Scheme 1). The reaction with the sterically hindered imine **2i** derived from *o*-toluidine afforded the 8-methyltetrahydroquinoline derivative **4i** in 72% yield (entry 11). The electronic properties of aromatic rings that came from aldehydes had little impact on the product yields, though the reaction with the electron rich substrate **2k** was slower than that with **2j** (entries 12 and 13). This reaction was also applicable to imines that were prepared from aldehydes other than benzaldehyde derivatives. When the reaction was carried out by using imine **2l** derived from furfural, 2-furyltetrahydroquinoline **4l** was obtained in moderate yield

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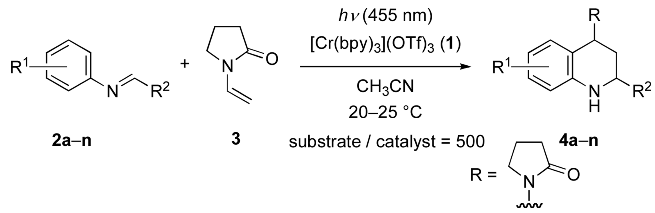
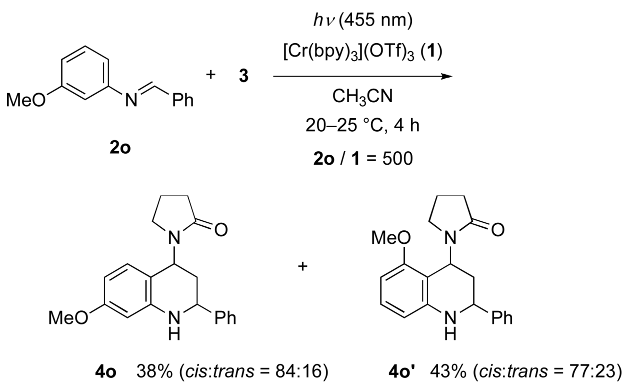
Table 3. Substrate Screen[a]



entry	imine	time (h)	product (*cis*:*trans*)[b]
1	2a	3	95% (97:3)
2[c]	2a	4	97% (96:4)
3[c,d]	2a	8	89% (97:3)
4	2b	3	93% (99:1)
5	2c	8.5	90% (95:5)
6	2d	5	90% (98:2)
7	2e	3	95% (95:5)
8	2f	10	26% (81:19)[e]
9	2g	8	95% (98:2)
10	2h	10	61% (94:6)
11	2i	10	72% (94:6)
12	2j	3	84% (96:4)
13	2k	10	89% (97:3)
14	2l	10	64% (94:6)[f]
15	2m	3	90% (>99:1)
16	2n	10	55% (96:4)

[a]Reactions were conducted at 20−25 °C using 0.75 mmol of **2**, 1.5 mmol of **3**, and 0.0015 mmol of **1** in 2 mL of solvent under irradiation with 455 nm LED. [b]Isolated yield. [c]Carried out with 1.5 mmol of **2** and 3 mmol of **3** (S/C = 1000). [d]Carried out with 15 mL of solvent. [e]**2f** was recovered in 33%. [f]**2l** was recovered in 18%.

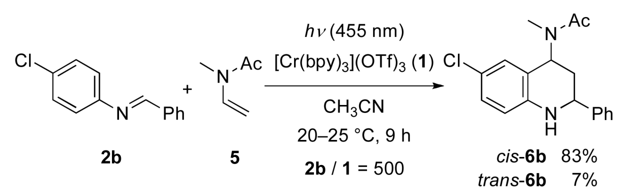
Scheme 1. Reaction with *m*-Methoxyphenylimine 2o



(entry 14). This adduct, **4l**, is known as a useful intermediate for the construction of isoindolo[2,1-*a*]quinoline frameworks.[28] The reaction with imine **2m** from pivalaldehyde proceeded smoothly to give the product **4m** in almost perfect diastereoselectivity (entry 15). The 2-cyclopropyltetrahydroquinoline derivative **4n** was also stereoselectively produced in moderate yield from imine **2n** (entry 16). Thus, our reaction is also suitable for the preparation of 2-alkyl-substituted tetrahydroquinolines.

We can employ functionalized alkenes other than 1-vinylpyrrolidin-2-one (**3**). In the reaction between imine **2b** and acyclic alkenyl amide **5**, the tetrahydroquinoline derivative **6b**, which has acetamide functionality at the 4-position, was obtained in high yield (Scheme 2). It should be commented that amide **5** exists as a mixture of rotamers (approximately 3:1), which was also the case with the product **6b**.

Scheme 2. Reaction with Acyclic Alkenyl Amide 5



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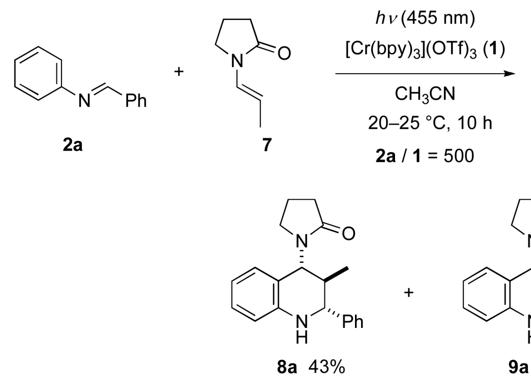
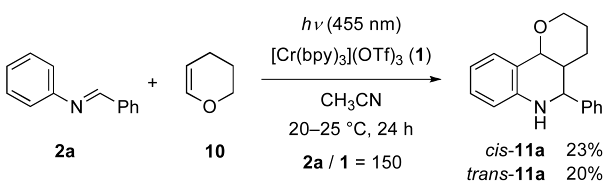
In addition to the terminal alkenes described above, the internal alkenyl amide was also employable as a reaction partner of imine **2a**, although the reactivity was relatively low. When imine **2a** was reacted with internal amide **7** under the conditions described in Table 3, the corresponding cycloaddition products **8a** and **9a** were obtained in moderate yields (Scheme 3). The relative configuration of **8a** and **9a** was determined by NOE experiments (see Supporting Information).

Scheme 3. Reaction with Internal Amide 7



The reaction was also applicable to an internal alkenyl ether. The reaction between imine **2a** and 3,4-dihydro-2*H*-pyrane (**10**) proceeded sluggishly, affording the corresponding cycloadduct **11a** in 43% yield with recovery of **2a** (approximately 45%) after irradiation of 24 h with increased catalyst loading (Scheme 4).

Scheme 4. Reaction with Cyclic Alkenyl Ether 10



It is known that the oxidation potentials of enamides (**3**: + 1.12 V vs SCE,[29] **5**: + 1.55 V vs SCE[30]) are lower than that of alkenyl ether **10** (+1.66 V vs SCE)[31] from an electrochemical point of view. As can be seen from the reactions described above, the reaction proceeded more smoothly with readily oxidizable **3** or **5** than with **10**. Though further investigations will be needed to disclose the reaction mechanism, we surmise that the reaction proceeds via single electron transfer from functionalized alkenes to the excited chromium complex, as discussed in the literature on the aza-Diels–Alder-type reactions via single electron transfer.[15,18]

In summary, we found that $[Cr(bpy)_3](OTf)_3$ (**1**) efficiently catalyzes the aza-Diels–Alder-type reaction between a range of imines and functionalized alkenes under irradiation of blue light (455 nm) to give the corresponding cycloaddition products in high yield. The reaction was completed with a substrate/catalyst molar ratio (S/C) as high as 1000 in the best case. This cycloaddition would be applicable to the preparation of diversely substituted tetrahydroquinoline derivatives with very small amounts of catalyst loading.

■ EXPERIMENTAL SECTION

General Remarks. NMR spectra were obtained on a JEOL JNM-ECS400 spectrometer. Carbon multiplicity (described as follows: methyl, CH_3; methylene, CH_2; methine, CH; quaternary, C) was assigned by a DEPT experiment. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Melting points were measured on a Yanaco Micro Melting Point Apparatus MP-S3 and were uncorrected. Silica gel column chromatography was performed using FL 60D or PSQ 60B silica gel from Fuji Silysia Chemical, Ltd. Preparative thin layer chromatography was carried out with Wako Gel B-5F from Wako Pure Chemical Industries, Ltd. Solvents for the cycloaddition reaction were of commercial dehydrated grade (Kanto Chemical Co., Inc.) and used as received. Gel permeation chromatography (GPC) was performed using an LC-918 recycling preparative HPLC equipped with JAIGEL-1H and -2H columns in series (Japan Analytical Industry Co., Ltd.). Mass spectrometry and elemental analyses were carried out at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University.

Preparation of the Catalyst and the Starting Materials. $[Cr(bpy)_3](OTf)_3$ (**1**) was prepared according to the procedure described in the literature.[20] All of the starting materials used in this study are known compounds. *N*-Benzylideneaniline (**2a**) is widely available from suppliers and was purified by recrystallization (from hexane) before use. 1-Vinyl-2-pyrrolidinone (**3**), *N*-methyl-*N*-vinylacetamide (**5**), and 3,4-dihydro-2*H*-pyrone (**10**) are commercially available and were purified by distillation before use. (*E*)-1-(1-Propenyl)-2-pyrrolidinone (**7**) was prepared according to the procedure described in the literature.[32] All imines except **2a** and **2n** were prepared by refluxing a benzene solution of an equimolar mixture of the corresponding amine and aldehyde with a Dean–Stark trap for several hours.[33] The crude products were purified by recrystallization or distillation. Imine **2n** was synthesized according to the procedure described in the literature.[34] The physical and spectral data of imines **2b**,[35] **2c**,[35] **2d**,[35] **2e**,[36] **2f**,[37] **2g**,[38] **2h**,[39] **2i**,[39] **2j**,[40] **2k**,[41] **2l**,[42] **2m**,[43] **2n**,[34] and **2o**[44] showed good accordance with those described in the literature.

General Procedure for the Cycloaddition of Imines and Functionalized Alkenes. The reaction between **2a** and **3** under S/C = 500 (Table 1, entry 1) is representative.

To a Pyrex test tube containing imine **2a** (146.0 mg, 0.806 mmol), alkenyl amide **3** (176.0 mg, 1.58 mmol), and Cr catalyst **1** (1.5 mg, 0.0015 mmol) under argon, acetonitrile (2 mL) that had been degassed by three freeze-thaw cycles was added via a syringe. The solution was irradiated by a 240 mW (radiant flux) blue LED (455 nm) externally for 3 h. The reaction mixture was concentrated under reduced pressure. Purification of the crude materials by silica gel column chromatography (PSQ 60B, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:2) gave pure *cis*-**4a** (225.5 mg) and a mixture of *cis*-**4a** and *trans*-**4a** (21.4 mg) as colorless viscous oil. Dichloromethane was used to combine the fractions. A small amount of solvent remained in these samples even after a long period of evacuation. The molar amounts of **4a** (*cis*-**4a**: 0.741 mmol; *trans*-**4a**: 0.024 mmol) were calculated by subtracting those of solvent based on the ^{1}H NMR integrals.

In the several cases listed below, the *cis*-product was spontaneously precipitated in the reaction mixture. Filtration followed by washing with cold acetonitrile gave a diastereomerically pure sample. The filtrate was concentrated and purified by silica gel column chromatography or preparative thin layer chromatography. The yields and the diastereomeric ratios shown in Table 3 were calculated from combined amounts of these samples.

Physical and Spectral Data of the Products. *(2R*,4R*)-1,2,3,4-Tetrahydro-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-4a).*[15a] Colorless viscous oil or foamy amorphous solid. IR (KBr) 3313, 3027, 2950, 1671, 1605, 1489, 1420, 1313, 1285, 1268, 751, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.14 (m, 4H), 2.42–2.58 (m, 2H), 3.18–3.28 (m, 2H), 4.00 (br s, 1H), 4.60–4.63 (m, 1H), 5.71–5.75 (m, 1H), 6.58 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.69–6.73 (m, 1H), 6.88

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(d, *J* = 7.6 Hz, 1H), 7.04−7.09 (m, 1H), 7.29−7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.4 (CH_2), 35.2 (CH_2), 42.3 (CH_2), 48.4 (CH), 56.4 (CH), 114.9 (CH), 118.2 (CH), 118.8 (C), 126.4 (CH), 126.8 (CH), 128.0 (CH), 128.2 (CH), 128.8 (CH), 143.0 (C), 145.9 (C), 175.8 (C).

(2R,4R*)-6-Chloro-1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4b**).*[15a] Compound **4b** was obtained from imine **2b** (163.2 mg, 0.757 mmol) according to the general procedure. Colorless solid (*cis*-**4b**, 190.2 mg, 0.582 mmol) was isolated as a precipitate. Purification of the filtrate by preparative thin layer chromatography (developed with $CHCl_3$/MeOH = 40:1, 2 times) gave pale yellow oil (46.8 mg with a small amount of inseparable **3**). ^{1}H NMR analysis revealed that the oil contained 0.116 mmol of *cis*-**4b** and 0.0070 mmol of *trans*-**4b**. The combined yield was 93% (*cis*:*trans* = 99:1). IR (KBr) 3357, 2951, 1673, 1601, 1491, 1458, 1433, 1364, 1341, 1296, 1255, 819, 769, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00−2.13 (m, 4H), 2.42−2.60 (m, 2H), 3.18−3.28 (m, 2H), 4.02 (br s, 1H), 4.57−4.61 (m, 1H), 5.66−5.70 (m, 1H), 6.51 (d, *J* = 8.6 Hz, 1H), 6.82 (obscured d, *J* = 2 Hz, 1H), 6.99−7.02 (m, 1H), 7.30−7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.2 (CH_2), 34.8 (CH_2), 42.2 (CH_2), 48.2 (CH), 56.3 (CH), 116.1 (CH), 120.5 (C), 122.8 (C), 126.3 (CH), 126.4 (CH), 128.1 (CH), 128.2 (CH), 128.8 (CH), 142.6 (C), 144.4 (C), 175.8 (C).

(2R,4R*)-1,2,3,4-Tetrahydro-6-methoxy-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4c**).*[15a] Compound **4c** was obtained from imine **2c** (159.8 mg, 0.756 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 1:1, then 1:2) gave colorless solid (*cis*-**4c**, 193.3 mg, 0.600 mmol) and pale yellow oil (27.1 mg with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that the oil contained 0.0468 mmol of *cis*-**4c** and 0.0328 mmol of *trans*-**4c**. The combined yield was 90% (*cis*:*trans* = 95:5). IR (KBr) 3354, 2992, 2950, 2828, 1679, 1497, 1472, 1429, 1286, 1270, 1234, 1041, 822, 767, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.14 (m, 4H), 2.41−2.57 (m, 2H), 3.18−3.28 (m, 2H), 3.73 (s, 3H), 3.80 (br s, 1H), 4.52−4.56 (m, 1H), 5.72 (dd, *J* = 11.0, 7.0 Hz, 1H), 6.48 (dd, *J* = 2.8, 1.0 Hz, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.68−6.71 (m, 1H), 7.29−7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.4 (CH_2), 35.2 (CH_2), 42.3 (CH_2), 48.6 (CH), 55.9 (CH_3), 56.7 (CH), 112.2 (CH), 114.4 (CH), 116.1 (CH), 120.2 (C), 126.5 (CH), 127.9 (CH), 128.7 (CH), 140.1 (C), 143.1 (C), 152.6 (C), 175.8 (C).

(2R,4R*)-1,2,3,4-Tetrahydro-6-methyl-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4d**).*[6] Compound **4d** was obtained from imine **2d** (147.1 mg, 0.753 mmol) according to the general procedure. Colorless solid (*cis*-**4d**, 136.1 mg, 0.444 mmol) was isolated as a precipitate. Purification of the filtrate by silica gel column chromatography (FL 60D, hexane/ethyl acetate = 1:2) gave pale yellow oil (72.3 mg with a small amount of inseparable **3** and residual ethyl acetate). ^{1}H NMR analysis revealed that the oil contained 0.217 mmol of *cis*-**4d** and 0.0135 mmol of *trans*-**4d**. The combined yield was 90% (*cis*:*trans* = 98:2). IR (KBr) 3342, 3027, 2954, 2913, 1661, 1504, 1300, 816, 768, 704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.13 (m, 4H), 2.22 (s, 3H), 2.42−2.59 (m, 2H), 3.17−3.27 (m, 2H), 3.88 (br s, 1H), 4.55−4.58 (m, 1H), 5.68−5.73 (m, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 6.68 (br s, 1H), 6.86−6.89 (m, 1H), 7.29−7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 20.6 (CH_3), 31.4 (CH_2), 35.4 (CH_2), 42.3 (CH_2), 48.4 (CH), 56.5 (CH), 115.1 (CH), 118.9 (C), 126.5 (CH), 127.1 (CH), 127.5 (C), 127.9 (CH), 128.7 (CH), 128.9 (CH), 143.2 (C), 143.6 (C), 175.8 (C).

(2R,4R*)-Ethyl 1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)-2-phenyl-6-quinolinecarboxylate (cis-**4e**).* Compound **4e** was obtained from imine **2e** (193.1 mg, 0.762 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:2) gave colorless solid (*cis*-**4e**, 227.5 mg with a trace of residual ethyl acetate, 0.617 mmol net) and colorless oil (33.3 mg with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that the oil contained 0.0751 mmol of *cis*-**4e** and 0.0345 mmol of *trans*-**4e**. The combined yield was 95% (*cis*:*trans* = 95:5). mp 177−179 °C. IR (KBr) 3338, 2981, 1693, 1667, 1610, 1511, 1364, 1291, 1244, 1177, 1132, 1102, 767, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.98−2.17 (m, 4H), 2.46 (ddd, *J* = 17.0, 9.3, 8.0 Hz, 1H), 2.58 (ddd, *J* = 17.0, 9.2, 5.7 Hz, 1H), 3.18−3.28 (m, 2H), 4.27−4.35 (m, 2H), 4.43 (br s, 1H), 4.69 (dd, *J* = 10.9, 3.3 Hz, 1H), 5.69 (dd, *J* = 11.6, 6.0 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 7.31−7.43 (m, 5H), 7.56 (br s, 1H), 7.74−7.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (CH_3), 18.3 (CH_2), 31.3 (CH_2), 34.7 (CH_2), 42.2 (CH_2), 48.0 (CH), 56.0 (CH), 60.3 (CH_2), 113.7 (CH), 117.6 (C), 119.3 (C), 126.3 (CH), 128.2 (CH), 128.5 (CH), 128.8 (CH), 130.2 (CH), 142.1 (C), 149.5 (C), 166.6 (C), 175.9 (C). HRMS (ESI-orbitrap) *m*/*z*: [M+Na]$^+$ Calcd for $C_{22}H_{24}N_2O_3Na$ 387.1679; Found 387.1682.

(2R,4R*)-1,2,3,4-Tetrahydro-6-nitro-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4f**).*[12] Compound **4f** was obtained from imine **2f** (171.2 mg, 0.757 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:2) followed by preparative thin layer chromatography (developed with $CHCl_3$/MeOH = 50:1) gave two portions of yellow viscous oil (*cis*-**4f**, 55.0 mg, *trans*-**4f**, 12.3 mg each with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that the portions contained 0.158 mmol of *cis*-**4f** and 0.0346 mmol of *trans*-**4f**, respectively. The combined yield was 26% (*cis*:*trans* = 81:19). IR (KBr) 3308, 2954, 1674, 1610, 1584, 1531, 1507, 1468, 1417, 1294, 1248, 1164, 1092, 824, 751, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03−2.20 (m, 4H), 2.48 (ddd, *J* = 17.0, 9.4, 8.1 Hz, 1H), 2.62 (ddd, *J* = 17.0, 9.4, 5.3 Hz, 1H), 3.24−3.28 (m, 2H), 4.75 (dd, *J* = 11.0, 3.3 Hz, 1H), 4.81 (br s, 1H), 5.69 (dd, *J* = 11.8, 5.5 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 1H), 7.34−7.44 (m, 5H), 7.76 (s, 1H), 7.97−8.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.0 (CH_2), 34.1 (CH_2), 42.1 (CH_2), 47.7 (CH), 56.1 (CH), 113.4 (CH), 117.8 (C), 122.8 (CH), 125.2 (CH), 126.3 (CH), 128.5 (CH), 129.0 (CH), 138.2 (C), 141.2 (C), 151.0 (C), 176.0 (C).

(2R,4R*)-6-Acetamido-1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4g**).* Compound **4g** was obtained from imine **2g** (179.3 mg, 0.752 mmol) according to the general procedure. Colorless solid (*cis*-**4g**, 229.9 mg, 0.658 mmol) was isolated as a precipitate. Purification of the filtrate by preparative thin layer chromatography (developed with $CHCl_3$/MeOH = 30:1, 2 times, then 15:1, 2 times) gave colorless oil (20.7 mg with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that the oil contained 0.0419 mmol of *cis*-**4g** and 0.0126 mmol of *trans*-**4g**. The combined yield was 95% (*cis*:*trans* = 98:2). mp 250−251 °C. IR (KBr) 3319, 3288, 3095, 2975, 1656, 1601, 1558, 1501, 1314, 1289, 1245, 829, 762, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99−2.13 (m, 4H), 2.13 (s, 3H), 2.42−2.59 (m, 2H), 3.21−3.31 (m, 2H), 3.96 (br s, 1H), 4.56−4.60 (m, 1H), 5.66−5.70 (m, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 6.91 (obscured d, *J* = 2 Hz, 1H), 7.08 (br s, 1H), 7.21 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.30−7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (CH_2), 24.3 (CH_3), 31.4 (CH_2), 35.1 (CH_2), 42.4 (CH_2), 48.4 (CH), 56.4 (CH), 115.2 (CH), 119.1 (C), 119.5 (CH), 121.6 (CH), 126.4 (CH), 128.0 (CH), 128.8 (CH), 128.9 (C), 142.8 (C), 142.9 (C), 168.2 (C), 176.0 (C). HRMS (ESI-orbitrap) *m*/*z*: [M+Na]$^+$ Calcd for $C_{21}H_{23}N_3O_2Na$ 372.1683; Found 372.1677.

(2R,4R*)-7-Bromo-1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4h**).* Compound **4h** was obtained from imine **2h** (159.8 mg, 0.756 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:2) gave three portions of colorless viscous oil (#1, 41.0 mg, #2, 138.2 mg, and #3, 19.6 mg each with a small amount of residual solvents). ^{1}H NMR analysis revealed that these portions contained 0.432 mmol of *cis*-**4h** and 0.0265 mmol of *trans*-**4h**. The combined yield was 61% (*cis*:*trans* = 94:6). Spectral data of portion #2 were shown. IR (KBr) 3296, 3031, 2960, 2927, 1656, 1598, 1486, 1456, 1440, 1338, 1307, 1286, 1240, 846, 706 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.13 (m, 4H), 2.41−2.57 (m, 2H), 3.15−3.26 (m, 2H), 4.06 (br s, 1H), 4.60 (dd, *J* = 10.5, 3.5 Hz, 1H), 5.64 (dd, *J* = 11.2, 6.5 Hz, 1H), 6.70−6.72 (m, 2H), 6.80 (dd, *J* = 8.2, 1.9 Hz, 1H),

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7.30–7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.3 (CH_2), 34.9 (CH_2), 42.2 (CH_2), 48.0 (CH), 56.2 (CH), 117.2 (CH), 117.8 (C), 120.8 (CH), 121.7 (C), 126.4 (CH), 128.1 (CH), 128.9 (CH), 142.4 (C), 147.0 (C), 175.8 (C). One of the aromatic methine signals should contain two signals. HRMS (ESI-orbitrap) *m*/*z*: [M+Na]$^+$ Calcd for $C_{19}H_{19}{}^{79}BrN_2ONa$: 393.0573; Found 393.0576.

(2R,4R*)-1,2,3,4-Tetrahydro-8-methyl-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-4i).*[6] Compound **4i** was obtained from imine **2i** (148.4 mg, 0.760 mmol) according to the general procedure. Colorless solid (*cis*-**4i**, 83.3 mg, 0.272 mmol) was isolated as a precipitate. Purification of the filtrate by silica gel column chromatography (FL 60D, hexane/ethyl acetate = 2:1) gave colorless solid (*cis*-**4i**, 67.2 mg with a trace of residual solvents, 0.216 mmol net) and colorless oil (17.6 mg with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that the oil contained 0.0237 mmol of *cis*-**4i** and 0.0328 mmol of *trans*-**4i**. The combined yield was 72% (*cis*:*trans* = 94:6). IR (KBr) 3363, 3028, 2974, 1681, 1601, 1504, 1475, 1433, 1310, 1285, 755, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97–2.13 (m, 4H, containing s, 3H at 2.11), 2.42–2.58 (m, 2H), 3.17–3.26 (m, 2H), 3.83 (br s, 1H), 4.62–4.65 (m, 1H), 5.74–5.79 (m, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.97–6.99 (m, 1H), 7.31–7.42 (m, 3H), 7.46–7.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (CH_3), 18.2 (CH_2), 31.4 (CH_2), 35.1 (CH_2), 42.3 (CH_2), 48.6 (CH), 56.3 (CH), 117.4 (CH), 118.3 (C), 121.9 (C), 124.5 (CH), 126.5 (CH), 127.9 (CH), 128.8 (CH), 129.3 (CH), 143.3 (C), 143.9 (C), 175.7 (C).

(2R,4R*)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)quinoline (cis-4j).*[6] Compound **4j** was obtained from imine **2j** (163.9 mg, 0.760 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate = 2:1) gave *cis*-**4j** (colorless solid, 199.4 mg with a small amount of residual solvents, 0.594 mmol net), *trans*-**4j** (colorless solid, 5.2 mg, 0.016 mmol), and a mixture of *cis*- and *trans*-**4j** (colorless oil, 9.2 mg with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that this oil contained 0.020 mmol of *cis*-**4j** and 0.0071 mmol of *trans*-**4j**. The combined yield was 84% (*cis*:*trans* = 94:6). IR (KBr) 3334, 3047, 2917, 1667, 1603, 1487, 1461, 1437, 1309, 1288, 1256, 1085, 824, 776, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.11 (m, 4H), 2.42–2.58 (m, 2H), 3.17–3.26 (m, 2H), 3.96 (br s, 1H), 4.58 (dd, *J* = 10.2, 3.7 Hz, 1H), 5.71 (dd, *J* = 11.0, 6.9 Hz, 1H), 6.58 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.71 (dt, J_t = 7.6 Hz, J_d = 1.0 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 7.03–7.08 (m, 1H), 7.31–7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_2), 31.3 (CH_2), 35.2 (CH_2), 42.2 (CH_2), 48.2 (CH), 56.7 (CH), 115.0 (CH), 118.3 (CH), 118.7 (C), 126.7 (CH), 127.8 (CH), 128.2 (CH), 128.8 (CH), 133.4 (C), 141.5 (C), 145.6 (C), 175.8 (C).

(2R,4R*)-1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-4-(2-oxopyrrolidin-1-yl)quinoline (cis-4k).*[16] Compound **4k** was obtained from imine **2k** (161.8 mg, 0.766 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:2) gave *cis*-**4k** (colorless foamy solid, 186.0 mg with a small amount of residual ethyl acetate, 0.548 mmol net) and a mixture of *cis*- and *trans*-**4k** (colorless oil, 46.9 mg with a small amount of residual ethyl acetate). ^{1}H NMR analysis revealed that this oil contained 0.111 mmol of *cis*-**4k** and 0.0211 mmol of *trans*-**4k**. The combined yield was 89% (*cis*:*trans* = 97:3). IR (KBr) 3315, 2951, 1672, 1606, 1513, 1489, 1421, 1312, 1286, 1246, 1173, 1035, 830, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.13 (m, 4H), 2.42–2.58 (m, 2H), 3.18–3.28 (m, 2H), 3.82 (s, 3H), 3.95 (br s, 1H), 4.53–4.59 (m, 1H), 5.70–5.74 (m, 1H), 6.55–6.58 (m, 1H), 6.68–6.72 (m, 1H), 6.86–6.92 (m, 3H), 7.03–7.07 (m, 1H), 7.33–7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_2), 31.3 (CH_2), 35.2 (CH_2), 42.2 (CH_2), 48.4 (CH), 55.2 (CH_3), 55.7 (CH), 114.0 (CH), 114.8 (CH), 118.0 (CH), 118.7 (C), 126.7 (CH), 127.5 (CH), 128.1 (CH), 135.0 (C), 145.9 (C), 159.2 (C), 175.7 (C).

(2R,4R*)-2-(2-Furyl)-1,2,3,4-tetrahydro-6-methoxy-4-(2-oxopyrrolidin-1-yl)quinoline (cis-4l).*[28] Compound **4l** was obtained from imine **2l** (153.9 mg, 0.765 mmol) according to the general procedure. Colorless solid (*cis*-**4l**, 87.0 mg, 0.279 mmol) was isolated as a precipitate. Purification of the filtrate by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, then 1:2, and finally 1:3) gave unreacted **2l** (27.5 mg, 18% recovery), *cis*-**4l** (pale yellow oil, 52.6 mg, 0.168 mmol), and a mixture of *cis*- and *trans*-**4l** (yellow oil, 19.5 mg with a small amount of an impurity). ^{1}H NMR analysis revealed that the mixture contained 0.0179 mmol of *cis*-**4l** and 0.0275 mmol of *trans*-**4l**. The combined yield was 64% (*cis*:*trans* = 94:6). IR (KBr) 3348, 3109, 2997, 1680, 1501, 1470, 1432, 1290, 1274, 1254, 1223, 1035, 1018, 818, 772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.06 (m, 2H), 2.15–2.30 (m, 2H), 2.43–2.57 (m, 2H), 3.14–3.20 (m, 1H), 3.23–3.29 (m, 1H), 3.72 (s, 3H), 3.90 (br s, 1H), 4.60 (dd, *J* = 11.1, 2.6 Hz, 1H), 5.68 (dd, *J* = 11.5, 6.6 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.46–6.47 (m, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 6.67–6.70 (m, 1H), 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.2 (CH_2), 31.4 (CH_2), 42.3 (CH_2), 48.0 (CH), 50.0 (CH), 55.8 (CH_3), 105.5 (CH), 110.2 (CH), 112.1 (CH), 114.5 (CH), 116.6 (CH), 120.5 (C), 139.2 (C), 142.0 (CH), 152.9 (C), 155.2 (C), 175.8 (C).

(2R,4R*)-2-(tert-Butyl)-1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)quinoline (cis-4m).* Compound **4m** was obtained from imine **2m** (122.8 mg, 0.762 mmol) according to the general procedure. Colorless solid (*cis*-**4m**, 87.0 mg, 0.407 mmol) was isolated as a precipitate. Purification of the filtrate by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:3) gave *cis*-**4m** (colorless solid, 75.5 mg, 0.277 mmol). The combined yield was 90% (*cis*:*trans* = > 99:1). mp 191–192 °C. IR (KBr) 3350, 3050, 2962, 1676, 1605, 1492, 1427, 1364, 1312, 1283, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.72 (q, *J* = 12 Hz, 1H), 1.95–2.07 (m, 3H), 2.45–2.59 (m, 2H), 3.14–3.29 (m, 3H), 3.81 (br s, 1H), 5.55 (dd, *J* = 12, 5.8 Hz, 1H), 6.54 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.62–6.66 (m, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.99–7.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 25.9 (CH_3), 27.1 (CH_2), 31.5 (CH_2), 33.2 (C), 42.3 (CH_2), 48.6 (CH), 60.1 (CH), 114.9 (CH), 117.6 (CH), 119.1 (C), 126.5 (CH), 128.0 (CH), 146.2 (C), 175.7 (C). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.96%; H, 8.88%; N, 10.28%. Found: C, 74.94%; H, 8.90%; N, 10.31%.

(2R,4R*)-2-Cyclopropyl-1,2,3,4-tetrahydro-4-(2-oxopyrrolidin-1-yl)quinoline (cis-4n).* Compound **4n** was obtained from imine **2n** (110.0 mg, 0.758 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 3:1, then 2:1, then 1:1, and finally 1:2) gave a mixture of **4n** and an unidentified byproduct (135.6 mg). Further purification of the mixture by preparative thin layer chromatography (developed with hexane/ethyl acetate = 1:1 once, then 2:1, 2 times) gave a mixture of *cis*- and *trans*-**4n** (faintly yellow solid, 107.0 mg, 0.417 mmol). The yield was 55% (*cis*:*trans* = 96:4). mp 149–151 °C. IR (KBr) 3339, 3081, 3000, 2952, 1664, 1605, 1492, 1423, 1312, 1284, 1262, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21–0.30 (m, 2H), 0.49–0.60 (m, 2H), 0.84–0.93 (m, 1H), 1.87–2.06 (m, 3H), 2.12–2.17 (m, 1H), 2.44–2.59 (m, 3H), 3.15–3.20 (m, 1H), 3.24–3.30 (m, 1H), 3.99 (br s, 1H), 5.51 (dd, *J* = 12.0, 6.1 Hz, 1H), 6.54 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.63–6.67 (m, 1H), 6.79–6.82 (m, 1H), 7.00–7.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.76 (CH_2), 2.93 (CH_2), 16.7 (CH), 18.1 (CH_2), 31.4 (CH_2), 32.3 (CH_2), 42.2 (CH_2), 47.9 (CH), 57.1 (CH), 114.4 (CH), 117.6 (CH), 118.8 (C), 126.6 (CH), 128.0 (CH), 145.5 (C), 175.6 (C). HRMS (ESI-orbitrap) *m*/*z*: [M+Na]$^+$ Calcd for $C_{16}H_{20}N_2ONa$: 279.1468; Found 279.1465.

(2R,4R*)-1,2,3,4-Tetrahydro-7-methoxy-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-4o).* Compounds **4o** and **4o′** were obtained from imine **2o** (161.6 mg, 0.765 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (FL 60D, hexane/ethyl acetate; initially 2:1, then 1:1, and finally 1:2) gave six portions (#1–6) as colorless viscous oil, all of which contained a small amount of residual ethyl acetate. #1:37.6 mg, *cis*-**4o**. #2:41.7 mg, *cis*-**4o** and *trans*-**4o** (96:4). #3:7.2 mg, *cis*-**4o** and *trans*-**4o** (57:43). #4:13.6 mg, *trans*-**4o** and *trans*-**4o′** (76:24). #5:33.7 mg, *trans*-**4o′** and unidentified

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compounds. #6:85.5 mg, *cis*-**4o′**. Further purification of #5 by preparative thin layer chromatography (developed with hexane/ethyl acetate = 1:2) gave *trans*-**4o′** (24.9 mg). The combined yield of **4o** was 38% (*cis*:*trans* = 84:16) and that of **4o′** was 43% (*cis*:*trans* = 77:23). *cis*-**4o**: IR (KBr) 3319, 3081, 3029, 2952, 1670, 1618, 1491, 1462, 1421, 1285, 1265, 1207, 1169, 731, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.97−2.13 (m, 4H), 2.41−2.56 (m, 2H), 3.17−3.26 (m, 2H), 3.75 (s, 3H), 4.00 (br s, 1H), 4.58 (dd, J = 10.5, 3.4 Hz, 1H), 5.67 (dd, J = 10.9, 6.6 Hz, 1H), 6.13 (d, J = 2.5 Hz, 1H), 6.30 (dd, J = 8.5, 2.5 Hz, 1H), 6.78 (dd, J = 8.5, 1.0 Hz, 1H), 7.29−7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2 (CH_2), 31.4 (CH_2), 35.4 (CH_2), 42.2 (CH_2), 48.0 (CH), 55.1 (CH_3), 56.4 (CH), 99.8 (CH), 104.3 (CH), 111.4 (C), 126.4 (CH), 127.86 (CH), 127.91 (CH), 128.7 (CH), 142.9 (C), 146.9 (C), 159.7 (C), 175.8 (C). HRMS (ESI-orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_2Na$: 345.1574; Found 345.1576.

(2R,4R*)-1,2,3,4-Tetrahydro-5-methoxy-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (cis-**4o′**)*. IR (KBr) 3303, 2952, 1667, 1604, 1494, 1477, 1459, 1435, 1421, 1286, 1247, 1118, 763, 734, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.69−1.89 (m, 2H), 2.10−2.18 (m, 1H), 2.26−2.39 (m, 3H), 2.82−2.88 (m, 1H), 3.04−3.09 (m, 1H), 3.75 (s, 3H), 4.02 (br s, 1H), 4.42 (dd, J = 10.6, 2.6 Hz, 1H), 5.61 (dd, J = 9.7, 7.5 Hz, 1H), 6.260 (d, J = 8.1 Hz, 1H), 6.264 (d, J = 8.1 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H), 7.27−7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_2), 31.3 (CH_2), 36.0 (CH_2), 42.9 (CH_2), 45.3 (CH), 55.45 (CH_3), 55.50 (CH), 100.1 (CH), 107.1 (C), 108.3 (CH), 126.3 (CH), 127.6 (CH), 128.6 (CH), 128.9 (CH), 142.9 (C), 149.2 (C), 158.9 (C), 174.8 (C). HRMS (ESI-orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_2Na$: 345.1574; Found 345.1576.

(2R,4S*)-1,2,3,4-Tetrahydro-5-methoxy-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (trans-**4o′**)*. IR (KBr) 3312, 2954, 2837, 1666, 1607, 1494, 1456, 1418, 1284, 1264, 1237, 1129, 1108, 753, 732, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.86−2.05 (m, 3H), 2.32−2.37 (m, 1H), 2.38−2.51 (m, 2H), 3.00−3.06 (m, 1H), 3.32−3.38 (m, 1H), 3.78 (s, 3H), 4.17 (br s, 1H), 4.32 (dd, J = 12.5, 2.9 Hz, 1H), 5.32 (dd, J = 4.5, 2.1 Hz, 1H), 6.23 (d, J = 8.1 Hz, 1H), 6.24 (d, J = 8.1 Hz, 1H), 7.08 (t, J = 8.1 Hz, 1H), 7.28−7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5 (CH_2), 31.6 (CH_2), 37.6 (CH_2), 43.5 (CH), 47.6 (CH_2), 52.7 (CH), 55.4 (CH_3), 98.9 (CH), 105.1 (C), 107.4 (CH), 126.7 (CH), 127.8 (CH), 128.6 (CH), 129.4 (CH), 143.2 (C), 146.2 (C), 158.7 (C), 174.5 (C). HRMS (ESI-orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_2Na$: 345.1574; Found 345.1569.

(2R,4R*)-6-Chloro-1,2,3,4-tetrahydro-4-(N-methylacetamido)-2-phenylquinoline (cis-**6b**)*. Compound **6b** was obtained from imine **2b** (122.8 mg, 0.762 mmol) and **5** (151.5 mg, 1.53 mmol) according to the general procedure. Colorless solid (*cis*-**6b**, 172.2 mg, 0.547 mmol) was isolated as a precipitate. Purification of the filtrate by preparative thin layer chromatography (developed with $CHCl_3$/MeOH = 20:1) gave a mixture of *cis*- and *trans*-**6b** (51.6 mg). Further purification by preparative thin layer chromatography (developed with toluene/ethyl acetate = 4:1, 2 times) afforded *cis*-**6b** (faintly yellow solid, 27.5 mg with a small amount of residual ethyl acetate) and *trans*-**6b** (pale yellow oil, 17.4 mg with a small amount of residual ethyl acetate). ^1H NMR analysis revealed that the portions contained 0.0834 mmol of *cis*-**6b** and 0.0522 mmol of *trans*-**6b**, respectively. All products were a mixture of amide rotamers (3:1). The combined yield was 90% (*cis*:*trans* = 92:8). mp 206−207 °C. IR (KBr) 3327, 2962, 1631, 1602, 1486, 1454, 1399, 1296, 813, 769, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.95−2.04 (m, 0.75H), 2.08−2.14 (m, 1H), 2.17−2.28 (m, 0.25H, including s, 0.25 × 3H at 2.20 and s, 0.75 × 3H at 2.26), 2.71 (s, 0.25 × 3H), 2.77 (s, 0.75 × 3H), 3.99 (br s, 0.75H), 4.04 (br s, 0.25H), 4.56−4.61 (m, 1H), 5.22−5.27 (m, 0.25H), 6.17−6.21 (m, 0.75H), 6.49−6.52 (m, 1H), 6.84 (br d, 0.75H), 6.91 (br s, 0.25H), 6.98−7.05 (m, 1H), 7.30−7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ *21.6 (CH_3)*, 22.2 (CH_3), *28.4 (CH_3)*, 31.1 (CH_3), 34.7 (CH_2), *35.7 (CH_2)*, 50.3 (CH), *55.8 (CH)*, 56.3 (CH), *56.5 (CH)*, 116.0 (CH), *120.4 (C)*, 121.1 (C), 122.8 (C), *123.0 (C)*, *126.2 (CH)*, 126.4 (CH), 126.46 (CH), 126.53 (CH), 128.00 (CH), 128.03 (CH), *128.3 (CH)*, *128.6 (CH)*, 128.8 (CH), *128.9 (CH)*, *142.1 (C)*, 142.6 (C), *144.2 (C)*, 145.0 (C), *170.9 (C)*, 171.7 (C). Clearly minor signals are written in italics. HRMS (ESI-orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}{}^{35}ClN_2ONa$: 337.1078; Found 337.1077.

(2R,3S*,4R*)-1,2,3,4-Tetrahydro-3-methyl-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (**8a**)*. Compound **8a** was obtained from imine **2a** (138.0 mg, 0.761 mmol) and enamide **7** (188.9 mg, 1.51 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (PSQ 60B, hexane/ethyl acetate; initially 3:1, then 2:1, and finally 1:2) gave **8a** (colorless solid, 100.2 mg, 0.327 mmol, 43%) and a mixture of **9a** and an unidentified compound (71.2 mg). This mixture was purified by GPC (eluent: chloroform) to afford **9a** as colorless solid (59.3 mg, 0.194 mmol, 25%). **8a**: mp 203−205 °C. IR (KBr) 3343, 3028, 2962, 2899, 1668, 1605, 1492, 1461, 1435, 1423, 1318, 1286, 1249, 752, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (d, J = 6.7 Hz, 3H), 2.01−2.21 (m, 3H), 2.48−2.61 (m, 2H), 3.16−3.25 (m, 2H), 4.01 (br s, 1H), 4.19 (d, J = 10.1 Hz, 1H), 5.32 (d, J = 11.1 Hz, 1H), 6.51−6.54 (m, 1H), 6.67−6.71 (m, 1H), 6.85 (d, J = 7.7 Hz, 1H), 7.02−7.07 (m, 1H), 7.31−7.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (CH_3), 18.3 (CH_2), 31.3 (CH_2), 36.5 (CH), 42.1 (CH_2), 54.7 (CH), 62.8 (CH), 114.2 (CH), 117.9 (CH), 118.8 (C), 126.7 (CH), 127.7 (CH), 128.07 (CH), 128.13 (CH), 128.6 (CH), 141.6 (C), 145.6 (C), 176.4 (C). HRMS (ESI-orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2ONa$: 329.1624; Found 329.1625.

(2R,3R*,4S*)-1,2,3,4-Tetrahydro-3-methyl-4-(2-oxopyrrolidin-1-yl)-2-phenylquinoline (**9a**)*. mp 196−197 °C. IR (KBr) 3296, 3026, 2972, 2877, 1662, 1607, 1493, 1453, 1438, 1421, 1330, 1286, 1271, 757, 743, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 7.0 Hz, 3H), 1.92−2.09 (m, 2H), 2.38−2.52 (m, 3H), 3.14 (ddd, J = 9.8, 8.1, 5.6 Hz, 1H), 3.29 (ddd, J = 9.8, 7.8, 6.2 Hz, 1H), 4.29 (br s, 1H), 4.48 (d, J = 4.0 Hz, 1H), 4.96 (d, J = 7.2 Hz, 1H), 6.62 (dd, J = 8.0, 1.1 Hz, 1H), 6.70 (dt, J_t = 7.5, J_d = 1.1 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.09−7.13 (m, 1H), 7.24−7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (CH_3), 18.5 (CH_2), 31.4 (CH_2), 35.8 (CH), 44.6 (CH_2), 52.2 (CH), 57.7 (CH), 114.1 (CH), 116.8 (C), 117.4 (CH), 127.0 (CH), 127.4 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 141.4 (C), 144.8 (C), 175.3 (C). HRMS (ESI-orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2ONa$: 329.1624; Found 329.1624.

(4aR,5R*,10bR*)-3,4,4a,5,6,10b-Hexahydro-5-phenyl-2H-pyrano[3,2-c]quinoline (cis-**11a**)*.[45] Compound **11a** was obtained from imine **2a** (110.0 mg, 0.758 mmol), **10** (133.9 mg, 1.59 mmol), and **1** (7.6 mg, 0.00785 mmol) according to the general procedure. Purification of the concentrated reaction mixture by silica gel column chromatography (PSQ 60B, hexane/ethyl acetate; initially 9:1, then 2:1) gave impure *cis*-**11a** (47.8 mg), a mixture of *cis*- and *trans*-**11a** (4.4 mg), and *trans*-**11a** (37.7 mg with a small amount of residual ethyl acetate). Further purification by preparative thin layer chromatography (developed with toluene/ethyl acetate = 9:1) finally gave *cis*-**11a** colorless oil, 47.7 mg (combined amount) with a small amount of residual ethyl acetate) and *trans*-**11a** (colorless oil, 40.5 mg (combined amount) with a small amount of residual ethyl acetate). ^1H NMR analysis revealed that these portions contained 0.173 mmol of *cis*-**11a** (23%) and 0.152 mmol of *trans*-**11a** (20%), respectively. IR (KBr) 3324, 3026, 2940, 1608, 1479, 1452, 1316, 1089, 1071, 753, 711, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.29−1.34 (m, 1H), 1.41−1.61 (m, 3H), 2.14−2.21 (m, 1H), 3.41−3.47 (m, 1H), 3.57−3.62 (m, 1H), 3.87 (br s, 1H), 4.70 (d, J = 2.4 Hz, 1H), 5.34 (d, J = 5.5 Hz, 1H), 6.61 (dd, J = 8.0, 1.0 Hz, 1H), 6.80 (dt, J_t = 7.5, J_d = 1.0 Hz, 1H), 7.08−7.12 (m, 1H), 7.29−7.33 (m, 1H), 7.36−7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 (CH_2), 25.4 (CH_2), 38.8 (CH), 59.2 (CH), 60.6 (CH_2), 72.7 (CH), 114.3 (CH), 118.2 (CH), 119.8 (C), 126.8 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 141.1 (C), 145.1 (C).

(4aR,5S*,10bR*)-3,4,4a,5,6,10b-Hexahydro-5-phenyl-2H-pyrano[3,2-c]quinoline (trans-**11a**)*.[45] IR (KBr) 3374, 3027, 2939, 2855, 1611, 1493, 1454, 1365, 1306, 1264, 1084, 1071, 1056, 1031, 1003, 913, 749, 731, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31−1.37 (m, 1H), 1.44−1.51 (m, 1H), 1.61−1.70 (m, 1H), 1.80−1.91 (m, 1H), 2.07−2.12 (m, 1H), 3.73 (dt, J_t = 11.6, J_d = 2.5 Hz, 1H), 4.07−4.13 (m, 1H, containing br s, 1H at 4.08), 4.40 (d, J = 2.8 Hz, 1H), 4.73 (d, J = 10.9 Hz, 1H), 6.52−6.55 (m, 1H), 6.69−6.73 (m, 1H),

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7.07–7.12 (m, 1H), 7.22–7.24 (m, 1H), 7.30–7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_2), 24.1 (CH_2), 38.8 (CH), 54.7 (CH), 68.6 (CH_2), 74.5 (CH), 114.1 (CH), 117.4 (CH), 120.6 (C), 127.77 (CH), 127.85 (CH), 128.6 (CH), 129.3 (CH), 130.9 (CH), 142.3 (C), 144.7 (C).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00838.

^{1}H and ^{13}C NMR spectra for the cycloaddition products **4**, **6b**, **8a**, **9a**, and **11a** and a figure explaining the NOE correlation for **8a** and **9a** (PDF)

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Notes

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