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Asymmetric domino aza-Michael–Michael reaction of *o*-*N*-protected aminophenyl α,β-unsaturated ketones: construction of chiral functionalized tetrahydroquinolines

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ABSTRACT

The diastereo- and enantioselective synthesis of 2,3,4-trisubstituted tetrahydroquinolines has been developed through organocatalytic domino aza-Michael–Michael reaction of *o*-*N*-tosylaminophenyl α,β-unsaturated ketones with nitroalkenes. This useful and simple domino process afforded diverse highly functionalized tetrahydroquinolines, some of which are not easily accessible using other methodologies, in good yields and with excellent diastereo- and enantioselectivities (up to >30:1 dr, >99% ee).

1. Introduction

The development of methodologies for the synthesis of chiral compound for the production of pharmaceuticals, agrochemicals, and functional materials is one of the most briskly pursued areas in synthetic chemistry.[1] Among the developed methods, asymmetric catalytic reaction, which includes enzymatic catalysis, metal catalysis, and organocatalysis, is the most efficient tool for the preparation of enantiomerically pure compound in regard to economical approaches and green chemistries.[2] In particular, asymmetric organocatalysis, which results in better reproducibility and greater operational simplicity than traditional metal catalysis, has attracted considerable attention during the past decade.[3] Organocatalysts have several important advantages in that they are usually inexpensive, generally non-toxic, readily available, and air-stable. Furthermore, asymmetric organocatalysis is a very promising strategy that provides cost-efficient and environment-friendly access to enantiomerically pure compounds in the synthesis of natural products and biologically active compounds.

The synthesis of complex natural products and biologically active compounds has attracted the attention of organic chemists for a very long time. Many new types of chemical reactions have been developed for easy access to the synthesis of complex compounds. Among the strategies, domino reactions,[4,5] in which two or more bond-forming transformations occur under identical reaction conditions and the subsequent reactions occur as a consequence of the functionality formed in the previous step, have received wide acceptance because of the improved synthetic efficiency by reducing the number of synthetic steps required and the quantities of chemicals and solvents used. These benefits are of particular interest in the efficient and stereoselective construction of complex molecules from simple precursors in a single process. In this area, domino Michael additions have especially emerged as one of the most powerful method for the synthesis of various important cyclic building blocks in the recent decades.[6] Herein, we report the organocatalytic asymmetric one-pot domino aza-Michael–Michael reaction of *o*-*N*-protected aminophenyl α,β-unsaturated ketones with nitroalkenes, thus affording highly functionalized tetrahydroquinolines in good yields and with excellent diastereo- and enantioselectivities.

Tetrahydroquinolines are valuable building blocks found in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[7] Molecules containing the tetrahydroquinoline scaffold exhibit a broad range of bioactivities, such as anti-HIV, antibacterial, antifungal, antimalarial, antitumor, and cardiovascular activities. In addition, the chiral tetrahydroquinoline scaffold is found in several important biologically active natural products and pharmaceutical compounds,[8] with notable examples

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such as Peniprequinolone isolated from *Penicillium simplicissimum* and the fungus *Penicillium janczewskii*, Benzastain D possessing antiviral activity, which is isolated from *Streptomyces* sp., and Torcetrapib, a potent cholesteryl ester transfer protein inhibitor (Fig. 1). In view of their immense significance, numerous synthetic methods for tetrahydroquinolines with careful stereochemical control have been reported.[9] Consequently, the development of an efficient enantioselective synthetic method for the tetrahydroquinoline scaffold still remains an active field of research.

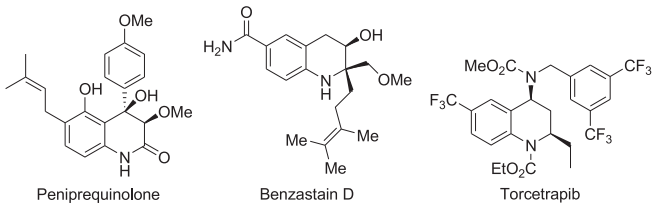
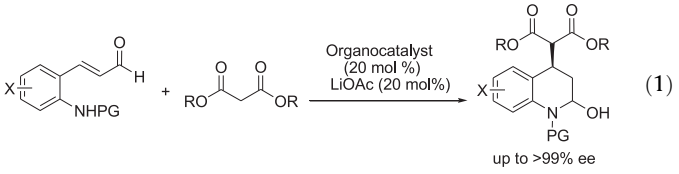
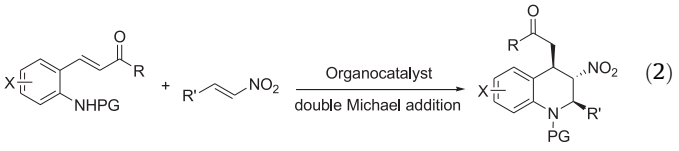


Fig. 1. Selected biologically active chiral tetrahydroquinolines.

Recently, we reported a novel method for the efficient preparation of chiral 4-substituted tetrahydroquinoline derivatives through an organocatalytic conjugate addition-cyclization domino reaction [Eq. 1].[10] In this process, the methylene carbon of the dialkyl malonate attacks the β-position carbon of the *o*-*N*-protected aminocinnamaldehyde to afford the Michael adduct first, followed by hemiacetalization. To further investigate the synthesis of highly functionalized tetrahydroquinoline and the utility of *o*-*N*-protected aminophenyl α,β-unsaturated carbonyl compounds, we considered a cascade Michael–Michael reaction that provides chiral tetrahydroquinoline in a single step [Eq. 2].[11] This reaction is initiated by the attack of the protected amine to nitroalkene, and a high level of stereocontrol is expected owing to the positive effect of the protecting group.



(1)



(2)

2. Results and discussion

First, the coupling of *o*-*N*-tosylaminophenyl α,β-unsaturated aldehyde and β-nitrostyrene **2a** was investigated in the presence of diphenylprolinol TMS ether catalyst **I** (Fig. 2) that activated the aldehyde through the iminium intermediate. However, this reaction afforded the desired tetrahydroquinoline product with a very low reaction efficiency (Table 1, entry 1). Next, the use of a co-catalyst system comprising organocatalyst **I** activating the aldehyde through the iminium intermediate and bifunctional thiourea **IIa**[12] activating the nitroalkene by hydrogen-bonding interactions, afforded the desired product but still with low enantioselectivity, albeit in a moderate yield and with good diastereoselectivity (58% yield, 18% ee; Table 1, entry 2). We also obtained similar results when only catalyst **IIa** was used (83% yield, 15% ee; Table 1, entry 3) and found that this catalytic reaction was achieved by activating the nitroalkene through hydrogen-bonding interactions with the thiourea catalyst.

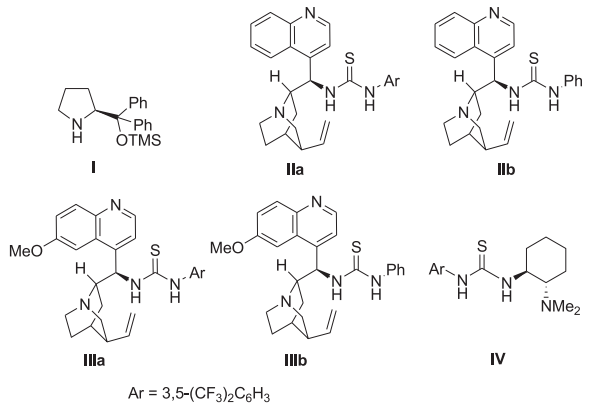
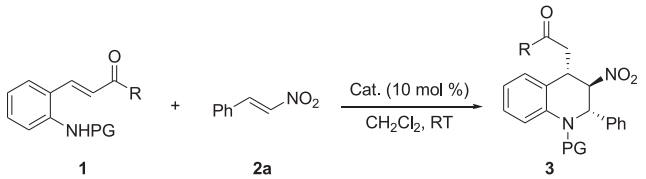


Fig. 2. Structure of candidate organocatalysts.

Table 1
Condition screening of the domino double Michael reactions of **1** and **2a**[a]



1 **2a** **3**

Entry	Cat.	R	PG	Time (h)	Yield (%)[b]	dr[c]	ee %[d]
1	**I**	H	TS	60	8	nd	nd
2	**I**+**IIa**	H	TS	60	58	10:1	18
3	**IIa**	H	TS	36	83	>30:1	15
4	**IIa**	Ph	TS	6	82	>30:1	96
5	**IIb**	Ph	TS	6	80	>30:1	91
6	**IIIa**	Ph	TS	6	71	>30:1	87
7	**IIIb**	Ph	TS	6	83	>30:1	92
8	**IV**	Ph	TS	8	74	24:1	87
9	**IIa**	Ph	CO_2Et	24	—[e]	nd	nd
10	**IIa**	Ph	Boc	24	—[e]	nd	nd
11	**IIa**	Ph	Cbz	24	—[e]	nd	nd

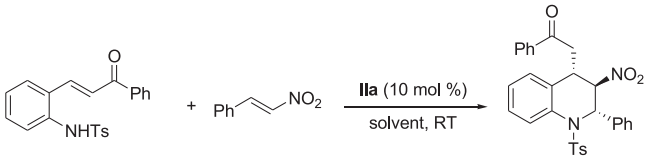
[a] All of the reactions were carried out in CH_2Cl_2 (0.25 M) with **1** (0.10 mmol) and β-nitrostyrene (**2a**, 0.15 mmol) in the presence of 10 mol % catalyst at room temperature.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.
[e] No reaction.

Having identified the hydrogen-bonding interactions as the activation mode for this domino double Michael reaction, we turned our attention to *o*-*N*-tosylaminophenyl α,β-unsaturated ketones as the starting materials. Surprisingly, excellent results were achieved in the reaction of (*E*)-1-phenyl-3-(2-(tosylamino) phenyl)prop-2-en-1-one **1a** with β-nitrostyrene **2a** catalyzed by thiourea **IIa** (10 mol %) in CH_2Cl_2 at room temperature that afforded the desired tetrahydroquinoline product **3aa** in 82% yield and with excellent diastereoselectivity (>30:1 dr) and enantioselectivity (96% ee, Table 1, entry 4). Other cinchona alkaloid-derived thiourea catalysts **IIb**, **IIIa**, and **IIIb** as well as Takemoto catalyst **IV**[13] provided inferior results when catalyst **IIa** was used (Table 1, entries 5–8). The reaction did not occur when the protecting group on the *o*-aminophenyl α,β-unsaturated ketone **1** was an ethoxycarbonyl,

tert-butoxycarbonyl (Boc), or benzyloxycarbonyl (Cbz). This result demonstrated that the more electron-withdrawing protecting group (Tosyl), providing a sufficient level of acidity to the NH group for the aza-Michael reaction, was necessary to activate this reaction and to provide a high level of stereoselectivity.

Next, other factors that influenced the reaction, such as solvent, catalyst loading, and reaction temperature, were thoroughly investigated. The reaction medium slightly affected the conversion and enantioselective induction. This asymmetric domino aza-Michael–Michael reaction could be smoothly performed in several conventional solvents, thus affording the desired products in good yields and with high enantioselectivities (72–86% yields, 89–97% ee; Table 2, entries 1–8). The use of toluene resulted in the highest enantioselectivity (97% ee; entry 4). The enantioselectivity of the reaction was further improved to 98% ee by lowering the reaction temperature to 0 °C (Table 2, entry 9). However, lowering the catalyst loading had a detrimental effect on the reaction rate and yield (Table 2, entry 10).

Table 2
Optimization of the reaction conditions[a]



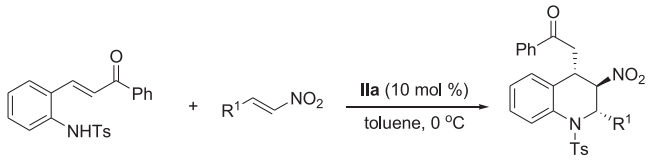
1a 2a 3aa

Entry	Solvent	Time (h)	Yield (%)[b]	dr[c]	ee %[d]
1	CH_2Cl_2	6	82	>30:1	96
2	$CHCl_3$	6	80	>30:1	93
3	DCE	6	82	>30:1	94
4	Toluene	6	84	>30:1	97
5	Xylene	6	86	>30:1	96
6	CH_3CN	8	72	20:1	89
7	THF	48	76	>30:1	96
8	EtOAc	12	80	>30:1	95
9[e]	Toluene	18	86	>30:1	98
10[f]	Toluene	48	72	>30:1	97

[a] Unless otherwise specified, the reaction was carried out in solvent (0.25 M) with **1a** (0.10 mmol) and β-nitrostyrene (**2a**, 0.15 mmol) in the presence of 10 mol % catalyst **IIa** at room temperature.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.
[e] The reaction was carried out at 0 °C.
[f] The reaction was carried out with 5 mol % catalyst at 0 °C.

With the optimal conditions in hand (10 mol % thiourea **IIa** in toluene at 0 °C), the substrate scope of the reaction was investigated. First, this reaction was confirmed to be suitable for a wide variety of nitroalkenes **2**. The results are summarized in Table 3. A wide range of nitroalkenes with diverse steric and electronic environments reacted smoothly with (*E*)-1-phenyl-3-(2-(tosylamino)phenyl)prop-2-en-1-one **1a**. Aromatic nitroalkenes with both electron-donating (Table 3, entries 1–6) and electron-withdrawing substituents (Table 3, entries 7–9) on the phenyl ring participated in this reaction with high efficiency, regardless of the substitution pattern. Excellent diastereoselectivity (>30:1 dr) and enantioselectivity (94–99% ee) were observed in all the cases except the nitro-substituted substrate with a slightly diminished diastereoselectivity (25:1 dr). Heteroaromatic-substituted nitroalkenes were also tolerated (Table 3, entries 11–12), even though 2-furanylnitroolefin required a slightly longer reaction time. A further broadening of the substrate scope to aliphatic alkene also resulted in an excellent yield and diastereoselectivity, albeit with a slightly diminished enantioselectivity (Table 3, entry 13).

Table 3
Variation of the nitroalkene[a]



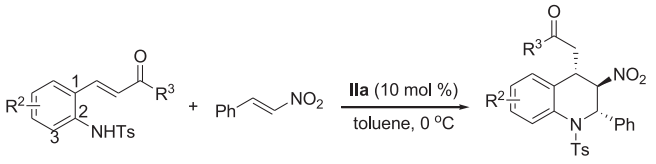
1a 2 3

Entry	R^1	Time (h)	3	Yield (%)[b]	dr[c]	ee %[d]
1	*p*-$MeOC_6H_4$	6	**3ab**	90	>30:1	98
2	*m*-$MeOC_6H_4$	8	**3ac**	96	>30:1	97
3	*o*-$MeOC_6H_4$	6	**3ad**	94	>30:1	97
4	3,4-$(MeO)_2C_6H_3$	6	**3ae**	86	>30:1	99
5	3,4-$(OCH_2O)C_6H_3$	36	**3af**	88	>30:1	98
6	*p*-MeC_6H_4	6	**3ag**	95	>30:1	97
7	*p*-ClC_6H_4	2	**3ah**	85	>30:1	98
8	*o*-ClC_6H_4	12	**3ai**	94	>30:1	95
9	*o*-BrC_6H_4	18	**3aj**	94	>30:1	94
10	*p*-$NO_2C_6H_4$	6	**3ak**	87	25:1	98
11	2-Furanyl	48	**3al**	65	>30:1	98
12	2-Thienyl	18	**3am**	94	>30:1	98
13	^{i}Pr	8	**3an**	97	>30:1	91

[a] All of the reactions were carried out in toluene (0.25 M) with **1a** (0.10 mmol) and nitroalkene (**2**, 0.15 mmol) in the presence of 10 mol % catalyst **IIa** at 0 °C.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.

To further expand the substrate scope of our methodology, a variety of *o*-*N*-tosylaminophenyl α,β-unsaturated ketone **1** was synthesized and subjected to the reaction conditions. The electronic nature of the R^2 group slightly affected the reaction efficiencies with regard to stereoselectivities and yields. Both electron-donating (Table 4, entries 1–2) and electron-withdrawing (Table 4, entries 3–5) groups were well tolerated. For the R^3 group, the reactions proceeded well with electron-donating substituents (Table 4, entries 6–7), as well as electron-withdrawing substituents (Table 4, entries 8–11). Notably, the *ortho*-halogen-substituent on the phenyl R^3 group afforded the corresponding product with lower enantioselectivity than the *meta*- and *para*-halogen-substituents

Table 4
Variation of the *o*-*N*-tosylaminophenyl α,β-unsaturated ketone[a]



1 2a 3

Entry	R^2	R^3	Time (h)	3	Yield (%)[b]	dr[c]	ee %[d]
1	5-Me	Ph	36	**3ba**	78	>30:1	96
2	3-Me	Ph	36	**3ca**	99	>30:1	97
3	5-Cl	Ph	36	**3da**	86	>30:1	98
4	4-Cl	Ph	36	**3ea**	89	>30:1	99
5	5-Br	Ph	36	**3fa**	76	>30:1	98
6	H	*p*-$MeOC_6H_4$	36	**3ga**	88	>30:1	>99
7	H	*p*-MeC_6H_4	24	**3ha**	95	>30:1	99
8	H	*p*-ClC_6H_4	36	**3ia**	91	>30:1	97
9	H	*m*-ClC_6H_4	18	**3ja**	94	>30:1	96
10	H	*o*-ClC_6H_4	36	**3ka**	83	>30:1	84
11	H	*p*-BrC_6H_4	28	**3la**	85	>30:1	98
12	H	2-Furanyl	2	**3ma**	84	>30:1	94
13	H	*t*-Bu	18	**3na**	91	>30:1	92
14	H	Cyclopropyl	18	**3oa**	97	>30:1	95
15	H	Me	36	**3pa**	83	>30:1	78

[a] All of the reactions were carried out in toluene (0.3 M) with **1** (0.10 mmol) and β-nitrostyrene (**2a**, 0.15 mmol) in the presence of 10 mol % catalyst **IIa** at 0 °C.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.

(Table 4, entry 10 vs entries 8–9). When a heteroaromatic group was introduced at the R^3 position, the reaction proceeded quickly to afford good stereocontrol (>30:1 dr, 94% ee; Table 4, entry 12). Furthermore, the reactions of aliphatic α,β-unsaturated ketones with a bulkier group, such as *tert*-butyl and cyclopropyl, proceeded smoothly to afford the corresponding products with high yields and excellent stereoselectivities (Table 4, entries 13–14), However, methyl α,β-unsaturated ketone provided the desired product with moderate enantioselectivity, albeit in a good yield and with excellent diastereoselectivity (83% yield, 78% ee; Table 4, entry 15). These results indicated that the steric hindrance of the R^3 group had a very important role toward the enantiocontrol in this reaction as observed in the case of *o*-*N*-tosylaminophenyl α,β-unsaturated aldehyde (Table 1, entry 3).

The absolute configuration of the tetrahydroquinoline compound **3fa** was determined by X-ray structure analysis and found to be 2*S*,3*R*,4*S* (Fig. 3).[14] The absolute configuration for the remaining examples was assigned by analogy as the same.

On the basis of these experimental results and previous proposed dual activation model,[15] a plausible transition state for this asymmetric domino reaction is shown in Fig. 4. In our catalytic system, PáPai's proposal[15e] is more suitable than others. The tertiary amine group of catalyst **IIa** first deprotonate acidic proton of tosylated amine in compound **1a**, and the resulting anion might be stabilized through multiple hydrogen bonding including the interaction between carbonyl and thiourea moieties. Meanwhile, nitroalkene **2a** is activated by the N–H of the protonated amine in catalyst **IIa**. In this model, the amine attacks the nitroalkene from the *Si* face preferentially resulting in the *S*-configurated intermediate followed by intramolecular Michael addition to give **3aa**.

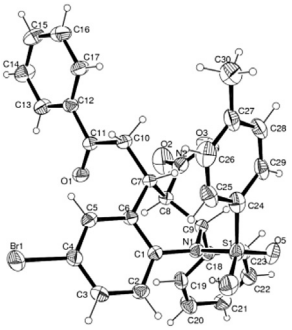


Fig. 3. X-ray crystal structure of compound **3fa**.

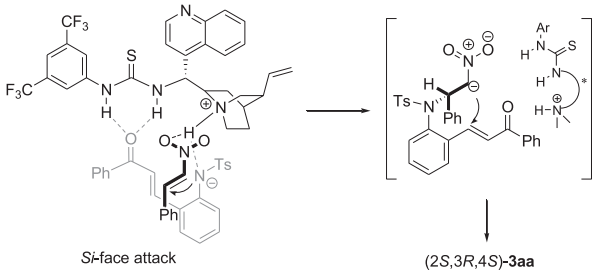


Fig. 4. Plausible transition state.

3. Conclusion

In conclusion, we have developed a highly diastereo- and enantioselective catalytic domino aza-Michael–Michael reaction of *o*-*N*-tosylaminophenyl α,β-unsaturated ketones with nitroalkenes using a cinchona alkaloid-derived thiourea catalyst. This domino reaction proceeded well with a wide range of *o*-*N*-tosylaminophenyl α,β-unsaturated ketones and nitroalkene, and provided efficient access to a variety of highly functionalized tetrahydroquinolines in good yields and with excellent diastereo- and enantioselectivities (up to >30:1 dr, 99% ee).

4. Experimental section

4.1. General procedure for asymmetric domino aza-Michael–Michael reaction of *o*-*N*-tosylaminophenyl α,β-unsaturated ketone with nitroalkene

An amber 2-dram vial equipped with a magnetic stir bar, containing catalyst **IIa** (0.01 mmol, 10 mol %), and *o*-*N*-tosylaminophenyl α,β-unsaturated ketone **1** (0.10 mmol, 1.0 equiv) was charged with toluene (0.4 mL) at 0 °C. The solution was stirred for 5 min before the addition of nitroalkene **2a** (0.15 mmol, 1.5 equiv). The resulting mixture was stirred at constant temperature until complete consumption of *o*-*N*-tosylaminophenyl α,β-unsaturated ketone **1** was observed as determined by TLC. The resulting mixture was directly purified by silica gel chromatography (25% EtOAc/hexane) to afford the desired tetrahydroquinoline compound **3** as white solid or colorless gum.

*4.1.1. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3aa**).* White solid; mp 186–188 °C; $[\alpha]_D^{20}$ −12.5 (*c* 0.22, $CHCl_3$); 98% ee; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.88 (d, *J*=7.7 Hz, 1H), 7.83 (d, *J*=7.7 Hz, 2H), 7.58 (d, *J*=7.7 Hz, 3H), 7.46 (t, *J*=7.7 Hz, 2H), 7.38 (t, *J*=7.7 Hz, 1H), 7.23–7.32 (m, 7H), 7.18 (t, *J*=7.7 Hz, 1H), 6.80 (d, *J*=7.7 Hz, 1H), 4.87 (dd, *J*=7.0, 10.5 Hz, 1H), 3.26 (dd, *J*=8.4, 18.4 Hz, 1H), 3.05–3.10 (m, 1H), 2.86 (dd, *J*=3.5, 18.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.2, 144.7, 139.6, 135.9, 135.7, 135.3, 133.7, 131.3, 129.9, 129.1, 128.8, 128.5, 128.4, 127.9, 127.2, 127.1, 126.2, 125.8, 94.3, 62.5, 37.0, 35.8, 21.7; IR (film) 2934, 1686, 1556, 1454, 1359, 1229, 1170, 1077 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{26}N_2NaO_5S$ $[M+Na]^+$: 549.1460 Found: 549.1457; Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=12.1 min and *minor*-isomer t_r=23.1 min.

*4.1.2. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3ab**).* White solid; mp 122–124 °C; $[\alpha]_D^{23}$ −29.5 (*c* 0.17, $CHCl_3$); 98% ee; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.84 (t, *J*=7.0 Hz, 3H), 7.56–7.63 (m, 3H), 7.45 (t, *J*=7.7 Hz, 2H), 7.36 (t, *J*=7.7 Hz, 1H), 7.29 (d, *J*=7.7 Hz, 2H), 7.13–7.22 (m, 3H), 6.81 (d, *J*=8.4 Hz, 3H), 6.02 (d, *J*=7.0 Hz, 1H), 4.86 (dd, *J*=7.0, 9.8 Hz, 1H), 3.75 (s, 3H), 3.27 (dd, *J*=8.4, 18.2 Hz, 1H), 3.05 (br s, 1H), 2.87 (dd, *J*=3.5, 18.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.3, 159.5, 144.6, 135.9, 135.7, 135.3, 133.7, 131.7, 131.3, 129.9, 128.8, 128.4, 127.9, 127.5, 127.2, 127.1, 127.0, 125.8, 114.5, 94.4, 62.3, 55.3, 37.0, 35.8, 21.7; IR (film) 2928, 1687, 1554, 1512, 1485, 1451, 1362, 1247, 1166, 1026 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_6S$ $[M+Na]^+$: 579.1566 Found: 579.1564; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=18.2 min and *minor*-isomer t_r=45.5 min.

*4.1.3. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-2-(3-methoxyphenyl)-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3ac**).* White solid; mp 103–104 °C; $[\alpha]_D^{23}$ −7.2 (*c* 0.16, $CHCl_3$); 97% ee; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.4 Hz, 1H), 7.82 (d, *J*=7.0 Hz, 2H), 7.59 (d, *J*=7.7 Hz, 3H), 7.45 (t, *J*=7.7 Hz, 2H), 7.36 (t, *J*=7.7 Hz, 1H), 7.29 (t, *J*=7.7 Hz, 2H), 7.20 (t, *J*=7.7 Hz, 1H), 7.16 (t, *J*=7.7 Hz, 1H), 6.81 (d, *J*=7.7 Hz, 2H), 6.78 (d, *J*=7.0 Hz, 1H), 6.10 (d, *J*=6.3 Hz, 1H), 4.89 (dd, *J*=7.0, 9.1 Hz, 1H), 3.70 (s, 3H), 3.26 (dd, *J*=8.4, 18.2 Hz, 1H), 3.10 (br

s, 1H), 2.85 (dd, *J*=3.5, 18.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.3, 160.0, 144.7, 141.1, 135.9, 135.7, 135.3, 133.7, 131.1, 130.1, 129.8, 128.9, 128.5, 127.9, 127.4, 127.1, 126.8, 125.9, 118.3, 113.8, 111.8, 94.0, 62.3, 55.2, 37.2, 35.7, 21.7; IR (film) 2938, 1691, 1595, 1547, 1449, 1353, 1236, 1160, 1088, 1025 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_6S$ $[M+Na]^+$: 579.1566 Found: 579.1566; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=16.4 min and *minor*-isomer t_r=29.7 min.

*4.1.4. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-2-(2-methoxyphenyl)-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3ad**).* White solid; mp 214–216 °C; $[\alpha]_D^{25}$ 60.3 (*c* 0.99, $CHCl_3$); 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J*=8.0 Hz, 1H), 7.81 (d, *J*=7.2 Hz, 2H), 7.68 (d, *J*=8.0 Hz, 2H), 7.60 (dd, *J*=7.2, 7.6 Hz, 1H), 7.23–7.51 (m, 7H), 7.16 (dd, *J*=7.2, 7.6 Hz, 1H), 6.92 (dd, *J*=7.2, 7.6 Hz, 1H), 6.85 (d, *J*=7.6 Hz, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 6.49 (d, *J*=5.6 Hz, 1H), 5.01 (dd, *J*=7.2, 7.6 Hz, 1H), 3.62 (s, 3H), 3.18–3.30 (m, 2H), 2.89 (d, *J*=14.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 156.0, 144.5, 136.7, 136.0, 135.6, 133.6, 130.4, 129.8, 129.6, 128.7, 128.2, 127.9, 127.8, 127.7, 127.4, 126.4, 126.1 (two signals overlapping), 120.9, 110.7, 92.1, 59.0, 54.8, 37.8, 35.8, 21.7; IR (film) 2934, 1686, 1552, 1488, 1456, 1352, 1247, 1163, 1095 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_6S$ $[M+Na]^+$: 579.1566 Found: 579.1569; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=17.8 min and *minor*-isomer t_r=29.0 min.

*4.1.5. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-2-(3,4-dimethoxyphenyl)-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3ae**).* White solid; mp 128–129 °C; $[\alpha]_D^{24}$ −12.7 (*c* 0.18, $CHCl_3$); 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.89 (m, 3H), 7.58–7.65 (m, 3H), 7.47 (t, *J*=8.0 Hz, 2H), 7.37 (t, *J*=7.6 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 2H), 7.19 (dt, *J*=1.2, 7.6 Hz, 1H), 6.72–6.88 (m, 4H), 6.12 (d, *J*=6.4 Hz, 1H), 4.97 (dd, *J*=6.4, 9.6 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.29 (dd, *J*=8.0, 18.0 Hz, 1H), 3.18 (dt, *J*=3.6, 9.2 Hz, 1H), 2.91 (dd, *J*=4.0, 18.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 149.3, 149.0, 144.6, 135.9, 135.8, 135.5, 133.8, 132.0, 131.1, 129.9, 128.8, 128.4, 127.9, 127.3, 126.9, 126.5, 126.1, 118.6, 111.4, 109.3, 93.9, 62.2, 55.9, 55.8, 37.3, 35.7, 21.7; IR (film) 2942, 1683, 1552, 1516, 1449, 1354, 1259, 1161, 1087, 1023 cm^{-1}; HRMS (ESI): calcd for $C_{32}H_{30}N_2NaO_7S$ $[M+Na]^+$: 609.1671 Found: 609.1671; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=17.3 min and *minor*-isomer t_r=40.4 min.

*4.1.6. 2-((2S,3R,4S)-2-(Benzo[d][1,3]dioxol-5-yl)-1,2,3,4-tetrahydro-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3af**).* White solid; mp 158–160 °C; $[\alpha]_D^{25}$ 15.1 (*c* 0.83, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J*=7.6 Hz, 3H), 7.56–7.64 (m, 3H), 7.49 (t, *J*=7.6 Hz, 2H), 7.40 (d, *J*=7.6 Hz, 1H), 7.32 (t, *J*=8.0 Hz, 2H), 7.21 (t, *J*=7.6 Hz, 1H), 6.81 (d, *J*=8.0 Hz, 1H), 6.74 (s, 2H), 6.69 (s, 1H), 5.96 (d, *J*=7.6 Hz, 1H), 5.94 (d, *J*=8.4 Hz, 2H), 4.82 (dd, *J*=7.6, 10.8 Hz, 1H), 3.31 (dd, *J*=8.4, 18.0 Hz, 1H), 3.00 (dd, *J*=3.2, 10.8 Hz, 1H), 2.90 (dd, *J*=3.6, 18.4 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 148.3, 147.7, 144.7, 135.9, 135.7, 135.2, 133.7, 133.6, 131.4, 129.9, 128.5, 127.9, 127.3, 127.2, 125.6, 120.1, 108.6, 106.6, 101.3, 94.6, 62.7, 36.7, 35.8, 29.7, 21.7; IR (film) 2930, 1688, 1555, 1486, 1447, 1347, 1246, 1160, 1085, 1032 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{26}N_2NaO_7S$ $[M+Na]^+$: 593.1358 Found: 593.1360; Chiralpak AD-H column and AD-H guard column (15% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=24.0 min and *minor*-isomer t_r=32.8 min.

*4.1.7. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-p-tolyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3ag**).* White solid; mp 89–91 °C; $[\alpha]_D^{24}$ −21.2 (*c* 0.15, $CHCl_3$); 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J*=0.8, 8.0 Hz, 1H), 7.85 (d, *J*=7.2 Hz, 2H), 7.58–7.64 (m, 3H), 7.48 (t, *J*=8.0 Hz, 2H), 7.39 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 2H), 7.19 (dt, *J*=0.8, 7.6 Hz, 1H), 7.10–7.16 (m, 4H), 6.83 (d, *J*=7.6 Hz, 1H), 6.08 (d, *J*=6.8 Hz, 1H), 4.89 (dd, *J*=6.8, 10.0 Hz, 1H), 3.28 (dd, *J*=8.4, 18.4 Hz, 1H), 3.10 (dt, *J*=4.0, 9.2 Hz, 1H), 2.87 (dd, *J*=4.0, 18.4 Hz, 1H), 2.45 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 144.6, 138.2, 136.6, 135.9, 135.8, 135.4, 133.7, 131.2, 129.9, 129.8, 128.8, 128.4, 127.9, 127.2, 127.0, 126.9, 126.1, 125.8, 94.2, 62.4, 37.2, 35.7, 21.7, 21.1; IR (film) 2924, 1682, 1554, 1486, 1351, 1207, 1164, 1086, 986 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_5S$ $[M+Na[^+$: 563.1617 Found: 563.1613; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=14.7 min and *minor*-isomer t_r=31.4 min.

*4.1.8. 2-((2S,3R,4S)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3ah**).* Colorless gum; $[\alpha]_D^{21}$ −23.7 (*c* 0.25, $CHCl_3$); 98% ee; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (t, *J*=7.0 Hz, 3H), 7.55–7.63 (m, 3H), 7.47 (t, *J*=7.0 Hz, 2H), 7.38 (t, *J*=7.0 Hz, 1H), 7.25–7.35 (m, 4H), 7.18 (d, *J*=7.0 Hz, 3H), 6.79 (d, *J*=7.0 Hz, 1H), 6.02 (d, *J*=6.3 Hz, 1H), 4.82 (t, *J*=8.4 Hz, 1H), 3.28 (dd, *J*=7.7, 17.5 Hz, 1H), 2.99 (br s, 1H), 2.89 (d, *J*=17.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 195.1, 144.9, 138.2, 135.8, 135.5, 135.0, 134.4, 133.8, 131.3, 130.0, 129.3, 128.8, 128.6, 127.9, 127.7, 127.3, 127.2, 127.1, 125.7, 94.3, 62.1, 36.6, 35.8, 21.7; IR (film) 2924, 1686, 1553, 1489, 1355, 1162, 1087, 1013 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ $[M+Na]^+$: 583.1070 Found: 583.1065; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=14.8 min and *minor*-isomer t_r=22.3 min.

*4.1.9. 2-((2S,3R,4S)-2-(2-Chlorophenyl)-1,2,3,4-tetrahydro-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3ai**).* White solid; mp 211–213 °C; $[\alpha]_D^{25}$ 21.2 (*c* 1.3, $CHCl_3$); 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J*=1.2, 9.2 Hz, 1H), 7.83 (dd, *J*=1.2, 8.4 Hz, 2H), 7.59–7.66 (m, 3H), 7.46 (dd, *J*=7.6, 8.8 Hz, 2H), 7.40 (dd, *J*=7.6, 8.8 Hz, 1H), 7.32–7.38 (m, 3H), 7.18–7.28 (m, 4H), 6.86 (d, *J*=8.0 Hz, 1H), 6.45 (d, *J*=7.2 Hz, 1H), 5.02 (dd, *J*=7.6, 9.6 Hz, 1H), 3.26 (dd, *J*=8.4, 18.0 Hz, 1H), 3.18 (dt, *J*=3.6, 9.2 Hz, 1H), 2.87 (dd, *J*=3.6, 18.0 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 144.8, 137.3, 136.3, 135.9, 134.9, 133.8, 132.4, 130.4, 130.3, 130.0, 129.8, 129.0, 128.8, 128.5, 127.9, 127.6, 127.4, 126.8, 126.5, 126.2, 91.9, 59.7, 37.4, 35.6, 21.7; IR (film) 2926, 1686, 1554, 1488, 1446, 1366, 1225, 1170, 1088, 1022 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ $[M+Na]^+$: 583.1070 Found: 583.1068; Chiralpak AD-H column and AD-H guard column (5% EtOH–hexanes, 1.0 mL/min flow, λ=254 nm); *minor*-isomer t_r=22.0 min and *major*-isomer t_r=32.6 min.

*4.1.10. 2-((2S,3R,4S)-2-(2-Bromophenyl)-1,2,3,4-tetrahydro-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3aj**).* White solid; mp 198–201 °C; $[\alpha]_D^{25}$ 30.9 (*c* 1.0, $CHCl_3$); 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.0 Hz, 1H), 7.83 (d, *J*=7.2 Hz, 2H), 7.65 (d, *J*=8.4 Hz, 2H), 7.61 (d, *J*=7.6 Hz, 1H) 7.54 (d, *J*=8.0 Hz, 1H), 7.47 (t, *J*=8.0 Hz, 2H), 7.41 (t, *J*=7.2 Hz, 1H), 7.34 (d, *J*=8.4 Hz, 2H), 7.13–7.30 (m, 4H), 6.88 (d, *J*=8.0 Hz, 1H), 6.46 (d, *J*=7.2 Hz, 1H), 5.03 (dd, *J*=7.2, 8.4 Hz, 1H), 3.20–3.31 (m, 2H), 2.82–2.92 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 144.8, 139.1, 136.3, 135.9, 134.9, 133.8, 133.6, 130.3, 130.0, 129.0, 128.8, 128.5, 128.3, 127.9, 127.5, 126.8, 126.4, 126.3, 122.3, 91.9, 61.2, 37.5, 35.5, 21.7; IR (film) 2924, 1685, 1557, 1486, 1448, 1360, 1228, 1168, 1086, 1020 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}BrN_2NaO_5S$ $[M+Na]^+$: 627.0565 Found: 627.0569; Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ=254 nm); *minor*-isomer t_r=15.3 min and *major*-isomer t_r=26.8 min.

*4.1.11. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-(4-nitrophenyl)-1-tosylquinolin-4-yl)-1-phenylethanone (**3ak**).* White solid; mp 198–200 °C; $[\alpha]_D^{24}$ −34.8 (*c* 0.17, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J*=8.8 Hz, 2H), 7.87–7.83 (m, 3H), 7.63 (t, *J*=7.6 Hz,

1H), 7.58 (d, *J*=8.4 Hz, 2H) 7.42–7.51 (m, 5H), 7.34 (d, *J*=8.0 Hz, 1H), 7.25 (ddd, *J*=0.4, 7.6, 8.4 Hz, 1H), 6.82 (d, *J*=7.6 Hz, 1H), 6.12 (d, *J*=7.6 Hz, 1H), 4.88 (dd, *J*=4.8, 9.2 Hz, 1H), 3.34 (dd, *J*=8.8, 18.8 Hz, 1H), 2.92–3.01 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 147.8, 146.7, 145.2, 135.8, 135.2, 134.6, 133.9, 131.4, 130.1, 128.9, 128.8, 127.9, 127.7, 127.6, 127.4, 127.2, 125.7, 124.4, 94.1, 62.2, 36.1, 36.0, 21.7; IR (film) 2928, 1686, 1597, 1555, 1520, 1487, 1449, 1346, 1167, 1087 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}N_3NaO_7S$ $[M+Na]^+$: 594.1311 Found: 594.1309; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=27.6 min and *minor*-isomer t_r=44.8 min.

*4.1.12. 2-((2S,3S,4R)-2-(Furan-2-yl)-1,2,3,4-tetrahydro-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3al**).* Colorless gum; $[\alpha]_D^{24}$ −37.9 (*c* 0.17, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J*=1.6, 8.8 Hz, 2H), 7.78 (dd, *J*=1.2, 8.4 Hz, 1H), 7.60–7.66 (m, 3H), 7.49 (t, *J*=8.0 Hz, 2H), 7.24–7.35 (m, 4H), 7.16 (dt, *J*=1.2, 7.6 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.41 (d, *J*=3.6 Hz, 1H), 6.36 (d, *J*=5.6 Hz, 1H), 6.32 (dd, *J*=2.0, 3.6 Hz, 1H), 5.17 (dd, *J*=5.6, 8.8 Hz, 1H), 3.24–3.46 (m, 2H), 2.78–2.87 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 150.7, 144.8, 143.0, 135.9, 135.3, 135.0, 133.7, 130.0, 129.9, 128.8, 128.2, 127.9, 127.4, 126.7, 126.4, 125.8, 110.9, 108.9, 89.5, 56.5, 38.2, 34.9, 21.7; IR (film) 2934, 1689, 1556, 1522, 1484, 1359, 1165 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{24}N_2NaO_6S$ $[M+Na]^+$: 539.1253 Found: 539.1251; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=11.8 min and *minor*-isomer t_r=28.6 min.

*4.1.13. 2-((2S,3S,4R)-1,2,3,4-Tetrahydro-3-nitro-2-(thiophen-2-yl)-1-tosylquinolin-4-yl)-1-phenylethanone (**3am**).* White solid; mp 172–174 °C; $[\alpha]_D^{24}$ −6.1 (*c* 1.3, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J*=0.8, 8.0 Hz, 2H), 7.83 (dd, *J*=0.8, 8.0 Hz, 1H), 7.58–7.65 (m, 3H), 7.49 (t, *J*=8.0 Hz, 2H), 7.38 (t, *J*=7.6 Hz, 1H), 7.32 (d, *J*=8.4 Hz, 1H), 7.18–7.25 (m, 2H), 6.99 (dd, *J*=0.8, 3.6 Hz, 1H), 6.94 (dd, *J*=3.6, 4.8 Hz, 1H), 6.82 (d, *J*=8.0 Hz, 1H), 6.42 (dd, *J*=0.8, 6.4 Hz, 1H), 4.99 (dd, *J*=6.4, 10.8 Hz, 1H), 3.36 (dd, *J*=8.4, 18.0 Hz, 1H), 3.06 (dt, *J*=3.6, 10.8 Hz, 1H), 2.94 (dd, *J*=3.6, 18.4 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 144.8, 143.4, 135.9, 135.2, 134.9, 133.8, 131.4, 130.0, 128.9, 128.5, 128.0, 127.9, 127.5, 127.3, 127.2, 125.9, 125.7, 125.3, 94.7, 59.1, 36.9, 35.7, 21.7; IR (film) 2928, 1686, 1551, 1458, 1352, 1228, 1167, 1091 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{24}N_2NaO_5S_2$ $[M+Na]^+$: 555.1024 Found: 555.1022; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=13.0 min and *minor*-isomer t_r=40.6 min.

*4.1.14. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-2-isopropyl-3-nitro-1-tosylquinolin-4-yl)-1-phenylethanone (**3an**).* White solid; mp 125–127 °C; $[\alpha]_D^{24}$ −16.1 (*c* 1.1, $CHCl_3$); 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.6 Hz, 2H), 7.79 (d, *J*=7.6 Hz, 1H), 7.63 (t, *J*=7.6 Hz, 1H), 7.55 (d, *J*=7.6 Hz, 2H), 7.50 (t, *J*=7.6 Hz, 2H), 7.37 (t, *J*=7.6 Hz, 1H), 7.25 (d, *J*=8.0 Hz, 2H), 7.18 (t, *J*=7.6 Hz, 1H), 6.75 (d, *J*=8.0 Hz, 1H), 4.79 (dd, *J*=5.2, 8.0 Hz, 1H), 4.72 (dd, *J*=5.2, 7.6 Hz, 1H), 3.35 (dd, *J*=8.8, 18.4 Hz, 1H), 3.04 (dd, *J*=2.4, 18.4 Hz, 1H), 2.75 (t, *J*=8.8 Hz, 1H), 2.41 (s, 3H), 1.80 (septet, *J*=6.8 Hz, 1H), 1.03 (d, *J*=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 144.3, 136.1, 136.0, 135.9, 133.7, 132.1, 129.7, 128.8, 128.4, 128.3, 127.9, 127.5, 127.2, 125.2, 93.0, 65.4, 36.2, 35.9, 34.6, 21.6, 19.0, 18.6; IR (film) 2988, 2930, 1686, 1548, 1449, 1349, 1231, 1162, 1078 cm^{-1}; HRMS (ESI): calcd for $C_{27}H_{28}N_2NaO_5S$ $(M+Na)^+$: 515.1617 Found: 515.1617; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=6.9 min and *minor*-isomer t_r=9.0 min.

*4.1.15. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-6-methyl-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3ba**).* White solid; mp 175–177 °C; $[\alpha]_D^{26}$ −34.8 (*c* 0.75, $CHCl_3$); 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J*=7.6 Hz, 2H), 7.78 (d, *J*=8.4 Hz, 1H), 7.56–7.66 (m, 3H), 7.48 (t, *J*=7.6 Hz, 2H), 7.25–7.36 (m, 7H), 7.19 (d, *J*=8.0 Hz, 1H), 6.63 (s, 1H), 6.12 (d, *J*=6.8 Hz, 1H), 4.89 (dd, *J*=6.8, 10.0 Hz, 1H), 3.27 (dd, *J*=8.0, 14.0 Hz, 1H), 3.06–3.13 (m, 1H), 2.89 (dd, *J*=4.0, 14.0 Hz, 1H), 2.45 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 144.5, 139.8, 136.9, 136.1, 135.5, 133.7, 133.2, 131.0, 129.9, 129.2, 129.1, 128.9, 128.4, 127.9, 127.3, 126.9, 126.4, 126.2, 94.3, 62.5, 37.1, 35.7, 21.7, 21.3; IR (film) 2980, 2931, 1686, 1557, 1493, 1356, 1221, 1169, 1076 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_5S$ $[M+Na]^+$: 563.1617 Found: 563.1613; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=10.4 min and *minor*-isomer t_r=15.0 min.

*4.1.16. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-8-methyl-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3ca**).* White solid; mp 217–219 °C; $[\alpha]_D^{26}$ 4.8 (*c* 0.84, $CHCl_3$); 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.2 Hz, 1H), 7.72 (d, *J*=7.6 Hz, 2H), 7.63 (t, *J*=7.2 Hz, 1H), 7.51 (t, *J*=7.6 Hz, 2H), 7.41 (d, *J*=8.4 Hz, 1H), 7.30–7.37 (m, 4H), 7.19 (t, *J*=7.6 Hz, 1H), 7.10–7.17 (m, 2H), 6.70 (d, *J*=7.6 Hz, 1H), 5.87 (d, *J*=7.6 Hz, 1H), 4.81 (dd, *J*=7.6, 12.0 Hz, 1H), 3.36 (dd, *J*=9.2, 18.4 Hz, 1H), 2.95–3.05 (m, 1H), 2.48 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 144.8, 139.6 (two signals overlapping), 136.2, 135.6, 134.9, 134.7, 133.7, 131.3, 130.2, 129.0, 128.8, 128.6, 128.0, 127.9 (two signals overlapping), 126.7, 123.0, 95.2, 63.9, 36.7, 36.1, 21.7, 19.6; IR (film) 2933, 1689, 1550, 1447, 1361, 1208, 1169, 1090 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_5S$ $[M+Na]^+$: 563.1617 Found: 563.1616; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=9.7 min and *minor*-isomer t_r=12.8 min.

*4.1.17. 2-((2S,3R,4S)-6-Chloro-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3da**).* White solid; mp 203–205 °C; $[\alpha]_D^{24}$ −67.4 (*c* 0.74, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.8 Hz, 1H), 7.80 (dd, *J*=1.2, 8.4 Hz, 2H), 7.59–7.65 (m, 3H), 7.47 (t, *J*=7.6 Hz, 2H), 7.24–7.38 (m, 8H), 6.85 (d, *J*=1.6 Hz, 1H), 6.19 (d, *J*=6.4 Hz, 1H), 4.99 (dd, *J*=2.4, 9.2 Hz, 1H), 3.16–3.24 (m, 2H), 2.84–2.93 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 144.9, 139.0, 135.8, 135.2, 134.3, 133.9, 132.7, 132.4, 130.1, 129.3, 128.8, 128.6, 128.5, 127.9, 127.5, 127.3, 126.5, 126.2, 93.0, 62.2, 37.5, 35.4, 21.7; IR (film) 2945, 1683, 1560, 1476, 1360, 1229, 1169, 1080 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ $[M+Na]^+$: 583.1070 Found: 583.1072; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=11.8 min and *minor*-isomer t_r=19.6 min.

*4.1.18. 2-((2S,3R,4S)-7-Chloro-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3ea**).* White solid; mp 181–183 °C; $[\alpha]_D^{25}$ −49.0 (*c* 0.83, $CHCl_3$); 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=2.4 Hz, 1H), 7.79 (dd, *J*=1.2, 6.0 Hz, 2H), 7.58–7.67 (m, 3H), 7.46 (t, *J*=8.0 Hz, 2H), 7.24–7.35 (m, 7H), 7.15 (dd, *J*=2.0, 8.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 1H), 6.21 (d, *J*=6.4 Hz, 1H), 4.99 (dd, *J*=6.4, 8.8 Hz, 1H), 3.17–3.26 (m, 2H), 2.80–2.91 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 145.0, 138.9, 136.7, 135.8, 135.1, 134.0, 133.9, 130.0, 129.3, 129.1, 128.8, 128.6, 127.9, 127.4, 127.3, 126.8, 126.2, 125.9, 92.8, 62.1, 37.8, 35.2, 21.7; IR (film) 2930, 1684, 1595, 1560, 1448, 1364, 1230, 1171, 1077 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ $[M+Na]^+$: 583.1070 Found: 583.1069; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=13.7 min and *minor*-isomer t_r=19.8 min.

*4.1.19. 2-((2S,3R,4S)-6-Bromo-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-phenylethanone (**3fa**).* White solid; mp 108–109 °C; $[\alpha]_D^{26}$ −65.4 (*c* 0.76, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J*=8.4 Hz, 1H), 7.79 (d, *J*=8.0 Hz, 2H), 7.56–7.67 (m,

3H), 7.44–7.53 (m, 3H), 7.23–7.37 (m, 7H), 7.01 (s, 1H), 6.21 (d, J=6.4 Hz, 1H), 5.00 (dd, J=6.4, 8.8 Hz, 1H), 3.15–3.28 (m, 2H), 2.87 (dd, J=4.0, 17.6 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 144.9, 138.9, 135.8, 135.2, 134.8, 133.8, 132.8, 131.5, 130.1, 129.5, 129.3, 128.8, 128.5, 127.9, 127.5, 127.4, 126.2, 120.1, 92.7, 62.1, 37.7, 35.3, 21.7; IR (film) 2980, 1683, 1558, 1475, 1359, 1228, 1167, 1085 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}BrN_2NaO_5S$ [M+Na]$^+$: 627.0565 Found: 627.0568; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=11.8 min and *minor*-isomer t_r=18.1 min.

*4.1.20. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-(4-methoxyphenyl)ethanone (**3ga**).* White solid; mp 86–88 °C; $[\alpha]_D^{24}$ −6.1 (*c* 0.98, $CHCl_3$); >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J=1.2, 8.0 Hz, 1H), 7.83 (d, J=8.8 Hz, 2H), 7.61 (d, J=8.4 Hz, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.17–7.34 (m, 8H), 6.94 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.0 Hz, 1H), 4.92 (dd, J=6.8, 10.0 Hz, 1H), 3.89 (s, 3H), 3.23 (dd, J=8.4, 18.0 Hz, 1H), 3.10 (dt, J=3.6, 10.0 Hz, 1H), 2.83 (dd, J=3.6, 18.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 163.9, 144.7, 139.7, 135.7, 135.3, 131.4, 130.3, 129.9, 129.1, 129.0, 128.5, 128.4, 127.3, 127.1, 126.9, 126.2, 125.9, 113.9, 94.3, 62.6, 55.6, 36.7, 35.9, 21.7; IR (film) 2980, 1681, 1604, 1552, 1454, 1351, 1230, 1159, 1068 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_6S$ [M+Na]$^+$: 579.1566 Found: 579.1565; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=17.3 min and *minor*-isomer t_r=33.6 min.

*4.1.21. 2-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-1-p-tolylethanone (**3ha**).* White solid; mp 110–111 °C; $[\alpha]_D^{24}$ −3.7 (*c* 1.1, $CHCl_3$); 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J=8.0 Hz, 1H), 7.76 (d, J=8.0 Hz, 2H), 7.40 (t, J=7.6 Hz, 1H), 7.26–7.35 (m, 9H), 7.20 (t, J=7.6 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H), 6.13 (d, J=6.8 Hz, 1H), 4.92 (dd, J=6.8, 10.0 Hz, 1H), 3.27 (dd, J=8.4, 18.0 Hz, 1H), 3.10 (dt, J=3.6, 11.2 Hz, 1H), 2.86 (dd, J=3.6, 18.0 Hz, 1H), 2.45 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 144.7, 139.7, 135.7, 135.3, 133.5, 131.4, 130.0, 129.5, 129.2, 128.5, 128.4, 128.1, 127.3, 127.1, 127.0, 126.3, 125.9 (two signals overlapping), 94.4, 62.6, 36.9, 35.8, 21.7, 21.6; IR (film) 2922, 1681, 1604, 1552, 1454, 1350, 1240, 1150, 1068 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{28}N_2NaO_5S$ [M+Na]$^+$: 563.1617 Found: 563.1615; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=14.7 min and *minor*-isomer t_r=26.1 min.

*4.1.22. 1-(4-Chlorophenyl)-2-((2S,3R,4S)-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)ethanone (**3ia**).* White solid; mp 100–102 °C; $[\alpha]_D^{21}$ −21.4 (*c* 0.98, $CHCl_3$); 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J=1.2, 8.4 Hz, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H), 7.45 (d, J=8.4 Hz, 2H), 7.40 (t, J=7.6 Hz, 1H), 7.24–7.36 (m, 7H), 7.20 (dt, J=1.2, 7.6 Hz, 1H), 6.81 (d, J=7.6 Hz, 1H), 6.14 (d, J=7.2 Hz, 1H), 4.99 (dd, J=7.2, 10.4 Hz, 1H), 3.25 (dd, J=8.4, 18.4 Hz, 1H), 3.11 (ddd, J=4.0, 8.8, 11.6 Hz, 1H), 2.84 (dd, J=4.0, 18.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 144.7, 140.3, 139.6, 135.8, 135.3, 134.2, 131.0, 129.4, 129.2, 129.1, 128.6, 128.5, 127.3, 127.1, 127.0, 126.2, 125.8, 94.1, 62.5, 37.1, 35.7, 21.7; IR (film) 2980, 1687, 1589, 1556, 1486, 1345, 1164, 1089 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ [M+Na]$^+$: 583.1070 Found: 583.1074; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=17.8 min and *minor*-isomer t_r=32.7 min.

*4.1.23. 1-(3-Chlorophenyl)-2-((2S,3R,4S)-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)ethanone (**3ja**).* White solid; mp 96–98 °C; $[\alpha]_D^{20}$ −7.8 (*c* 0.28, $CHCl_3$); 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J=7.6 Hz, 1H), 7.80 (t, J=1.6 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 7.56–7.64 (m, 3H), 7.38–7.45 (m, 2H), 7.25–7.36 (m, 7H), 7.21 (t, J=7.6 Hz, 1H), 6.81 (d, J=8.0 Hz, 1H), 3.25 (dd, J=8.0, 18.0 Hz, 1H), 3.11 (ddd, J=4.0, 10.8, 13.2 Hz, 1H), 2.86 (dd, J=4.0, 18.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 144.7, 139.5, 137.4, 135.7, 135.3, 135.2, 133.7, 130.9, 130.2, 130.0, 129.2, 128.6, 128.5, 128.1, 127.3, 127.1, 127.0, 126.2, 126.0, 125.8, 94.0, 62.4, 37.3, 35.7, 21.7; IR (film) 2921, 1682, 1555, 1486, 1347, 1160, 1069 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ [M+Na]$^+$: 583.1070 Found: 583.1069; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=12.2 min and *minor*-isomer t_r=19.7 min.

*4.1.24. 1-(2-Chlorophenyl)-2-((2S,3R,4S)-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)ethanone (**3ka**).* White solid; mp 85–86 °C; $[\alpha]_D^{24}$ 15.1 (*c* 0.96, $CHCl_3$); 84% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J=8.0 Hz, 1H), 7.60 (d, J=8.0 Hz, 2H), 7.40–7.45 (m, 4H), 7.23–7.37 (m, 9H), 6.97 (d, J=7.6 Hz, 1H), 6.13 (d, J=6.8 Hz, 1H), 4.89 (dd, J=7.2, 10.0 Hz, 1H), 3.28 (dd, J=8.0, 19.2 Hz, 1H), 2.93–3.03 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 144.7, 139.6, 137.9, 135.8, 135.3, 132.4, 130.9 (two signals overlapping), 130.8, 129.9, 129.3, 129.1, 128.6, 128.4, 127.3, 127.2, 127.1, 127.0, 126.2, 125.9, 94.1, 62.5, 41.1, 36.1, 21.7; IR (film) 2928, 1680, 1585, 1553, 1486, 1348, 1159, 1068 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}ClN_2NaO_5S$ [M+Na]$^+$: 583.1070 Found: 583.1067; Chiralpak AD-H column and AD-H guard column (15% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=20.5 min and *minor*-isomer t_r=25.2 min.

*4.1.25. 1-(4-Bromophenyl)-2-((2S,3R,4S)-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)ethanone (**3la**).* White solid; mp 89–91 °C; $[\alpha]_D^{20}$ −14.3 (*c* 0.37, $CHCl_3$); 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J=1.4, 8.4 Hz, 1H), 7.58–7.72 (m, 6H), 7.40 (t, J=8.0 Hz, 1H), 7.24–7.35 (m, 7H), 7.20 (dt, J=1.4, 8.0vHz, 1H), 6.80 (d, J=7.6 Hz, 1H), 6.13 (d, J=6.8 Hz, 1H), 4.89 (dd, J=6.8, 10.0 Hz, 1H), 3.24 (dd, J=8.0, 18.0 Hz, 1H), 3.07–3.13 (m, 1H), 2.83 (dd, J=4.0, 18.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 144.7, 139.6, 135.8, 135.3, 134.6, 132.1, 130.9, 129.9, 129.4, 129.0, 128.6, 128.5, 127.3, 127.1, 127.0, 126.2, 125.8, 94.1, 62.5, 37.1, 35.7, 21.7; IR (film) 2980, 1687, 1585, 1552, 1456, 1359, 1167, 1082 cm^{-1}; HRMS (ESI): calcd for $C_{30}H_{25}BrN_2NaO_5S$ [M+Na]$^+$: 627.0565 Found: 627.0560; Chiralpak AD-H column and AD-H guard column (15% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=22.4 min and *minor*-isomer t_r=39.1 min.

*4.1.26. 1-(Furan-2-yl)-2-((2S,3R,4S)-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)ethanone (**3ma**).* White solid; mp 156–158 °C; $[\alpha]_D^{24}$ −7.2 (*c* 1.2, $CHCl_3$); 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J=1.2, 8.4 Hz, 1H), 7.69 (dd, J=0.8, 4.8 Hz, 1H), 7.57–7.62 (m, 3H), 7.41 (t, J=8.0 Hz, 1H), 7.20–7.36 (m, 8H), 7.15 (dd, J=3.6, 4.8 Hz, 1H), 6.94 (d, J=7.6 Hz, 1H), 4.89 (dd, J=6.8, 10.4 Hz, 1H), 3.21 (dd, J=8.4, 17.6 Hz, 1H), 3.07 (ddd, J=3.6, 9.2, 12.0 Hz, 1H), 2.84 (dd, J=3.6, 17.6 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 144.7, 143.0, 139.6, 135.7, 135.3, 134.4, 132.1, 131.1, 129.9, 129.2, 128.6, 128.5, 128.3, 127.2, 127.1, 127.0, 126.2, 125.9, 94.3, 62.5, 37.7, 35.8, 21.7; IR (film) 2980, 1675, 1551, 1468, 1351, 1162, 1092 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{24}N_2NaO_6S$ [M+Na]$^+$: 539.1253 Found: 539.1253; Chiralpak AD-H column and AD-H guard column (15% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=14.4 min and *minor*-isomer t_r=26.4 min.

*4.1.27. 1-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)-3,3-dimethylbutan-2-one (**3na**).* White solid; mp 132–134 °C; $[\alpha]_D^{25}$ 12.0 (*c* 0.98, $CHCl_3$); 92% ee; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.87 (dd, J=0.8, 8.0 Hz, 1H), 7.59 (d, J=8.4 Hz, 2H), 7.20–7.39 (m, 9H), 6.80 (d, J=8.0 Hz, 1H), 6.14 (d, J=6.4 Hz, 1H), 4.89 (dd, J=6.4, 9.6 Hz, 1H), 2.86–2.93 (m, 1H), 2.77 (dd, J=7.2, 18.8 Hz, 1H), 2.47 (dd, J=4.4, 18.8 Hz, 1H), 2.39 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 144.6, 139.5, 135.6, 135.4, 130.9, 129.9, 129.1, 128.4, 128.3, 127.3, 126.7, 126.4, 126.3, 125.8, 93.5, 62.2, 44.2, 35.4, 35.2, 26.6, 21.6; IR (film) 2980, 1693, 1553, 1453, 1339, 1238, 1158, 1087 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{30}N_2NaO_5S$ $[M+Na]^+$: 529.1773 Found: 529.1771; Chiralpak AD-H column and AD-H guard column (15% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=8.2 min and *minor*-isomer t_r=12.6 min.

*4.1.28. 1-Cyclopropyl-2-((2S,3R,4S)-1,2,3,4-tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)ethanone (**3oa**).* White solid; mp 145–146 °C; $[\alpha]_D^{25}$ 11.9 (*c* 1.2, $CHCl_3$); 95% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J=8.0 Hz, 1H), 7.58 (d, J=7.6 Hz, 1H), 7.40 (t, J=7.6 Hz, 1H), 7.20–7.36 (m, 8H), 6.88 (d, J=7.6 Hz, 1H), 6.07 (d, J=6.8 Hz, 1H), 4.80 (dd, J=7.2, 8.8 Hz, 1H), 2.81–2.89 (m, 2H), 2.54 (dd, J=7.2, 21.2 Hz, 1H), 2.41 (s, 3H), 1.73–1.81 (m, 1H), 0.83–1.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 144.5, 139.7, 135.7, 134.4, 131.3, 129.9, 129.1, 128.5, 128.4, 127.3, 127.2, 127.1, 126.2, 125.6, 94.4, 62.6, 41.5, 35.7, 21.6, 21.4, 11.3, 11.2; IR (film) 2978, 1694, 1550, 1455, 1338, 1160, 1090 cm^{-1}; HRMS (ESI): calcd for $C_{27}H_{26}N_2NaO_5S$ $[M+Na]^+$: 513.1460 Found: 513.1455; Chiralpak AD-H column and AD-H guard column (15% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=13.2 min and *minor*-isomer t_r=22.9 min.

*4.1.29. 1-((2S,3R,4S)-1,2,3,4-Tetrahydro-3-nitro-2-phenyl-1-tosylquinolin-4-yl)propan-2-one (**3pa**).* White solid; mp 186–188 °C; $[\alpha]_D^{26}$ 10.4 (*c* 0.84, $CHCl_3$); 78% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.4 Hz, 1H), 7.42 (t, J=7.6 Hz, 1H), 7.20–7.37 (m, 8H), 6.83 (d, J=8.0 Hz, 1H), 6.06 (d, J=7.2 Hz, 1H), 4.71 (dd, J=7.2, 10.4 Hz, 1H), 2.82 (ddd, J=3.6, 10.4, 13.2 Hz, 1H), 2.72 (dd, J=8.4, 18.0 Hz, 1H), 2.43 (s, 3H), 2.36 (dd, J=3.6, 18.0 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 144.6, 139.6, 135.8, 135.4, 131.2, 129.9, 129.1, 128.7, 128.5, 127.4, 127.2 (two signals overlapping), 126.2, 125.4, 94.4, 62.5, 41.8, 35.7, 29.6, 21.6; IR (film) 2980, 1712, 1548, 1487, 1360, 1306, 1165, 1095 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{24}N_2NaO_5S$ $[M+Na]^+$: 487.1304. Found: 487.1303; Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ=254 nm); *major*-isomer t_r=13.5 min and *minor*-isomer t_r=35.8 min.

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Supplementary data

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References and notes

1. (a) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, Germany, 2009; (b) Nicolaou, K. C.; Montagnon, T. *Molecules That Changed the World*; Wiley-VCH: Weinheim, Germany, 2008.
2. Ojima, P. *Catalytic Asymmetric Synthesis*; Wiley: New Jersey, 2010.
3. For selected reviews on organocatalysis, see: (a) Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*; RSC: Cambridge, UK, 2010; (b) *Asymmetric Organocatalysis*; List, B., Ed.Topics in Current Chemistry; Springer: Berlin/Heidelberg, 2010; vol. 291; (c) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2007; (d) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005; (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178; (f) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138; (g) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638; (h) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267; (i) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (j) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.
4. For selected reviews on domino reactions, see: (a) MacMillan, D. W. C.; Walji, A. M. *Synthesis* **2007**, 1477; (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1; (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143; (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134; (e) Guo, H. C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (f) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.
5. For selected reviews on organocatalytic domino reaction, see: (a) Pellissier, H. *Asymmetric Domino Reactions*; RSC: Cambridge, UK, 2013; (b) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237; (c) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492; (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; (e) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037; (f) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.
6. For selected recent Michael addition reviews, see: (a) Córdova, A. *Catalytic Asymmetric Conjugate Reactions*; Wiley-VCH: Weinheim, Germany, 2010; (b) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions*; RSC: Cambridge, UK, 2010; (c) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299; (d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.
7. For reviews on tetrahydroquinolines, see: (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157; (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357; (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *17*, 2862; (d) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761; (e) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.
8. (a) DePasquale, M.; Cadelina, G.; Knight, D.; Loging, W.; Winter, S.; Blasi, E.; Perry, D.; Keiser, J. *Drug Dev. Res.* **2009**, *70*, 35; (b) Sikorski, J. A. *J. Med. Chem.* **2006**, *49*, 1; (c) He, J.; Lion, U.; Sattler, I.; Gollmick, F. A.; Grabley, S.; Cai, J.; Meiners, M.; Schünke, H.; Schaumann, K.; Dechert, U.; Krohn, M. *J. Nat. Prod.* **2005**, *68*, 1397; (d) Kusano, M.; Koshino, H.; Uzawa, J.; Fujioka, S.; Kawano, T.; Kimura, Y. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2559; (e) Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fourasté, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167; (f) Morimoto, Y. J. *Heterocycl. Chem.* **1998**, *35*, 279.
9. (a) Jia, Z.-X.; Luo, Y.-C.; Wang, Y.; Chen, L.; Xu, P.-F.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12958; (b) Tan, H. R.; Ng, H. F.; Chang, J.; Wang, J. *Chem.—Eur. J.* **2012**, *18*, 3865; (c) Dagousset, G.; Zhu, J.-P.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804; (d) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166; (e) Jia, Z.-X.; Luo, Y.-C.; Xu, P.-F. *Org. Lett.* **2011**, *13*, 832; (f) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847; (g) Xie, M.; Chen, X.; Zhu, Y.; Gao, B.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799; (h) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986; (i) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598; (j) Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánche-Roselló, M.; del Pozo, C. *Chem.—Eur. J.* **2008**, *14*, 9868; (k) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683.
10. Heo, S.; Kim, S.; Kim, S.-G. *Tetrahedron Lett.* **2013**, *54*, 4978.
11. (a) During our initial studies, Xu and co-workers disclosed organocatalytic aza-Michael–Michael cascade reactions of *o*-aminophenyl α,β-unsaturated ketones and limited nitroalkenes in which only moderate to good diastereoselectivities in most cases were reported, see: Ref. 9a. (b) During the preparation of this manuscript Du and co-workers reported chiral squaramide-catalyzed aza-Michael–Michael cascade reactions of *o*-*N*-tosyl aminophenyl α,β-unsaturated ketones and β-methyl-β-nitrostyrene, see: Yang, W.; He, H.-X.; Gao, Y.; Du, D.-M. *Adv. Synth. Catal.* **2013**, *355*, 3670.
12. For selected reviews on bifunctional thiourea catalysts, see: (a) Marques-Lopez, E.; Herrera, R. P. In *New Strategies in Chemical Synthesis and Catalysis*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, Germany, 2010; p 175; (b) Han, B.; Li, J.-L.; Xiao, Y.-C.; Zhou, S.-L.; Chen, Y.-C. *Curr. Org. Chem.* **2011**, *15*, 4128; (c) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593; (d) Song, C. E. *Cinchona Alkaloids in Synthesis & Catalysis*; Wiley-VCH: Weinheim, Germany, 2009.
13. (a) Sakamoto, S.; Inokuma, T.; Takemoto, Y. *Org. Lett.* **2011**, *13*, 6374; (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.
14. CCDC 983605 (**3la**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
15. (a) Li, X.; Yang, C.; Jin, J.-L.; Xue, X.-S.; Cheng, J.-P. *Chem.—Asian J.* **2013**, *8*, 997; (b) Zhu, J. L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813; (c) Baslé, O.; Raimondi, W.; Duque, M. M. S.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246; (d) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682; (e) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151; (f) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.