EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801423

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801423

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10.1002/ejoc.201801423

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Stereoselective Synthesis of Tetrahydroquinolines via Asymmetric Domino Reaction Catalyzed by Recyclable Ionic-Liquid-supported Bifunctional Tertiary Amine

Rinat S. Tukhvatshin[a], Alexander S. Kucherenko*[a], Yulia V. Nelyubina,[b] and Sergei G. Zlotin*[a]

Dedication ((optional))

Abstract: The most recyclable ionic liquid-supported bifunctional tertiary amine–squaramide organocatalyst for the asymmetric domino reaction has been found. Over this catalyst, ortho-aminochalcones protected with Tosyl or Nosyl groups underwent the aza-Michael/Michael domino reaction with nitroolefins to afford corresponding 2,3,4-trisubstituted tetrahydroquinolines as single diastereomers in nearly quantitative yield with up to 99% *ee*. The catalyst was readily separated from the reaction mixture via a simple centrifugation/decantation workup and 19 times reused in the catalytic reaction without noticeable conversion or enantioselectivity reduction. The *N*-nosylated products proved their synthetic value for pharmacology given their facile conversion to fused pirrolidino-tetrahydroquinolines of high diastreomeric and enantiomeric purity via successive deprotection and reductive amination.

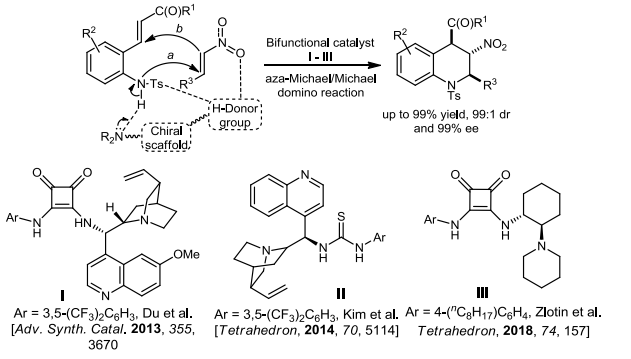
Introduction

Asymmetric organocatalysis is an extensively growing area of modern organic chemistry.[1] It allows a straightforward enantioselective synthesis of complex organic compounds from available achiral or racemic precursors without a risk of their contamination with toxic heavy metals inherent to organometal catalysis. A major recent trend in this research area is associated with the extensive application of organocatalysts for promoting stereoselective domino reactions.[2] These reactions, in which a generated intermediate spontaneously undergoes further (often intramolecular) transformations without adding fresh reagents and/or a catalyst,[3] are commonly less material- and energy-consuming than sequences of corresponding reactions performed separately, which makes them perspective in terms of green chemistry.[4] In particular, domino reactions significantly simplify a multi-step syntheses of valuable natural compounds and enantiomerically pure medications.[5]

However, the applicability of organocatalytic domino reactions in practice is limited by a lack of sustainable (recyclable) versions of organocatalysts to be readily separated from products (often poorly soluble in organic solvents) which can control reactions multiply (batch conditions) or continuously (continuous flow conditions). The known α, α -diarylprolinole,[6] prolinamide,[7] pyrrolidine[8] or benzotetramisole[9] derivatives tagged to polymers or ionic groups efficiently promote cascade reactions, which proceed through the formation of active iminium, enamine or enolate-type intermediates, only over the first 3-6 cycles. Afterwards, their activity and, in some cases, stereoinduction significantly reduce, apparently due to undesirable by-side transformations of these intermediates which destroy immobilized catalysts.[10]

On the other hand, polystyrene (PS) or textile-supported chiral tertiary amines, in particular Cinchona alkaloid derivatives capable of activating reagents via their deprotonation without the formation of covalent bonds (hydrogen bonding), were found to retain high yield and enantiomeric purity of products in asymmetric α-aminations of 2-oxindoles[11] or desymmetrizations of cyclic anhydrides[12] over 100 and 300 cycles, respectively. We expected immobilized chiral tertiary amines to act as sustainable catalysts in asymmetric domino reactions as well, provided no active covalent intermediates responsible for their unproductive by-side transformations are generated in either step of the cascade process.

A highly diastereoselective and enantioselective synthesis of 2,3,4-trisubstituted tetrahydroquinolines via organocatalytic aza-Michael (*a*) – intramolecular Michael (*b*) domino reactions of *o*-*N*-tosylamino-chalcones with nitroolefins, developed by Du[13] and Kim[14] with co-authors, belongs to this type of catalytic reactions (Scheme 1). It is efficiently promoted by bifunctional chiral tertiary amines **I–III** bearing thiourea[14] or squaramide fragments[13,15] which activate reagents and properly locate them in space solely by means of stereocontrolling hydrogen bonds.



Scheme 1. Known bifunctional organocatalysts **I–III** of asymmetric aza-Michael–Michael domino reactions of *o*-*N*-tosylamino-chalcones with nitroolefins.

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However, PS-supported bifunctional tertiary amine – thiourea catalyst could be recycled only 5 times in similar oxa-Michael−aza-Henry cascade reaction between α-amido sulfones derived from salicyladehydes and nitrostyrenes.[16] We hypothesized that supported tertiary amines bearing resistant to chemical reagents squaramide group[17] would be more robust catalysts of domino reactions which include asymmetric Michael addition step. To verify our hypothesis, we examined tertiary amine-derived squaramides **IVa** and **IVb**, recently developed in our laboratory,[18] which may be considered as ionic liquid-supported[19] versions of catalyst **III** in the aforementioned domino reactions (Figure 1). Catalyst **IVb** exhibited excellent recyclability in asymmetric Michael additions of β-dicarbonyl compounds to nitroolefins under "on-water" conditions and retained its activity and high stereoinduction over 30 reaction cycles. However, to our knowledge, no successful applications of supported bifunctional tertiary amines to asymmetric domino reactions controlled by stereoselective hydrogen bonds between a chiral catalyst and reagents in corresponding transition state have been reported so far.

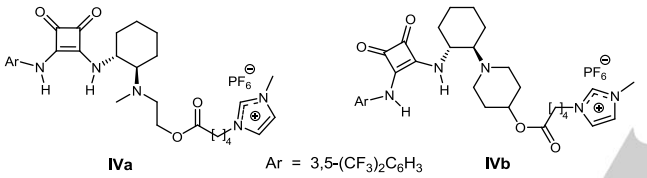


Figure 1. Tertiary amine-derived ionic liquid-supported squaramides **IVa** and **IVb.**.

It should be noted that the tetrahydroquinoline scaffold is present in a number of natural and synthetic bioactive molecules which exhibit various biological activities functioning as sodium[20] or calcium channel (BKCa) antagonists,[21]androgen receptor agonists/antagonists,[22] bradykinin (BK) receptor antagonists,[23] CEPT inhibitors,[24] liver x receptor (LXR) modulators,[25] etc. (Figure 2).

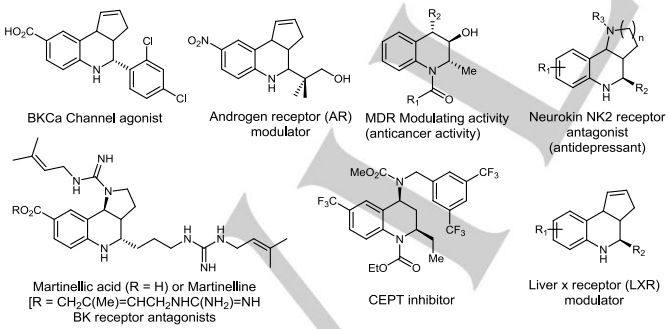
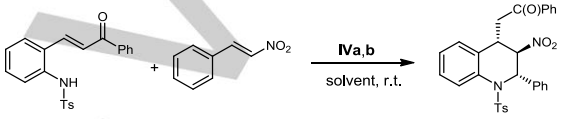


Figure 2. Bioactive tetrahydroquinoline derivatives.

Results and Discussion

At first, we compared catalytic performance of ionic liquid-supported catalysts **IVa** and **IVb** in a model reaction between ortho-(*N*-tosylamino)chalcone **1a** and β-nitrostyrene **1b** under comparable conditions (catalyst loading 10 mol%, CH_2Cl_2, r.t.). From the two, compound **IVb** proved to be a much more efficient catalyst of the model reaction. Tetrahydroquinoline derivative **3a** generated in its presence in 98% yield was a single diastereomer with enantiomeric enrichment 98% *ee*. Its performance was superior to that of catalyst **IVa** (72% yield and 74% *ee*) and the required reaction time was shorter (12 h *vs*. 20 h, Table 1, entries 1 and 2). Replacing of CH_2Cl_2 for another aprotic (MePh, EtOAc) or proton-containing solvents (*i*-PrOH, H_2O) exerted a negative impact on enantioselectivity or the reaction rate (Entries 3-6). Catalytic efficiency remained the same in the reaction with the catalyst loading reduced to 5 mol% (Entry 7); however, further reduction of the I**Vb** amount (to 1 mol% or 0.5 mol%) noticeably decreased its activity and the streoinduction level (Entries 8 and 9).

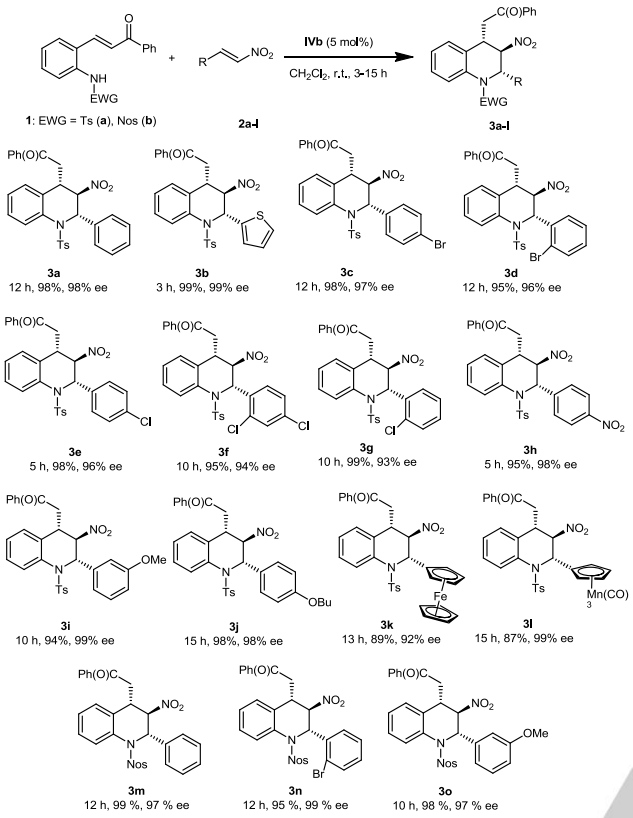
Table 1. Optimization of conditions for the model reaction between compounds **1a** and **2a**. [a]



entry	Catalyst	solvent	t, h	yield of **13a**, %[b]	*ee*, %[c]
1	**IVa** (10)	CH_2Cl_2	20	72	74
2	**IVb** (10)	CH_2Cl_2	12	99	98
3	**IVb** (10)	Toluene	18	99	95
4	**IVb** (10)	EtOAc	12	75	85
5	**IVb** (10)	*i*-PrOH	12	46	90
6	**IVb** (10)	H_2O	120	50	97
7	**IVb** (5)	CH_2Cl_2	12	98	98
8	**IVb** (1)	CH_2Cl_2	24	93	94
9	**IVb** (0.5)	CH_2Cl_2	24	90	93

[a] Unless otherwise specified, all reactions proceeded with **1a** (9.0 mg, 0.024 mmol), **2a** (5.2 mg, 0.036 mmol), and an organic solvent (100 μL) at ambient temperature. [b] Isolated yield after flash chromatography on silica gel. [c] HPLC data (Chiralpak AD-H, *n*-hexane : *i*-PrOH = 90 : 10; 254 nm, flow rate: 1.0 mL/min, t_R(*S*) = 18.23 min (major), t_R(*R*) = 32.63 min).

Next, we evaluated the capability of supported catalyst **IVb** to promote domino reactions of chalcons **1a** with various nitroolefins **2**. Much to our satisfaction, substrates **2** bearing acceptor or donor groups at different positions of the aromatic ring and heteroaromatic nitroolefin **1b** were tolerant to the proposed heterogeneous conditions and gave corresponding compounds **3b-j** in nearly quantitative yield with 93-99% *ee* (Scheme 2). Furthermore, catalyst **IVb** allowed an easy access to ferrocene and cymantren derivatives **3k** and **3l** of high enantiomeric purity. Chiral metallocenes attract considerable attention due to their potent anticancer activity.[26] Importantly, the catalyst also appeared suitable for facile preparation of tetrahydroquinoline derivatives **3m-o** containing a readily removable (unlike a tosyl group[27]) nosyl protecting group.[28] Furthermore, nearly quantitative chemical yields and excellent stereoselection were maintained at 3-5 mmol scaled reactions which makes the catalytic procedure valuable for the asymmetric synthesis.



Scheme 2. Known bifunctional organocatalysts **I–III** of asymmetric aza-Michael–Michael domino reactions of *o*-*N*-tosylamino-chalcones with nitroolefins (Reaction conditions for **3a-l**: **1a** (29 mg, 0.079 mmol), **2** (0.11 mmol), **IVb** (5 mol %), CH_2Cl_2 (0.2 mL), r.t. Reaction conditions for **3m-o**: **1b** (1.40 g, 3.4 mmol), **2m-o** (5.1 mmol), **IVb** (5 mol %), CH_2Cl_2 (2.0 mL), r.t. Yields were determined after chromatographic purification of the products, *ee* values – by HPLC analysis on a chiral stationary phase).

The key point was sustainability of supported catalyst **IVb** in the domino reaction. We studied its recyclability in a model reaction between compounds **1a** and **2a**. To facilitate isolation of product **3a** and minimize the catalyst loss during the workup in recycling experiments, we increased loadings of substrates **1a** and **2a** to 1.20 g (3.40 mmol) and 0.76 g (5.10 mmol), respectively, and that of catalyst **IVb** to 10 mol% with respect to **1a** in the first cycle. The catalyst was recovered after each cycle by centrifugation of the resulting reaction mixture followed by separation from the clear product solution by simple decantation. Fresh portions of reagents **1a** and **2a** were then added to the vessel containing the pre-dried (20 Torr, 30 min) recovered catalyst and the catalytic reaction was re-performed. In this manner, a single catalyst specimen could be 19 times reused in the reaction (total operation period ~230 h) without any negative impact on the conversion of starting compounds or enantiomeric purity of product **3a** (Figure 3). These characteristics became a somewhat lower in the 20th cycle only, which may be attributed to catalyst mass reduction during multiple workups.

Noteworthy is that HRMS of 19-fold used catalyst **IVb** was similar to corresponding spectra of the freshly prepared specimen (See Figure 4 and the Supporting Information). Furthermore, the fresh and the 19-fold used specimens exhibited close catalytic activity in the experiments where conversions were measured at a 4 h period (60% in the first cycle vs 45% in the 20th) which provides a strong evidence of its sustainability under the proposed conditions (See the Supporting Information). As far as we know, such sustainability has not been attained for supported organocatalysts in asymmetric domino reactions so far.

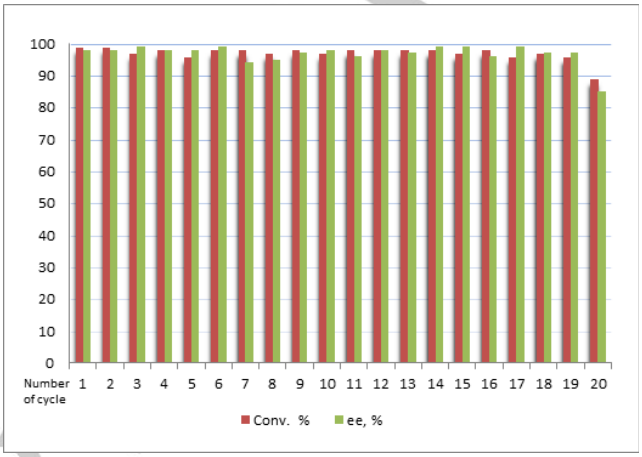


Figure 3. Catalytic performance and recyclability of catalyst **IVb** in the asymmetric domino reaction between **1a** and **2a.**

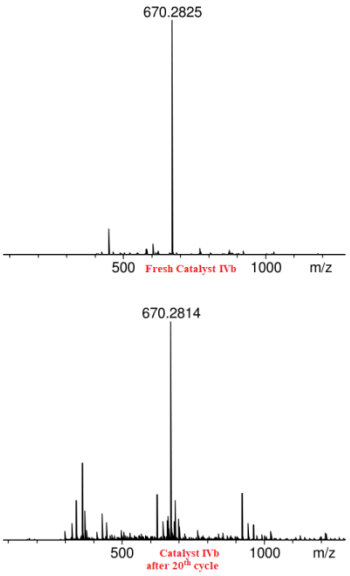
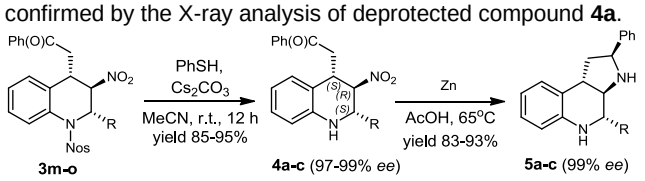


Figure 4. HRMS of freshly prepared and multiply used (after 20th cycle) catalyst **IVb**.

The synthetic utility of prepared compounds **3** was demonstrated by a facile conversion of *N*-nosylated products **3m-o** to fused pirrolidino-tetrahydroquinolines **5a-c** via successive deprotection with $PhSH/Cs_2CO_3$ followed by reductive amination of resulting tetrahydroquinolines **4a-c** with Zn/AcOH (Scheme 3).[29]

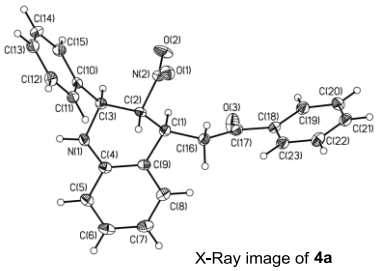
The tricyclic backbone of compounds **5** is incorporated into Neurukin NK2 receptor antagonists, BKCa channel agonists, and liver x receptor (LXR) modulators.[25] Compound **5b** was prepared earlier as a mixture of diastereomers (dr 87:13) from

diastereomerically diverse tetrahydroquinoline **4b** derived from unprotected ortho-aminochalcone **1'**.[30] Using *N*-nosylated tetrahydroquinolines **3m-o**, diastereomerically pure and readily attainable via the **IVb**-catalyzed asymmetric cascade reaction of **1b** with **2a**, **2d** and **2i**, respectively, we fulfilled a convenient stereospecific synthesis of compounds **4a-c** and **5a-c** as single diastereomers. The absolute (2*S*,3*R*,4*S*)-configuration of stereogenic centers in compounds **3-5** was unambiguously confirmed by the X-ray analysis of deprotected compound **4a**.



3m-o **4a-c** (97-99% *ee*) **5a-c** (99% *ee*)

R = Ph (**3m**, **4a**, **5a**); 2-BrC_6H_4 (**3n**, **4b**, **5b**); 3-MeOC_6H_4 (**3o**, **4c**, **5c**)



X-Ray image of **4a**

Scheme 3. Chemical transformations of *N*-nosyl-protected tetrahydroquinolines **3m-o.**

Conclusions

To conclude, the most recyclable ionic liquid-supported bifunctional tertiary amine–squaramide organocatalyst for the asymmetric domino reaction has been found. Over this catalyst, *N*-protected (with Ts or Nos groups) ortho-aminochalcones underwent the aza-Michael/Michael domino reaction with nitroolefins to afford corresponding 2,3,4-trisubstituted tetrahydroquinolines as single diastereomers in nearly quantitative yield with up to 99% *ee*. The catalyst could be readily separated from the reaction mixture via a simple centrifugation/decantation workup and 19 times reused in the catalytic reaction without a noticeable conversion or enantioselectivity reduction. The synthetic utility of *N*-nosylated products was demonstrated by their facile conversion to pharmacology-useful fused pirrolidino-tetrahydroquinolines of high diastreomeric and enantiomeric purity via the deprotection/reductive amination sequence.

Experimental Section

General remarks. HRMS (high-resolution mass spectrometry) spectra were measured using electrospray ionization (ESI) and a time-of-flight (TOF) mass analyzer. The measurements were taken in the positive ion mode (interface capillary voltage 4500 V) in the mass range from m/z = 50 Da tom/z = 3000 Da; external or internal calibration was done with an electrospray calibrant solution. NMR spectra were recorded on a 300 MHz spectrometer. The chemical shifts of ^{1}H and ^{13}C were measured relative to Me_4Si, $CDCl_3$, respectively. IR spectra were recorded using BRUKER ALPHA-T instrument and are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a polarimeter and calibrated with pure solvent as a blank. Atoms in the X-ray image of compound **4a** are represented *via* thermal ellipsoids at the 50% probability level. CCDC 1827154 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. The HPLC analyses were performed on chiral stationary phase columns Chiralpak AD-H and Chiralcel OD-H detection at 254 nm. Silica gel (0.060−0.200 mm) was used for column chromatography. All reagents and solvents were purified according to common methods. Centrifugation was performed at 3500 rpm. Racemic compounds **3** were prepared from **1** and **2** using TEA as catalyst.

General procedure for the asymmetric aza-Michael–Michael reaction

Method 1. A mixture of chalcone **1** (0.08 mmol), nitroolefin **2** (0.11 mmol), catalyst **IVb** (3.1 mg, 4.0 μmol, 5 mol%) and CH_2Cl_2 (0.2 mL) was stirred at ambient temperature for 3-15 h (TLC-monitoring). The reaction mixture was evaporated in *vacuo* and Et_2O/*n*-hexane (8:2) mixture (5 mL) was added to the residue. Finely dispersed catalyst **IVb** was collected at the bottom of flask via centrifugation and the upper clear solution containing product **3** and excess of **2**, was carefully decanted. Then, fresh Et_2O/*n*-hexane (8:2) mixture (5 mL) was added to the residue and the centrifugation procedure was four times re-performed as described above. The combined organic extracts were evaporated under reduced pressure (20 Torr). The remaining raw product was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 5:1 to 1:1) to afford corresponding tetrahydroquinoline **3**.

Method 2 (scaled procedure for compounds 3a, 3m, 3n and 3o). A mixture of chalcone **1** (3.4 mmol), nitroolefin **2** (5.1 mmol), catalyst **IVb** (0.138 g, 0.17 mmol, 5 mol%) and CH_2Cl_2 (2.0 mL) was stirred at ambient temperature for 10-12 h (TLC-monitoring). The reaction mixture was evaporated in *vacuo* and Et_2O/*n*-hexane (8:2 solvent system (5 mL) was added to the residue. Finely dispersed catalyst **IVb** was collected at the bottom of flask via centrifugation and the upper clear solution containing product **3** and excess of **2**, was carefully decanted. Then, fresh Et_2O/*n*-hexane (8:2) mixture (5 mL) was added to the residue and the centrifugation procedure was four times re-performed as described above. The combined organic extracts were evaporated under reduced pressure (20 Torr). The remaining raw product was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 5:1 to 1:1) to afford corresponding tetrahydroquinoline **3**.

General procedure for recycling of catalyst IVb.

After separation from the reaction mixture, catalyst **IVb** was dried under reduced pressure (50 Torr, 50 °C) for 30 min. Then, fresh portions of reagents (**1a** and **2a**) and solvent (CH_2Cl_2) were added to the recovered catalyst and the reaction was re-performed as described above.

Characterization data on novel compounds **3c,f,j-o** prepared by methods **1** and **2** are given below.

2-((2*S*,3*R*,4*S*)-2-(4-Bromophenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3c**).

Colorless solid. Yield 46 mg (98%); m.p. 95-97 °C; $[\alpha]^{20}_D$: -18.0 (c 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.3 Hz, 3H), 7.67 –

7.55 (m, 3H), 7.54 – 7.36 (m, 5H), 7.35 – 7.27 (m, 2H), 7.25 – 7.11 (m, 3H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.04 (d, *J* = 7.0 Hz, 1H), 4.86 (dd, *J* = 10.3, 7.2 Hz, 1H), 3.31 (dd, *J* = 18.1, 8.1 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.92 (dd, *J* = 18.1, 3.3 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 195.1, 144.8, 138.8, 135.9, 135.5, 135.1, 133.8, 132.3, 131.3, 130.0, 128.8, 128.6, 128.0, 127.9, 127.3, 127.2, 125.8, 122.6, 94.1, 62.2, 36.7, 35.8, 21.7; HRMS (ESI): m/z = 627.0554 and 629.0540, calcd. for $C_{30}H_{25}BrN_2NaO_5S$ $[M+Na]^+$: 627.0560 and 629.0541.

2-((2*S*,3*R*,4*S*)-2-(2,4-Dichlorophenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3f**).

Colorless solid. Yield 44 mg (95%); m.p. 103-105 °C; $[\alpha]^{20}_D$: 11.0 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.94 – 7.81 (m, 3H), 7.61 (d, *J* = 7.9 Hz, 3H), 7.54 – 7.41 (m, 3H), 7.40 – 7.31 (m, 3H), 7.26 – 7.15 (m, 3H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 7.3 Hz, 1H), 5.01 – 4.90 (m, 1H), 3.28 (dd, *J* = 18.1, 8.1 Hz, 1H), 3.16 – 3.05 (m, 1H), 2.97 – 2.85 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 195.2, 144.9, 136.1, 135.9, 135.1, 134.6, 133.8, 133.2, 130.5, 130.0, 129.9, 128.8, 128.6, 128.0, 127.9, 127.3, 127.0, 126.8, 126.0, 92.0, 59.4, 35.8, 21.7. HRMS (ESI): m/z = 612.1111 and 614.1085, calcd. for $C_{30}H_{28}Cl_2N_3O_5S$ $[M+NH_4]^+$: 612.1121 and 614.1094.

2-((2*S*,3*R*,4*S*)-2-(4-Butoxyphenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3j**)

Colorless solid. Yield 46 mg (98%); m.p. 68-70 °C; $[\alpha]^{20}_D$: -15.0 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.86 (d, *J* = 7.6 Hz, 3H), 7.60 (d, *J* = 8.0 Hz, 3H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.18 (dd, *J* = 14.6, 8.1 Hz, 3H), 6.82 (d, *J* = 8.6 Hz, 3H), 6.05 (d, *J* = 6.9 Hz, 1H), 4.89 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.30 (dd, *J* = 18.1, 8.3 Hz, 1H), 3.15 – 3.03 (m, 1H), 2.89 (dd, *J* = 18.1, 3.6 Hz, 1H), 2.44 (s, 3H), 1.83 – 1.69 (m, 2H), 1.58 – 1.40 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 195.2, 159.1, 144.5, 135.9, 135.7, 135.4, 133.6, 131.4, 131.3, 129.9, 128.7, 128.3, 127.9, 127.5, 127.2, 127.0, 126.9, 125.8, 115.0, 94.3, 67.7, 62.3, 37.1, 35.8, 31.2, 21.6, 19.2, 13.8; HRMS (ESI): m/z = 599.2231, calcd. for $C_{34}H_{35}N_2O_6S[M+H]^+$: 599.2210.

2-((2*S*,3*R*,4*S*)-3-Nitro-2-ferrocenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3k**)

Reddish-violet solid. Yield 44 mg (89%); m.p. 107-109 °C; $[\alpha]^{20}_D$: -10.0 (c 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d6): *δ* = 7.95 (d, *J* = 7.6 Hz, 2H), 7.76 – 7.64 (m, 1H), 7.60 – 7.51 (m, 5H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.96 (d, *J* = 4.5 Hz, 1H), 5.39 (dd, *J* = 9.1, 4.4 Hz, 1H), 4.21 (s, 1H), 4.17 (s, 1H), 4.11 (s, 1H), 4.01 (s, 5H), 3.96 (s, 1H), 3.65 (dd, *J* = 18.4, 6.2 Hz, 1H), 3.29 (d, *J* = 4.6 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): *δ* = 201.9, 149.7, 141.4, 140.7, 140.4, 138.8, 136.3, 135.2, 134.0, 133.3, 132.3, 132.1, 131.9, 131.2, 98.5, 93.5, 74.1, 73.8, 73.2, 71.5, 63.4, 42.3, 40.3, 26.4; HRMS (ESI): m/z = 634.1217, calcd. for $C_{34}H_{30}N_2O_5SFe$ $[M]^+$: 634.1220.

2-((2*S*,3*R*,4*S*)-3-Nitro-2-cymantrenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3l**)

Violet solid. Yield 44 mg (87%); m.p. 130-132 °C; $[\alpha]^{20}_D$: -8.0 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d6): *δ* = 7.93 (d, *J* = 7.0 Hz, 2H), 7.73 – 7.63 (m, 1H), 7.59 – 7.49 (m, 5H), 7.44 – 7.32 (m, 3H), 7.25 (t, *J* = 6.5 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 5.86 (d, *J* = 3.6 Hz, 1H), 5.19 – 5.11 (m, 2H), 5.00 (d, *J* = 14.2 Hz, 2H), 4.83 (s, 1H), 3.71 (dd, *J* = 18.6, 6.7 Hz, 1H), 3.24 (dd, *J* = 18.9, 3.0 Hz, 1H), 3.11 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6): *δ* = 229.5, 201.7, 149.9, 141.3, 140.4, 139.4, 138.9, 136.7, 135.4, 134.1, 133.2, 132.7, 132.2, 131.5, 106.6, 97.4, 90.8, 90.2, 89.3, 85.9, 61.9, 42.1, 40.2, 26.4. HRMS (ESI): m/z = 653.0777, calcd. for $C_{32}H_{26}N_2O_8SMn$ $[M+H]^+$: 653.0785.

2-((*2S*,3R,4*S*)-3-Nitro-1-((2-nitrophenyl)sulfonyl)-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3m**):

Colorless solid. Yield 1.80 g (99%); m.p. 108-110 °C; $[\alpha]^{20}_D$: +8.7 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.90 (d, *J* = 7.6 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.72 (dd, *J* = 14.7, 7.5 Hz, 2H), 7.66 – 7.60 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.47 (dt, *J* = 14.8, 7.4 Hz, 5H), 7.33 (d, *J* = 5.2 Hz, 2H), 7.25 – 7.20 (m, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.16 (d, *J* = 7.1 Hz, 1H), 4.89 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.56 – 3.39 (m, 2H), 3.04 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 195.4, 139.1, 139.0, 135.9, 135.6, 134.5, 133.8, 132.1, 131.9, 131.82, 131.3, 130.9, 129.4, 129.1, 129.1, 128.8, 128.7, 128.7, 127.9, 127.9, 127.6, 126.4, 125.5, 124.1, 94.9, 62.9, 36.4. HRMS (ESI): m/z = 575.1598, calcd. for $C_{29}H_{27}N_4O_7S$ $[M+NH_4]^+$: 575.1595.

2-((2*S*,3*R*,4*S*)-2-(2-Bromophenyl)-3-nitro-1-((2-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3n**)

Yellow solid. Yield 2.00 g (95%); m.p. 95-97 °C; $[\alpha]^{20}_D$: +15.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 8.02 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.84 – 7.72 (m, 3H), 7.71 – 7.55 (m, 4H), 7.47 (dd, *J* = 13.3, 6.9 Hz, 3H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 20.7, 7.3 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 1H), 5.04 (dd, *J* = 10.3, 7.4 Hz, 1H), 3.60 (t, *J* = 9.1 Hz, 1H), 3.41 (dd, *J* = 17.9, 8.3 Hz, 1H), 3.07 (d, *J* = 15.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 138.9, 136.2, 135.9, 134.6, 133.8, 133.6, 131.9, 131.5, 131.0, 130.2, 128.8, 128.8, 128.4, 127.9, 127.6, 126.9, 125.9, 124.5, 122.3, 93.1, 61.6, 36.5; HRMS (ESI): m/z = 652.0257 and 660.0225, calcd. for $C_{29}H_{22}BrN_3NaO_7S$ $[M+Na]^+$: 658.0254 and 660.0235.

2-((2*S*,3*R*,4*S*)-2-(3-Methoxyphenyl)-3-nitro-1-((2-nitrophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**3o**)

Yellow solid. Yield 1.90 g (98%); m.p. 86-88 °C; $[\alpha]^{20}_D$: +17.0 (c 1.0, $CHCl_3$); IR (KBr) 3422, 3070, 3018, 2939, 2838, 1686, 1602, 1544, 1489, 1451, 1372, 1278, 1228, 1174, 1127, 1042, 990, 852, 755, 691, 589 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.90 (d, *J* = 7.5 Hz, 2H), 7.83 (t, *J* = 7.6 Hz, 2H), 7.72 (dd, *J* = 13.5, 7.4 Hz, 2H), 7.63 (dd, *J* = 6.7, 5.3 Hz, 2H), 7.54 – 7.41 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.81 (dd, *J* = 18.2, 10.2 Hz, 3H), 6.13 (d, *J* = 7.0 Hz, 1H), 4.89 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.85 (d, *J* = 10.6 Hz, 1H), 3.75 (s, 3H), 3.56 – 3.39 (m, 2H), 3.03 (d, *J* = 15.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 195.4, 159.9, 140.6, 135.9, 135.5, 134.5, 133.8, 131.9, 130.9, 130.3, 128.8, 128.7, 128.0, 127.8, 127.4, 125.6, 124.2, 118.5, 114.1, 112.1, 94.7, 62.7,

55.2, 36.4; HRMS (ESI): m/z = 588.1430, calcd. for $C_{30}H_{26}N_3O_8S$ $[M+H]^+$: 588.1435.

Synthesis of 4a-c (general procedure)

Thiophenol (0.28 mL, 2.72 mmol) and Cs_2CO_3 (1.12 g, 4.30 mmol) were added to a solution of **3** (2.50 mmol) in MeCN (30 ml). The reaction mixture was stirred at ambient temperature for 12 h. The solvents were evaporated *in vacuo* and the residue diluted with EtOAc (20 mL). Inorganic materials were filtrated off, the resulting solution of the raw product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1) to afford corresponding compound **4**.

2-((2*S*,3*R*,4*S*)-3-Nitro-2-phenyl-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**4a**)

Yellow solid. Yield 0.79 g (85%); m.p. 172-174 °C; $[\alpha]^{20}_D$: +41.0 (c 1.0, $CHCl_3$); IR (KBr) 3373, 3060, 3016, 2903, 2880, 1685, 1545, 1495, 1478, 1325, 1305, 1230, 980, 748, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.84 – 7.72 (m, 3H), 7.71 – 7.55 (m, 4H), 7.47 (dd, *J* = 13.3, 6.9 Hz, 3H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 20.7, 7.3 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 1H), 5.04 (dd, *J* = 10.3, 7.4 Hz, 1H), 3.60 (t, *J* = 9.1 Hz, 1H), 3.41 (dd, *J* = 17.9, 8.3 Hz, 1H), 3.07 (d, *J* = 15.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 142.9, 137.9, 136.4, 133.4, 129.1, 129.1, 128.6, 127.9, 127.8, 127.4, 127.3, 121.4, 119.2, 114.6, 90.7, 59.6, 41.1, 37.0; HRMS (ESI): m/z = 373.1549, calcd. for $C_{23}H_{21}N_2O_3$ $[M+H]^+$: 373.1547.

2-((2*S*,3*R*,4*S*)-2-(2-Bromophenyl)-3-nitro-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**4b**)

Yellow solid. Yield 1.00 g (89%); m.p. 71-73 °C; $[\alpha]^{20}_D$: +151.0 (c 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.31 (m, 1H), 7.21 – 7.03 (m, 3H), 6.83 – 6.75 (m, 1H), 6.74 – 6.69 (m, 1H), 5.59 – 5.47 (m, 2H), 4.54 – 4.45 (m, 1H), 3.24 (d, *J* = 6.1 Hz, 2H);; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.80, 137.23, 136.35, 133.84, 133.44, 130.22, 129.11, 128.58, 128.13, 128.11, 127.99, 127.87, 123.52, 119.56, 114.91, 86.63, 57.37, 41.82, 36.22; HRMS (ESI): m/z = 451.0657 and 453.0640, calcd. for $C_{23}H_{20}BrN_2O_3$ $[M+H]^+$: 451.0652 and 453.0633.

2-((2*S*,3*R*,4*S*)-2-(3-Methoxyphenyl)-3-nitro-1,2,3,4-tetrahydroquinolin-4-yl)-1-phenylethanone (**4c**)

Yellow solid. Yield 0.95 g (95%); m.p. 81-83 °C; $[\alpha]^{20}_D$: +249.2 (c 2.0, $CHCl_3$); IR (KBr) 3350, 3058, 3023, 2968, 2943, 2898, 2839, 1683, 1610, 1585, 1545, 1487, 1450, 1410, 1359, 1287, 1229,1156, 1045, 983, 754, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.55 – 7.43 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 6.8 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.06 – 6.99 (m, 1H), 6.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.23 (t, *J* = 8.4 Hz, 1H), 4.90 (d, *J* = 8.1 Hz, 1H), 4.48 – 4.39 (m, 1H), 3.78 (s, 3H), 3.39 (qd, *J* = 18.5, 5.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9, 160.0, 142.8, 139.6, 136.4, 133.5, 130.1, 129.1, 128.6, 128.0, 127.9, 127.5, 127.2, 121.3, 119.5, 119.1, 114.7, 114.5, 112.8, 90.4, 59.4, 55.3, 41.2, 36.9; HRMS (ESI): m/z = 403.1647, calcd. for $C_{24}H_{23}N_2O_4$ $[M+H]^+$: 403.1652.

Synthesis of 5a-c (**general procedure**)

Zinc powder (30 equiv., 0.51 g) was added to a stirred solution of **4** (0.26 mmol) in AcOH (4.0 mL). The reaction mixture was heated with stirring at 70 ºC for 4.0 h (TLC monitoring). Inorganic materials were filtered off. The filtrate was diluted with EtOAc (10 mL) and neutralized with concentrated aq. $NaHCO_3$. The mixture was extracted with EtOAc (3 x 10 mL), washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*. The residue was purified by column chromatography (*n*-hexane/EtOAc 6:1) to afford corresponding compound **5.**

(2*S*,3a*R*,4*S*,9b*S*)-2,4-Diphenyl-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline (**5a**)

Yellow solid. Yield 70 mg (83%); m.p. 120-122 °C; $[\alpha]^{20}_D$: -140.0 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 – 7.45 (m, 5H), 7.42 – 7.30 (m, 5H), 7.24 (br s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 4.72 (d, *J* = 8.8 Hz, 1H), 4.61 – 4.49 (m, 1H), 3.32 – 3.16 (m, 2H), 2.47 – 2.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9, 143.9, 142.4, 128.6, 128.1, 127.9, 127.2, 126.8, 126.6, 125.5, 122.8, 116.4, 112.0, 65.8, 62.9, 60.4, 42.1, 36.5; HRMS (ESI): m/z = 327.1858, calcd. for $C_{23}H_{23}N_2$ $[M+H]^+$: 327.1856.

(2*S*,3a*R*,4*S*,9b*S*)-4-(2-Bromophenyl)-2-phenyl-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline (**5b**)

Brownish solid. Yield 97 mg (93%); m.p. 94-96 °C; $[\alpha]^{20}_D$: -109.0 (c 1.0, $CHCl_3$); IR (KBr) 3391, 3040, 2916, 1668, 1585, 1550, 1490, 1351, 1259, 990, 756, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 6.7, 3.2 Hz, 1H), 7.59 – 7.49 (m, 3H), 7.38 (dd, *J* = 14.0, 6.7 Hz, 5H), 7.13 – 7.07 (m, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.60 (dd, *J* = 16.0, 8.1 Hz, 1H), 5.30 (d, *J* = 8.9 Hz, 1H), 4.85 (d, *J* = 9.3 Hz, 1H), 4.67 – 4.56 (m, 2H), 3.37 (dd, *J* = 17.5, 9.2 Hz, 1H), 3.25 (dd, *J* = 20.9, 11.2 Hz, 1H), 2.43 (dd, *J* = 13.2, 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 141.6, 133.3, 129.5, 128.8, 128.5, 127.6, 127.4, 127.3, 126.8, 125.8, 116.9, 112.4, 66.1, 61.6, 43.1, 36.3; HRMS (ESI): m/z = 405.0961 and 407.0950, calcd. for $C_{23}H_{22}BrN_2$ $[M+H]^+$: 405.0961 and 407.0941.

(2*S*,3a*R*,4*S*,9b*S*)-4-(3-Methoxyphenyl)-2-phenyl-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline (**5c**)

Brownish solid. Yield 83 mg (90%); m.p. 75-76 °C; $[\alpha]^{20}_D$: -78.0 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 – 7.46 (m, 2H), 7.40 – 7.35 (m, 2H), 7.32 (d, *J* = 7.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.18 – 7.04 (m, 4H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.69 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.86 – 4.66 (m, 1H), 4.54 – 4.46 (m, 1H), 3.94 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 3H), 3.33 – 3.20 (m, 1H), 3.18 – 3.08 (m, 1H), 2.42 – 2.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 144.9, 143.9, 137.4, 129.9, 128.9, 128.4, 127.7, 127.5, 127.2, 126.5, 125.8, 125.4, 119.5, 116.8, 112.4, 68.1, 65.9, 55.2, 42.4, 38.7; HRMS (ESI): m/z = 357.1954, calcd. for $C_{24}H_{25}N_2O$ $[M+H]^+$: 357.1961.

Acknowledgements

This research was supported by the Russian Science Foundation (Project No. 14-50-00126). The contribution of the Center for Molecular Composition Studies of INEOS RAS by way of an X-ray analysis of compound **4a** is gratefully acknowledged.

Keywords: Asymmetric catalysis • Supported organocatalysts • squaramides • Asymmetric domino reaction • Tetrahydroquinolines

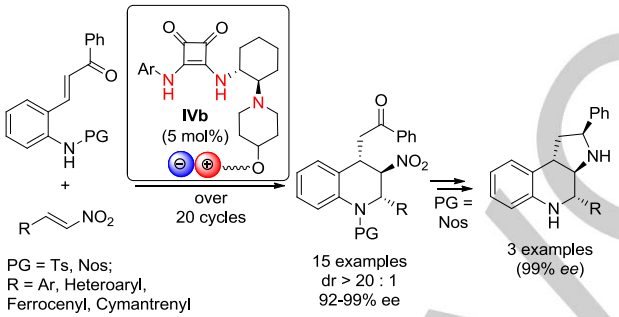
[1] a) *Science of Synthesis: Asymmetric Organocatalysis* (Eds.: B. List, K. Maruoka), Thieme, Stuttgart, **2012**; b) P. I. Dalco, *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Wiley-VCH, Weinheim, **2013**.
[2] a) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev*. **2014**, *114 (4)*, 2390−2431; b) Y. Wang, H. Lu, P.-F. Xu, *Acc. Chem. Res*. **2015**, *48*, 1832−1844; c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D, Enders, *Adv. Synth. Catal*. **2015**, *357*, 253–281; d) L. Tian, Y.-C. Luo, X.-Q. Hu, P.-F. Xu, *Asian J. Org. Chem*. **2016**, *5*, 580–607; e) S. Nayak, P. Panda, S. Bhakta, S. K. Mishra, S. Mohapatra, *RSC Adv*. **2016**, *6*, 96154–96175; f) F. Vetica, R. M. Figueiredo, M. Orsini, D. Tofani, T. Gasperi, *Synthesis* **2015,** *47*, 2139–2184; g) H. Pellissier, *Asymmetric Domino Reactions*, RSC, Cambridge, UK, **2013**, pp.502.
[3] L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*; Wiley-VCH ,Weinheim, **2006**.
[4] a) R. A. Sheldon, *Chem. Soc. Rev*. **2012**, *41*, 1437-1451; b)P.-F. Xu, W. WANG, *Catalytic Cascade Reactions*. John Wiley & Sons, pp 419, **2013**.
[5] a) B.-C. Hong, A. Raja, V. M. Sheth, *Synthesis* **2015,** *47*, 3257–3285;b) Y. Zhu, X. Li, Q. Chen, J. Su, F. Jia, S. Qiu, M. Ma, Q. Sun, W. Yan, K. Wang, R. Wang, *Org. Lett*. **2015**, *17*, 3826-3829.
[6] a) F. Dai, Z. Zhao, G. Xie, D. Feng, X. Ma, *ChemCatChem* **2017**, *9*, 89–93; b) P. Chintala, S. K. Ghosh, E. Long A, D. Headley, B. Ni, *Adv. Synth. Catal.* **2011**, *353*, 2905-2909; c) E. Alza, S. Sayalero, X. C. Cambeiro, R. Martín-Rapun, P. O. Miranda, M. A. Pericas, *Synlett* **2011**, *4*, 464–468; c) O. V. Maltsev, A. S. Kucherenko, A. L. Chimishkyan, S. G. Zlotin, *Tetrahedron: Asymm.* **2010**, *21*, 2659.
[7] A. Banon-Caballero, G. Guillena, C. Najera, *J. Org. Chem*. **2013**, *78*, 5349−5356.
[8] A.B. Xia, D.Q. Xu, S.P. Luo, J.R. Jiang, J. Tang, Y.F. Wang, Z.Y. Xu, *Chem. Eur. J*. **2010**, *16*, 801-804.
[9] J. Izquierdo, M. A. Pericas, *ACS Catal.* **2016**, *6*, 348-356.
[10] a) O. V. Maltsev, A. O. Chizhov, S. G. Zlotin, *Chem. Eur. J*. **2011**, *17*, 6109–6117; b) D. Seebach, X. Sun, C. Sparr, M. O. Ebert, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2012**, *95*, 1064-1078; c) A. S. Kucherenko, D. E. Siyutkin, A. G. Nigmatov, A. O. Chizhov, S. G. Zlotin, *Adv. Synth. Catal*. **2012**, *354*, 3078–3086; d) J. Wan, Z. Zhao, F. Wang, X. Ma, *Eur. J. Org. Chem*. **2015**, 5755–5763; e) V. V. Gerasimchuk,A. S. Kucherenko, A. N. Fakhrutdinov, M. G. Medvedev, Y. V. Nelyubina, S. G. Zlotin, *Eur. J. Org. Chem*. **2017**, 2540–2544; f)
[11] R. P. Jumde, A. Mandoli, *ACS Catal*. **2016**, *6(7)*, 4281−4285.
[12] J.-Wo. Lee, T. Mayer-Gall, K. Opwis, C. E. Song, J. S. Gutmann, B. List, *Science* **2013**, *341*, 1225−1229.
[13] a) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417; b) K. S. Yang, A. E. Nibbs, Y. E. Turkmen, V. H. Rawal, *J. Am. Chem. Soc.* **2013**, *135*, 16050-16053; c) M. Rombola , C. S. Sumaria, T. D. Montgomery, V. H. Rawal, *J. Am. Chem. Soc.*, **2017**, *139*, 5297–5300; d)W. Yang, H. X. He, Y Gao, D.M. Du, *Adv. Synth. Catal*. **2013**, *355*, 3670–3678.
[14] S. Kim, K.-T. Kang, S.-G. Kim, *Tetrahedron* **2014**, *70*, 5114–5121.
[15] E. V. Filatova, O. V. Turova, A. G. Nigmatov, S. G. Zlotin, *Tetrahedron* **2018**, *74*, 157-164.
[16] J. M. Andres, A. Maestro, M. Valle, R. Pedrosa, *J. Org. Chem.* **2018**, *83*, 5546–5557.
[17] a) P. Kasaplar, P. Riente, C. Hartmann, M. A. Pericas, *Adv. Synth. Catal*. **2012**, *354*, 2905–2910; b) G. Kardos, T. Soos, *Eur. J. Org. Chem*. **2013**, 4490–4494; c)P. Kasaplar, C. Rodriguez-Escrich, M. A. Pericas, *Org. Lett.* **2013**, *15*, 3498–3501; d) X. Xu, T. Cheng, X. Liu, J. Xu,; R. Jin, G. Liu, *ACS Catal*. **2014**, *4*, 2137−2142; e) E. Veverkova, S. Bilka, R. Baran, R. Sebesta, *Synthesis* **2016,** *48*, 1474–1482.
[18] R. S.Tukhvatshin, A. S. Kucherenko, Y. V. Nelyubina, S. G. Zlotin, *ACS Catal*. **2017**, *7*, 2981−2989.
[19] a) A. S. Amarasekara, *Chem. Rev.* **2016**, *116*, 6133–6183; b) R. Ratti, *Adv. Chem.* **2014**, *2014*, 16.
[20] M. C. Maillard, M. E. Perlman, O. Amitay, D. Baxter, D. Berlove, S. Connaughton, J. B. Fischer, J. Q. Guo, L.-Y. Hu, R. N. McBurney, P. I. Nagy, K. Subbarao, E. A. Yost, L. Zhang, G. J. Durant, *J. Med. Chem*. **1998**, *41*, 3048-3061.
[21] V. K. Gore, V. V. Ma, R. Yin, J. Ligutti, D. Immke, E. M. Doherty, M. H. Norman, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 3573- 3578.
[22] a) L. G. Hamann, R. I. Higuchi, L. Zhi, J. P. Edwards, X.-N. Wang, K. B. Marschke, J. W. Kong, L. J. Farmer, T. K. Jones, *J. Med. Chem*. **1998**, *41*, 623-639; b) J. P. Edwards, R. I. Higuchi, D. T. Winn, C. L. F. Pooley, T.R. Caferro, L.G. Hamann, L. Zhi, K.B. Marschke, M.E. Goldman, T. K. Jones, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1003-1008; c) L. G. Hamann, N. S. Mani, R. L. Davis, X.-N. Wang, K. B. Marschke, T. K. Jones, *J. Med. Chem*. **1999**, *42*, 210-212; d) R. I. Higuchi, J. P. Edwards, T. R. Caffeno, J. D. Ringgenberg, J. W. Kong, L. G. Hamann, K. L. Arienti, K. B. Marschke, R. L. Davis, L. J. Farmer, T. K. Jones, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 1335-1340.
[23] a) A. Gentry, K. Cook, J. *Ethnopharmacol*. **1984**, *11*, 337- 343; b) D. A. Powell, R. A. Batey, *Org. Lett*. **2002**, *4*, 2913-2916; c) D.-W. Ma, C.-F. Xia, J.-Q. Jiang, J.-H. Zhang, *Org. Lett*. **2001**, *3*, 2189-2191; d) P. Y. Ng, C. E. Masse, J. T. Shaw, *Org. Lett*. **2006**, *8*, 3999-4002; e) Y. Yoshitomi, H. Arai, K. Makino, Y. Hamada, *Tetrahedron* **2008**, *64*, 11568- 11579.
[24] a) J. A. Sikorski, *J. Med. Chem.* **2006**, *49*, 1-22; b) M. DePasquale, G. Cadelina, D. Knight, W. Loging, S. Winter, E. Blasi, D. Perry, J. Keiser, Drug Dev. Res. **2009**, *70*, 35-48.
[25] a) V. Sridharan, P. A. Suryavanshi, J. Carlos Menendez, *Chem. Rev*. **2011**, *111*, 7157–7259; b) B. Cerra, S. Mostarda, C. Custodi, A. Macchiarulo, A. Gioiell, *Med. Chem. Commun*. **2016**, *7*, 439–446.
[26] a) E. Melendez, Inorg. Chim. Acta **2012,** 393, 36-52; b) D. Plazuk, A. Vessieres, E. A. Hillard, O. Buriez, E. Labbe, P. Pigeon, M.-A. Plamont, C. Amatore, J. Zakrzewski, G. Jaouen, *J. Med. Chem*. **2009**, *52*, 4964–4967; c) E. A. Hillard, A. Vessieres, S. Top, P. Pigeon, K. Kowalski, M. Huché, G. Jaouen, *J. Organomet. Chem*. **2007**, *692*, 1315–1326; d) E. A. Hillard, A. Vessieres, L.Thouin, G. Jaouen, C. Amatore, *Angew.Chem. Int. Ed*. **2006**, *45*, 285–290; e) A. Vessieres, S. Top, W. Beck, E. A. Hillard, G. Jaouen, *Dalton Trans*. **2006**, *4*, 529–541; f) E. A. Hillard, P. Pigeon, A. Vessieres, C. Amatore, G. Jaouen, *Dalton Trans*. **2007**, 5073–5081; g) J. Spencer, J. Amin, M. Wang, G. Packham, S. S. Syed Alwi, G. J. Tizzard, S. J. Coles, R. M. Paranal, J. E. Bradner, T. D. Hightman, *Med. Chem. Lett*. **2011**, *2*, 358-362; h) M. Librizzi, A. Longo, R. Chiarelli, J. Amin, J. Spencer, C. Luparello, *Chem. Res. Toxicol*. **2012**, *25*, 2608−2616.
[27] a) E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron* **1997**, *53*, 14355-14368; b) H. Chen, X. Lu, X. Xia, Q. Zhu, Y. Song, J. Chen, W. Cao, X. Wu, *Org. Lett.* **2018**, 20, 1760–1763.
[28] a) C. S. Schindler, C. R. J. Stephenson, E. M. Carreira, *Angew.Chem. Int. Ed*. **2008**, *47*, 8852 –8855;b) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, 132, 6286–6287; c) C. Guisado, J. E. Waterhouse, W. S. Price, M. R. Jorgensen, A. D. Miller, *Org. Biomol. Chem.* **2005**, ***3***, 1049-1057; d) Y. Harrak, C. M. Barra, A. Delgado, A. R. Castaño, A. Llebaria, *J. Am. Chem. Soc.* **2011**, 133, 12079–12084; e)_Y.Yoshimitsu, J.Miyagaki, S.Oishi, N.Fujii, H. Ohno, *Tetrahedron* **2013**, *69*, 4211-4220;f) K. Koteva, A. M. King, A. Capretta, G. D. Wright, *Angew.Chem. Int. Ed.* **2016**, *55*,2210 –2212; g) J. M. Aizpurua, C. Palomo, E. Balentová, A. Jimenez, E. Andreieff, M. Sagartzazu-Aizpurua, J. I. Miranda, A. Linden, *J. Org. Chem.* **2013**, *78*, 224–237.
[29] Z.-X. Jia, Y.-C. Luo, P.-F. Xu, *Org. Lett.* **2011**, *13*, 832–835.
[30] Z. X. Jia, Y. C. Luo, Y. Wang, L. Chen, P. F. Xu, B. Wang, *Chem. Eur. J*. **2012**, *18*, 12958-12961.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Asymmetric aza-Michael / Michael domino reaction of *N*-Ts or *N*-Nos ortho-aminochalcones with nitroolefins has been performed in the presence of highly recyclable (19 cycles) IL-supported tertiary amine–squaramide organocatalyst to afford trisubstituted tetrahydro-quinolines as single diastereomers with up to 99% *ee*. *N*-Nosylated products were converted to fused pirrolidino-tetrahydroquinolines.



Organocatalysis

Rinat S. Tukhvatshin, Alexander S. Kucherenko, Yulia V. Nelyubina,. Sergei G. Zlotin**

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Stereoselective Synthesis of Tetrahydroquinolines via Asymmetric Domino Reaction Catalyzed by Recyclable Ionic-Liquid-supported Bifunctional Tertiary Amine