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Asymmetric nucleophilic dearomatization of diazaarenes by anion-binding catalysis†

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The first anion-binding organocatalyzed enantioselective Reissert-type dearomatization of diazaarenes has been developed. This reaction represents a synthetic challenge since diazaarenes have various reactive sites. The use of a chiral tetrakis(triazole) as a C–H-based hydrogen-donor catalyst allowed the straightforward highly regio- and enantioselective synthesis of a variety of chiral diazaheterocycles.

Introduction

Chiral diazaheterocycles and their partial unsaturated derivatives are important naturally occurring substances and building blocks for the synthesis of bioactive compounds with a broad activity spectrum.¹ A few examples of relevant natural and synthetic bioactive di-nitrogen-containing chiral heterocycles are shown in Fig. 1.

Among some interesting quinazoline derivatives, *letermovir*² is one of the top-selling antiviral drugs developed for the treatment of *Cytomegalovirus* infections and the alkaloid *vasicine*³

is a cardiac-depressant. Moreover, based on a pyrazine moiety, *matlystain B* shows collagenase inhibitor properties.⁴ Other di- or tetrahydro-structures based on diazaarenes such as quinoxaline, naphthyridine or phthalazine present relevant biological activities such as CETP inhibition against atherosclerosis,⁵ anti-dyslipidemia⁶ or dihydrofolate reductase inhibition towards antibiotic-resistant Gram-positive bacteria.⁷

Despite the great diversity of applications of chiral diazaheterocycles, there is still a demand of simple, mild and direct synthesis methods. Most of the common routes to chiral diazaheterocycles require long and tedious synthesis from chiral starting materials and normally involve the generation of at least one of the *N*-heterocyclic rings.¹ A more appealing and straightforward approach consists of the enantioselective dearomatization of readily available diazaarenes (Scheme 1).⁸

In this regard, the main method for inducing chirality relies on catalyzed asymmetric hydrogenation reactions of

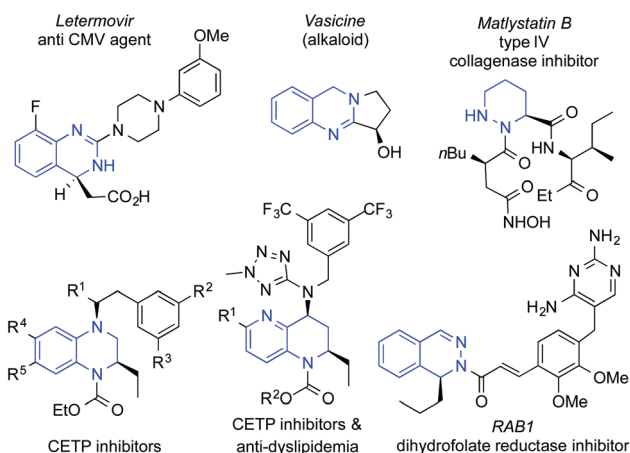
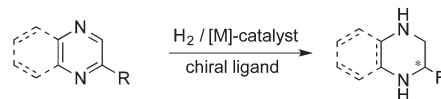
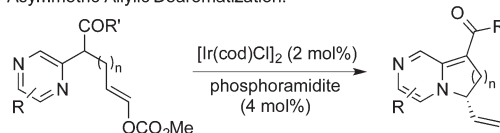


Fig. 1 Selected bioactive chiral diazaheterocycles.

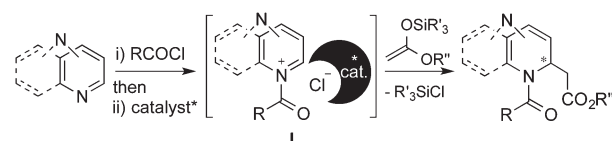
(1) Asymmetric Hydrogenation:



(2) Asymmetric Allylic Dearomatization:



(3) This work: Anion-Binding Catalysis Approach



Scheme 1 Asymmetric dearomatization of diazaarenes.

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substituted azarenes (Scheme 1, (1)).⁹ Several methods based on enantioselective nucleophilic additions have been developed for mono *N*-heteroarenes.¹⁰ However, to the best of our knowledge only one example for diazaarenes, the intramolecular allylic amination of pyrazines, has been described to date (Scheme 1, (2)).¹¹ This fact could be attributed to the more challenging dearomatization of diazaarenes due to the presence of a larger number of reactive sites and the possible generation of a complex mixture of products.

Recently, we have described the use of a family of triazole-based H-bond donors¹² as efficient anion-binding catalysts¹³ for the asymmetric nucleophilic dearomatization of *N*-heteroarenes such as isoquinolines, quinolines and pyridines.¹⁴ Aiming at the development of a new entry for the synthesis of chiral diazaheterocycles, we decided to explore these H-donor catalysts for the related dearomatization of various types of 6-membered ring-containing diazaarenes (Scheme 1, (3)). Accordingly, we anticipated successful chiral transfer from a contact ion-pair **I** formed between an ionic intermediate and the catalyst-counter anion complex. In this article, we present a highly enantioselective dearomatization of *in situ* generated *N*-acyldiazaarene chloride salts (Reissert-type reaction)¹⁵ with silyl ketene acetals catalyzed by a chiral tetrakis-triazazole.

Results and discussion

Our studies started with quinazoline (**3a**) as the model substrate (Table 1). Various chiral H-donor catalysts such as

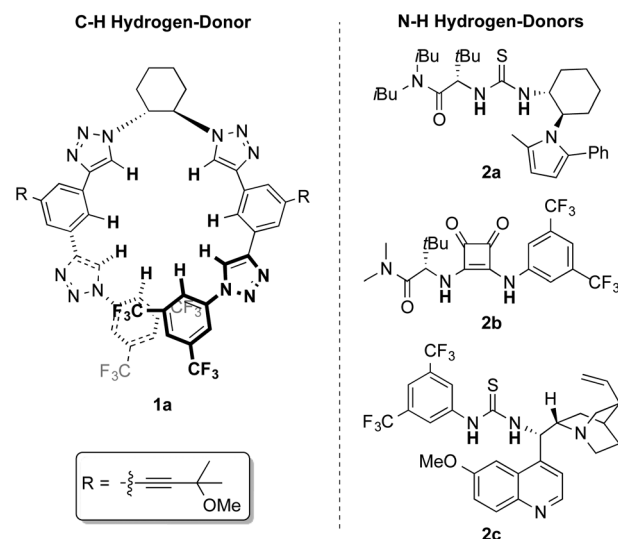


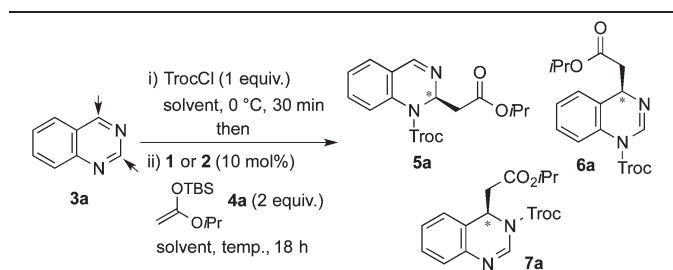
Fig. 2 H-donor catalysts tested in this study.

tetrakis-triazazole **1a**,¹⁴ Jacobsen's thiourea **2a**,¹⁶ squaramide **2b**¹⁷ and bifunctional thiourea-cinchona alkaloid **2c**¹⁸ were initially explored (Fig. 2).

Following previously reported procedures,^{14,16} 2,2,2-trichloroethyl chloroformate (TrocCl) was employed to generate *in situ* the required quinazolinium chloride salt in MTBE at 0 °C. Subsequent addition of the silyl ketene acetal **4** and the H-donor catalyst **1** or **2** at –78 °C (allowing the reaction mixture to warm up to room temperature overnight) delivered the dearomatized product. It is worth mentioning that there was an appreciable background reaction in the absence of a catalyst (entry 1, 56%). Fortunately the heterocycle **5a** was formed regioselectively, not observing the formation of other possible isomers **6a** and **7a**. The catalytic reactions also showed complete regioselectivity towards **5a**. From the catalysts tested in this study (entries 2–5), the triazole-based H-donor **1a** proved to be the most efficient in terms of both reactivity and enantioselectivity. Thus, **5a** was obtained in 65% yield and 96:4 er (entry 2),¹⁹ whereas the other catalysts delivered the dearomatized product in significantly low yields (13–34%) and low to moderate enantiomeric inductions (45:55–61:39 er vs. 96:4 er). The change to other ethereal solvents such as Et₂O was not beneficial, hampering the enantioselectivity (84:16 er, entry 6). When the reaction was carried out at a continuous temperature of –78 °C, the same enantiomeric result (96:4 er, entry 7) was obtained. A similar procedure at –40 °C led to **5a** in a lower 86:14 er (entry 8). Lastly, the use of 5 mol% of catalyst **1a** provided an inferior chiral induction (91:9 er, entry 9). Therefore, 10 mol% of catalyst loading and a slow temperature-gradient (from –78 °C to r.t.) were employed as optimal conditions for further studies.

Next, screening of the acylation reagents and silyl ketene acetals **4** was carried out (Table 2). CbzCl and methoxycarboxylic chloride could also be employed as acylating reagents (entries 2 and 3). However, a significantly lower

Table 1 Optimization of the reaction with **3a**^a



Entry	Catalyst	Solvent	T (°C)	Yield ^b (%)	5a : 6a : 7a ^c	5a, er ^d
1	—	MTBE	–78–rt	56	91 : 9 : — ^e	—
2	1a	MTBE	–78–rt	65	92 : 8 : — ^e	96 : 4
3	2a	MTBE	–78–rt	34	92 : 8 : — ^e	61 : 39
4	2b	MTBE	–78–rt	21	92 : 8 : — ^e	46 : 54
5	2c	MTBE	–78–rt	13	92 : 8 : — ^e	45 : 55
6	1a	Et ₂ O	–78–rt	61	91 : 9 : — ^e	84 : 16
7	1a	MTBE	–78	88	92 : 8 : — ^e	96 : 4
8	1a	MTBE	–40	54	92 : 8 : — ^e	86 : 14
9	1a	MTBE	–78–rt	66	92 : 8 : — ^e	91 : 9 ^f

^a Conditions: (i) **3a** (1 equiv.) and TrocCl (1 equiv.) were stirred in an appropriate dry solvent at 0 °C for 30 min; then (ii) catalyst **1** or **2** (10 mol%) and **4a** (2 equiv.) were added at –78 °C and stirred for 18 h while allowing to reach slowly rt. ^b Isolated yield. ^c Isomeric ratios determined by ¹H-NMR of the crude reaction. ^d Enantiomeric ratios determined by chiral HPLC. ^e Isomer **7a** was not detected by NMR. ^f Reaction using 5 mol% of catalyst **1a**.



Table 2 Screening of the acylating agent and silyl ketene acetal 4^a

Entry	R ¹ C(O)Cl	XR ² /R ³	Product 5	Yield ^b (%)	5, er ^c
1	TrocCl	O <i>i</i> Pr/H		65	96 : 4 (98 : 2) ^d
2	CbzCl	O <i>i</i> Pr/H		71	60 : 40 (n.d.) ^d
3	MeOCOC	O <i>i</i> Pr/H		n.d. ^e	n.d. ^e (84 : 16) ^d
4	TrocCl	OMe/H		72	72 : 28 (94 : 6) ^d
5	TrocCl	O <i>t</i> Bu/H		62	83 : 17 (95 : 5) ^d
6	TrocCl	OEt/Me		91	88 : 12 (major) 73 : 27 (minor) [5 : 1 dr] ^f

^a Conditions: (i) **3a** (1 equiv.) and R¹COCl (1 equiv.) were stirred in dry MTBE at 0 °C for 30 min; then (ii) catalyst **1a** (10 mol%) and **4** (2 equiv.) were added at –78 °C and stirred for 18 h while allowing to reach slowly rt. ^b Isolated yield. ^c Enantiomeric ratios determined by chiral HPLC. ^d Isomeric ratios **5** : **6** determined by ¹H-NMR of the crude reaction in brackets. ^e An inseparable mixture of **5ac**, **6ac** and starting material **3a**. ^f Reaction with a 1 : 0.8 isomeric mixture of silyl ketene acetal **4d**. The diastereomeric ratio of **5af** was determined by ¹H-NMR of the crude reaction. n.d. = not determined.

enantioselectivity and a deficient conversion accompanied by a poor regioselectivity were respectively observed.

Silyl ketene acetals **4** derived from acetic acid presenting different substitution such as less hindered MeO (**4b**, entry 4) or bulkier *t*BuO (**4c**, entry 5) groups, as well as a propionic acid derivative (**4d**, entry 6) were then explored. Moderate to good enantioselectivities were achieved (72 : 28 to 88 : 12 er), where the initial *i*PrO-substituted ketene acetal **4a** remained the most efficient nucleophile.

Based on these results, the screening of the substrate scope was next carried out with catalyst **1a**, TrocCl, silyl ketene acetal **4a** and a number of representative, readily available mono- and bicyclic diazaarenes in MTBE (Table 3).¹⁹ It is important to mention that the reaction could be scaled-up to approximately 40 times (0.5 g scale) without any significant detriment to the

enantioselectivity of the reaction (92 : 8 er, entry 1). Moreover, the catalyst could be re-isolated in a good 74% yield and reused, delivering the same reactivity and stereochemical results. The study continued with the dearomatization of the analogous diazaarene quinoxaline (**3b**), which also presents both nitrogen atoms in the same aromatic unit (entry 2). Although this substrate reminds of the structure of quinoline, only a complex mixture was obtained, in which the double addition of the TrocCl to both nitrogen atoms could also be observed. The dearomatization of the highly symmetric phthalazine (**3c**), exhibiting only one equivalent reactive α-position, yielded compound **5c** in a good 93% yield and 76 : 24 enantiomeric ratio (entry 3). In the case of 1,5-naphthyridine (**3d**), which has one nitrogen atom in each ring, the challenge was again the control of the regioselectivity since both the C4 and



Table 3 Scope of the reaction with various diazares^a

Entry	Diazarene 3	Products 5/6	Yield ^b (%) [5 : 6] ^c	5, er ^d	6, er ^d
1			65% (42%), ^e 5a [92 : 8]	96 : 4 (92 : 8) ^e	—
2			5b , decomp.	—	—
3			93% (45%), ^g 5c	76 : 24 (79 : 21) ^g	—
4			86%, 5d 5%, 6d [95 : 5]	83 : 17	62 : 38
5			56%, 5e ^f	80 : 20	—
6			74% (38%), ^g 5f	63 : 37 (61 : 39) ^g	—
7			87%, 5g 6%, 6g [94 : 6]	73 : 27	52 : 48
8			72%, 5h	66 : 34	—
9			5i , decomp.	—	—

^a Conditions: (i) **3** (1 equiv.) and TrocCl (1 equiv.) were stirred in dry MTBE at 0 °C for 30 min; (ii) catalyst **1a** (10 mol%) and **4** (2 equiv.) were added at –78 °C, and stirred for 18 h while allowing to reach slowly rt. ^b Isolated yield. ^c Isomeric ratios determined by ¹H-NMR. ^d Enantiomeric ratios determined by chiral HPLC. ^e Scale-up reaction in brackets: **3a** (500 mg, 3.85 mmol). ^f Other possible isomers were not detected by NMR. ^g Reaction at –78 °C in brackets.

C2 positions of each heteroaromatic ring are prone to nucleophilic addition (entry 4). A good regioselectivity of 95 : 5 was obtained in favour of the desired C2-addition product **5d**. After the separation from the minor 4-addition product **6d**, compound **5d** was obtained in a 86% yield and a good 83 : 17 enantiomeric ratio. Next, 1,6-naphthyridine (**3e**) was explored as a substrate (entry 5). Since this compound contains both

the quinoline and the isoquinoline unit, it was interesting to get a deeper understanding about the reactivity, regioselectivity and enantioselectivity of this type of mixed structure. Due to the higher intrinsic reactivity of the benzylic position within the isoquinoline core, a high regioselectivity could be expected. Consequently, **5e** was obtained as a single isomer and with high enantioselectivity (80 : 20 er). The



reaction with methyl-substituted 1,8-naphthyridine (**3f**) proceeded smoothly, providing exclusively compound **5f** in a good 74% yield and a significantly lower enantioselectivity (63:37 er, entry 6). This unexpected result compared to other naphthyridines cannot be easily rationalized, since in the previous work the related monoazarene quinolines provided very high enantioselectivities for this type of reaction (typically >95:5 er).^{14a} As the dearomatization of the bicyclic diazaenes showed a good performance and a moderate to excellent enantioselectivity, a more challenging six-membered monocyclic heteroarene was next explored. Pyridazine (**3g**) was again nicely enrolled in the catalytic dearomatization reaction, providing a good 93% overall yield and a 94:6 mixture of the 2- (**5g**) and 4-addition (**6g**) products (entry 7). Remarkably, an acceptable 73:27 enantiomeric ratio was obtained for the more interesting 2-addition product **5g**, whereas for the minor regioisomer **6g** an almost racemic compound was formed. This can be explained by the greater distance of the newly introduced stereocenter at the C4 with respect to the C2 position to the positive nitrogen present in the key ionic intermediate. Consequently, the catalyst-chloride anion complex should stay in close proximity to the nitrogen atom and therefore, the chirality transfer might be more efficient in the adjacent C2-position. Lastly, the reaction with five membered diazaenes was carried out. While *N*-methyl benzimidazole provided the desired dearomatized heterocycle **5h** in a good yield and moderate enantioselectivity (72%, 66:34 er; entry 8), *N*-methyl pyrazole led to a complex mixture of decomposition products.²⁰

Finally, the synthetic utility of this method was demonstrated by the derivatization of **5a**. Thus, the corresponding

tetrahydro derivative **8** was synthesized by reduction with NaBH₄ in the presence of B(OH)₃^{21,22} and the dimethyl derivative **9** by trans-esterification with *in situ* generated KOMe with K₂CO₃ in MeOH (Scheme 2). Moreover, the Troc protecting group could easily be removed from **5a** using Zn and NH₄OAc at room temperature, providing the corresponding *N*-deprotected product **10** in 97% yield.

Conclusions

In conclusion, the first enantioselective nucleophilic dearomatization of diazaenes using an anion-binding organocatalysis approach has been developed. Tetrakis-triazole-based H-bond donor catalysts were superior to other known hydrogen-bond donors, providing the corresponding products in high regioselectivities and up to 96:4 er. This method allows rapid access to substituted chiral di- or tetrahydro diazaheterocycles.

Experimental section

General methods

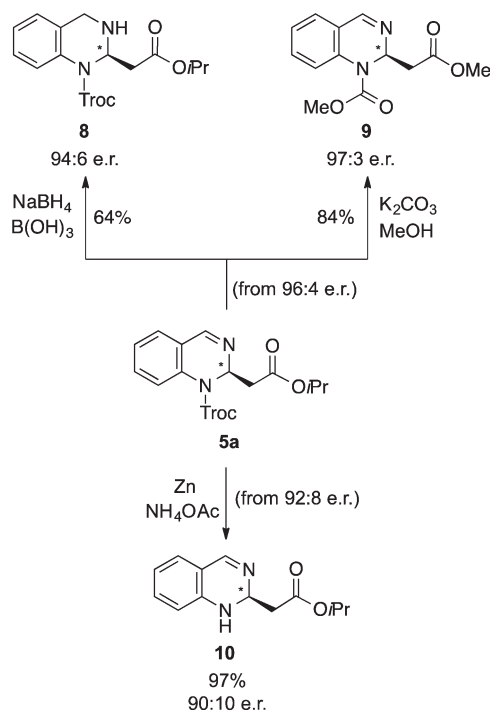
¹H- and ¹³C-NMR spectra were recorded in CDCl₃ (reference signals: ¹H = 7.26 ppm, ¹³C = 77.16 ppm) on a Bruker ARX-300 and a Varian AV-300, 400 or 600 MHz. Chemical shifts (δ) are given in ppm and spin-spin coupling constants (*J*) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and a solution of KMnO₄ served as the staining agent. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). Exact masses (HRMS) were recorded on an Agilent Q-TOF 6540 UHD spectrometer using electrospray (ES) or chemical (CI) ionization techniques. Chiral High Pressure Liquid Chromatography (HPLC) analyses were performed on an Agilent 1200 series instrument.

MTBE and Et₂O were distilled and dried over Na. The catalysts **1a**¹⁴ and **2a–c**,^{16–18} and the silyl ketene acetals **4**,^{14a,16} were prepared following the known literature procedures. The starting materials and other commercially available reagents were used without further purification.

General organocatalytic procedure

The diazaene **3** (0.10 mmol, 1.0 equiv.) was dissolved in freshly distilled anhydrous MTBE (1 mL, 0.1 M) and cooled to 0 °C. After the addition of 2,2,2-trichloroethyl chloroformate (14 μ L, 0.10 mmol, 1.0 equiv.) the reaction was stirred for 30 min at 0 °C and then cooled to –78 °C. Isopropyl TBS-ketene acetal **4a** (51 μ L, 0.20 mmol, 2.0 equiv.) and the catalyst **1a** (11.2 mg, 0.01 mmol, 10 mol%) were added and stirred overnight. The solution was allowed to warm slowly to room temperature during that time. The crude product was purified by flash column chromatography (petrol ether/EtOAc 10:1).

2,2,2-Trichloroethyl (R)-2-(2-isopropoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5a). Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to a



Scheme 2 Derivatization of the quinazoline derivative **5a**.



98:2 mixture of **5a** and **6a**. The main product **5a** (26.5 mg, 0.065 mmol, 65%) was isolated by column chromatography. The enantiomeric ratio was determined as 96:4 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min⁻¹, λ = 300 nm: t_r (minor): 14.0 min, t_r (major): 22.2 min]. [α]₅₈₉²⁰: -91.5 (c 0.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 8.08 (s, 1H), 7.36–7.31 (m, 2H), 7.25–7.15 (m, 2H), 5.77–5.60 (m, 1H), 5.14–4.75 (m, 3H), 2.81–2.70 (m, 1H), 2.70–2.58 (m, 1H), 1.16 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.9, 150.8, 140.7, 138.7, 129.2, 127.7, 126.1, 126.2, 124.8, 94.3, 75.7, 68.6, 50.7, 41.8, 21.7, 21.6; HRMS (ESI): m/z calculated for [C₁₆H₁₈Cl₃N₂O₄]⁺: 407.0327; found 407.0333.

Benzyl (R)-2-(2-isopropoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ab). Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 equiv.), benzylchloroformate (14.2 μ L, 0.100 mmol, 1.0 equiv.), catalyst **1a** and **4a** were added according to the general procedure, leading to the desired product **5ab** (26.1 mg, 0.071 mmol, 71%). The enantiomeric ratio was determined as 60:40 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min⁻¹, λ = 300 nm: t_r (minor): 26.6 min, t_r (major): 38.2 min]. [α]₅₈₉²⁰: -13.2 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 8.07 (s, 1H), 7.44–7.35 (m, 5H), 7.32–7.28 (m, 2H), 7.19 (m, 2H), 5.66 (t, J = 6.3 Hz, 1H), 5.32 (d, J = 3.5 Hz, 2H), 4.97–4.84 (sept, 1H), 2.63 (m, 2H), 1.14 (d, J = 5.9 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): 169.1, 145.6, 141.8, 134.8, 129.1, 128.8, 128.8, 128.4, 127.4, 126.1, 125.9, 125.0, 69.0, 68.5, 50.5, 42.0, 29.7, 21.6; HRMS (ESI): m/z calculated for [C₂₁H₂₃N₂O₄]⁺: 367.1652; found 367.1658.

Methyl (R)-2-(2-isopropoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ac). Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 equiv.), MeOCOCl (7.7 μ L, 0.100 mmol, 1.0 equiv.), catalyst **1a** and **4a** were added according to the general procedure, leading to an inseparable mixture of the desired product **5ac**, the 4-addition by-product **6ac** and the starting material (see the ESI† for the NMR of the mixture).

2,2,2-Trichloroethyl (R)-2-(2-methoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ad). Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalyst **1a** and the silyl ketene acetal **4b** (45.0 μ L, 0.200 mmol, 2.0 equiv.) were added according to the general procedure, leading to the desired product **5ad** (27.2 mg, 0.072 mmol, 72%). The enantiomeric ratio was determined as 72:28 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min⁻¹, λ = 300 nm: t_r (minor): 28.0 min, t_r (major): 36.7 min]. [α]₅₈₉²⁰: -39.6 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 8.03 (s, 1H), 7.29 (m, 2H), 7.20–7.08 (m, 2H), 5.65 (t, J = 6.2 Hz, 1H), 4.87 (s, 2H), 3.58 (s, 3H), 2.68 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 169.8, 147.1, 138.7, 129.3, 127.8, 126.4, 126.1, 124.8, 94.3, 75.7, 52.1, 50.7, 29.7; HRMS (ESI): m/z calculated for [C₁₄H₁₄Cl₃N₂O₄]⁺: 379.0014; found 379.0019.

2,2,2-Trichloroethyl (R)-2-(2-(tert-butoxy)-2-oxoethyl)quinazoline-1(2H)-carboxylate (5ae). Quinazoline (**3a**) (13.0 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalyst **1a** and the silyl ketene acetal **4c** (54.0 μ L, 0.200 mmol, 2.0 equiv.) were added according to the general procedure, leading to the desired product **5ae** (26.2 mg, 0.062 mmol, 62%). The enantiomeric ratio was

determined as 83:17 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98:2), 1.0 mL min⁻¹, λ = 300 nm: t_r (minor): 13.90 min, t_r (major): 21.4 min]. [α]₅₈₉²⁰: -1.7 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 8.09 (s, 1H), 7.36–7.30 (m, 2H), 7.24–7.16 (m, 2H), 5.72–5.61 (t, J = 11.8, 1H), 4.91 (s, 2H), 2.80–2.53 (m, 2H), 1.35 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.56, 150.85, 138.68, 129.20, 127.67, 126.28, 124.89, 94.36, 81.48, 75.67, 50.80, 40.86, 27.89; HRMS (ESI): m/z calculated for [C₁₇H₂₀Cl₃N₂O₄]⁺: 421.0483; found 421.0487.

2,2,2-Trichloroethyl (R)-2-(1-ethoxy-1-oxopropan-2-yl)quinazoline-1(2H)-carboxylate (5af). Quinazoline (**3a**) (26.0 mg, 0.20 mmol, 1.0 equiv.), TrocCl, catalyst **1a** and the silyl ketene acetal **4d** (150.0 μ L, 0.20 mmol, 2.0 equiv.; 1:0.8 *E/Z* mixture) were added according to the general procedure, leading to the desired product **5af** (74.5 mg, 0.18 mmol, 91%) as a 5:1 mixture of diastereomers. The enantiomeric ratio was determined as 88:12 er for the major diastereoisomer and 73:27 for the minor diastereoisomer by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (95:5), 1.0 mL min⁻¹, λ = 290 nm: major isomer: t_r (minor): 9.23 min, t_r (major): 16.54 min; minor: t_r (minor): 7.78 min, t_r (major): 11.76 min]. ¹H NMR (300 MHz, CDCl₃) (major): δ 8.13 (s, 1H), 7.33 (d, J = 3.9 Hz, 2H), 7.21 (m, 1H), 7.02 (d, J = 7.3 Hz, 1H), 5.70 (bs, 1H), 5.03–4.79 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.89 (bs, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H); ¹H NMR (300 MHz, CDCl₃) (minor): δ 8.11 (s, 1H), 7.33 (d, J = 3.9 Hz, 2H), 7.21 (m, 1H), 7.12 (d, J = 7.5 Hz, 1H), 5.54 (bs, 1H), 5.03–4.77 (m, 2H), 4.07–3.95 (m, 2H), 2.80–2.69 (m, 1H), 1.15 (t, J = 4.5 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 172.8, 172.2, 172.1, 151.4, 141.3, 139.4, 129.3, 129.2, 127.6, 126.6, 126.5, 126.2, 126.1, 94.3, 75.8, 75.7, 61.1, 55.3, 46.6, 24.0, 14.2, 14.0; HRMS (ESI): m/z calculated for [C₁₆H₁₈Cl₃N₂O₄]⁺: 407.0327; found 407.0329.

2,2,2-Trichloroethyl (R)-1-(2-isopropoxy-2-oxoethyl)phthalazine-2(1H)-carboxylate (5c). Phthalazine (**3c**) (13.0 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to the desired product **5c** (38 mg, 0.093 mmol, 93%). The enantiomeric ratio was determined as 76:24 er by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (99:1), 1.0 mL min⁻¹, λ = 290 nm: t_r (minor): 44.4 min, t_r (major): 46.8 min]. [α]₅₈₉²⁰: -145.0 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.81 (bs, 1H), 7.56–7.38 (m, 2H), 7.36–7.29 (m, 2H), 5.97 (t, J = 7.1 Hz, 1H), 5.12–5.00 (m, 1H), 4.94 (sept, J = 6.3 Hz, 1H), 4.90–4.81 (m, 1H), 2.83–2.50 (m, 2H), 1.20 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.9, 145.1, 144.2, 132.4, 132.0, 128.9, 126.5, 126.3, 123.2, 95.0, 75.6, 68.5, 50.7, 39.5, 21.7, 21.7; HRMS (ESI): m/z calculated for [C₁₆H₁₈Cl₃N₂O₄]⁺: 407.0327; found 407.0333.

2,2,2-Trichloroethyl (R)-2-(2-isopropoxy-2-oxoethyl)-1,5-naphthyridine-1(2H)-carboxylate (5d) and 2,2,2-trichloroethyl (R)-4-(2-isopropoxy-2-oxoethyl)-1,5-naphthyridine-1(4H)-carboxylate (6d). 1,5-Naphthyridine (**3d**) (13.0 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to a 95:5 mixture of **5d** and **6d**. The mixture of isomers were separated and isolated by flash



column chromatography to yield the 2-addition product **5d** (35.6 mg, 0.086 mmol, 86%) and the 4-addition **6d** (2.0 mg, 0.005 mmol, 5%).

5d: The enantiomeric ratio was determined as 83 : 17 er by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 280 nm: t_r (minor): 13.8 min, t_r (major): 29.7 min]. [α]₅₈₉²⁰: -147.2 (c 0.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 8.33 (d, J = 4.6 Hz, 1H), 8.01 (bs, 1H), 7.19 (dd, J = 8.3, 4.8 Hz, 1H), 6.75 (d, J = 9.9 Hz, 1H), 6.43 (dd, J = 9.8, 5.8 Hz, 1H), 5.53 (dd, J = 13.4, 6.9 Hz, 1H), 5.01 (bs, 1H), 4.97 (sept, J = 6.3 Hz, 1H), 4.72 (bs, 1H), 2.60–2.40 (m, 2H), 1.17 (d, J = 8.9 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 169.1, 152.0, 145.7, 132.3, 127.3, 122.5, 94.8, 75.6, 68.5, 50.2, 38.9, 21.8, 21.7; HRMS (ESI): m/z calculated for [C₁₆H₁₈Cl₃N₂O₄]⁺: 407.0327; found 407.0332.

6d: The enantiomeric ratio was determined as 62 : 38 er by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 230 nm: t_r (minor): 8.9 min, t_r (major): 9.7 min]. [α]₅₈₉²⁰: +4.8 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 8.43 (d, J = 8.5 Hz, 1H), 8.37 (dd, J = 4.7, 1.4 Hz, 1H), 7.21 (dd, J = 8.4, 4.6 Hz, 1H), 7.07 (dd, J = 8.0, 0.9 Hz, 1H), 5.50 (dd, J = 8.0, 4.5 Hz, 1H), 5.03 (sept., J = 6.3 Hz, 1H), 4.94 (d, J = 11.9 Hz (AB system), 1H), 4.80 (d, J = 11.9 Hz (AB system), 1H), 4.04 (dt, J = 9.2, 4.6 Hz, 1H), 2.92 (dd, J = 15.7, 5.1 Hz, 1H), 2.64 (dd, J = 15.7, 8.9 Hz, 1H), 1.21 (d, J = 6.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 171.0, 150.6, 150.5, 148.6, 146.0, 128.5, 124.7, 121.8, 113.1, 94.7, 75.6, 67.9, 40.9, 36.7, 21.8; HRMS (ESI): m/z calculated for [C₁₆H₁₈Cl₃N₂O₄]⁺: 407.0327; found 407.0331.

2,2,2-Trichloroethyl (R)-5-(2-isopropoxy-2-oxoethyl)-1,6-naphthyridine-6(5H)-carboxylate (5e). 1,6-Naphthyridine (**3e**) (13.0 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to a 1 : 1.6 mixture of rotamers of the titled product **5e** (23.0 mg, 0.056 mmol, 56%). The enantiomeric ratio was determined as 80 : 20 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 290 nm: t_r (minor): 15.8 min, t_r (major): 23.2 min]. [α]₅₈₉²⁰: -65.0 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 8.45 (dd, J = 4.9, 1.5 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.21–7.14 (m, 1H), 7.13–7.04 (m, 1H), 6.21 (d, J = 8.1 Hz, 1H, minor rotamer), 6.16 (d, J = 8.0 Hz, 1H, major rotamer), 5.86 (dd, J = 7.5, 6.3 Hz, 1H), 5.07–4.86 (m, 2H), 4.78 (bd, J = 15.2, 1H), 2.94–2.58 (m, 2H), 1.22–1.07 (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 169.2, 150.8, 149.3, 134.4, 129.3, 129.2, 128.2, 126.5, 126.4, 122.03, 121.8, 111.0, 94.9, 75.8, 68.6, 52.9, 40.4, 39.6, 21.8; HRMS (ESI): m/z calculated for [C₁₆H₁₈Cl₃N₂O₄]⁺: 407.0327; found 407.0334.

2,2,2-Trichloroethyl (R)-2-(2-isopropoxy-2-oxoethyl)-7-methyl-1,8-naphthyridine-1(2H)-carboxylate (5f). 2-Methyl-1,8-naphthyridine (**3f**) (14.4 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to the desired product **5f** (31.0 mg, 0.074 mmol, 74%). The enantiomeric ratio was determined as 63 : 37 er by chiral HPLC [Chiralcel OD-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 290 nm: t_r (minor): 13.4 min, t_r (major): 22.1 min]. [α]₅₈₉²⁰: +4.0 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.31 (d, J = 7.6 Hz, 1H), 6.94 (dd, J = 7.7,

0.4 Hz, 1H), 6.47 (d, J = 9.5 Hz, 1H), 6.16 (dd, J = 9.5, 5.8 Hz, 1H), 5.51 (dt, J = 10.0, 5.5 Hz, 1H), 5.05–4.92 (m, 1H), 4.99 (d, J = 11.9 Hz, 1H), 4.72 (d, J = 11.9 Hz, 1H), 2.64 (dd, J = 15.3, 5.3 Hz, 1H), 2.51 (s, 3H), 2.48 (dd, J = 15.3, 9.7 Hz, 1H), 1.22 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 169.3, 156.7, 152.1, 146.6, 134.4, 128.3, 124.1, 120.4, 119.2, 94.9, 75.7, 68.3, 51.2, 39.3, 24.3, 21.8; HRMS (ESI): m/z calculated for [C₁₇H₂₀Cl₃N₂O₄]⁺: 421.0483; found 421.0486.

2,2,2-Trichloroethyl (R)-6-(2-isopropoxy-2-oxoethyl)pyridazine-1(6H)-carboxylate (5g) and 2,2,2-trichloroethyl (R)-4-(2-isopropoxy-2-oxoethyl)pyridazine-1(4H)-carboxylate (6g). Pyridazine (**3g**) (7.3 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to a 94 : 6 mixture of **5g** and **6g**. The mixture of isomers was separated and isolated by flash column chromatography to yield the 2-addition product **5g** (31.0 mg, 0.087 mmol, 87%) and the 4-addition product **6g** (2.2 mg, 0.006 mmol, 6%).

5g: The enantiomeric ratio of the main product was determined as 73 : 27 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 300 nm: t_r (minor): 15.3 min, t_r (major): 18.2 min]. [α]₅₈₉²⁰: -245.0 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.24 (bs, 1H), 6.39 (ddd, J = 9.6, 6.1, 1.7 Hz, 1H), 5.97 (dd, J = 9.7, 3.2 Hz, 1H), 5.43–5.23 (m, 1H), 5.16–4.61 (m, 3H), 2.83–2.30 (m, 2H), 1.22 (d, J = 6.3 Hz, 6H); ¹³C NMR (75 MHz, acetone-*d*₆): δ 168.9, 152.7, 141.4, 132.0, 117.4, 95.0, 75.5, 68.5, 47.8, 38.1, 21.8; HRMS (ESI): m/z calculated for [C₁₂H₁₆Cl₃N₂O₄]⁺: 357.0175; found 357.0175.

6g: The enantiomeric ratio was determined as 52 : 48 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 230 nm: t_r (minor): 17.8 min, t_r (major): 19.9 min]. [α]₅₈₉²⁰: -2.0 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.06 (d, J = 8.4 Hz, 1H), 7.02 (bs, 1H), 5.18–4.95 (m, 2H), 4.92 (s, 2H), 3.46–3.27 (m, 1H), 2.53 (dd, J = 16.1, 6.9 Hz, 1H), 2.43 (dd, J = 16.1, 7.3 Hz, 1H), 1.24 (d, J = 6.2 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 169.9, 154.0, 142.7, 123.2, 94.7, 75.5, 68.6, 39.7, 28.8, 21.8; HRMS (ESI): m/z calculated for [C₁₂H₁₆Cl₃N₂O₄]⁺: 357.0175; found 357.0183.

2,2,2-Trichloroethyl 2-(2-isopropoxy-2-oxoethyl)-3-methyl-2,3-dihydro-1H-benzo[d]imidazole-1-carboxylate (5h). 1-Methyl-benzimidazole (**3h**) (13.2 mg, 0.100 mmol, 1.0 equiv.), TrocCl, catalysts **1a** and **4a** were added according to the general procedure, leading to the desired product **5h** (29.4 mg, 0.072 mmol, 72%). The enantiomeric ratio was determined as 66 : 34 er by chiral HPLC [Chiralcel OJ-H, hexane/iPrOH (98 : 2), 1.0 mL min⁻¹, λ = 300 nm: t_r (minor): 10.5 min, t_r (major): 12.0 min]. (Note: unstable compound. Partial decomposition occurred during the structural analysis.) [α]₅₈₉²⁰: -12.7 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.62–7.39 (m, 1H), 6.94 (dd, J = 7.7, 6.9 Hz, 1H), 6.71 (bd, J = 7.0 Hz, 1H), 6.48 (d, J = 7.7 Hz, 1H), 5.79 (bd, J = 9.8 Hz, 1H), 5.15–4.68 (m, 3H), 2.92 (s, 5H), 1.14 (d, J = 6.3 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 169.3, 149.2, 142.3, 124.6, 118.9, 118.7, 114.1, 109.9, 107.3, 78.8, 78.3, 75.7, 75.0, 68.4, 40.3, 38.9, 34.7, 34.2, 21.8, 21.7; HRMS (ESI): m/z calculated for [C₁₆H₂₀Cl₃N₂O₄]⁺: 409.0483; found 409.0480.



Derivatization of 5a

2,2,2-Trichloroethyl (R)-2-(2-isopropoxy-2-oxoethyl)-3,4-dihydro-quinazoline-1(2H)-carboxylate (8). To a solution of 5a (0.1 mmol, 40 mg, 1 equiv.; 96:4 er) in anhydrous MeOH (1 mL) at 0 °C, B(OH)₃ (0.2 mmol, 12.2 mg, 2 equiv.) and NaBH₄ (0.2 mmol, 7.2 mg, 2 equiv.) were added slowly and stirred for 1 h at room temperature. The reaction mixture was quenched with H₂O (2 mL), filtered and washed with EtOAc (3 x 3 mL). Purification by solid phase extraction (MeOH : Et₃N 50 : 1) yielded the desired product 8 (26 mg, 0.064 mmol, 64%). The enantiomeric ratio was determined as 94 : 6 er by chiral HPLC [Chiralpack AD, hexane/iPrOH (90 : 10), 1.0 mL min⁻¹, λ = 300 nm: t_r (major): 18.1 min, t_r (minor): 19.1 min]. [α]_D²⁰: -4.6 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.09 (t, J = 7.2 Hz, 2H), 6.82 (t, J = 7.1 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.64 (t, J = 6.9 Hz, 1H), 5.22 (d, J = 12.1 Hz, 1H), 5.00 (m, 1H), 4.77 (s, 1H), 4.43 (m, 1H), 2.84 (bs, 2H), 1.23 (d, J = 6.2 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 169.7, 152.8, 141.8, 128.1, 127.6, 122.9, 120.0, 117.4, 95.3, 75.3, 68.4, 51.4, 42.6, 29.7, 21.8; HRMS (ESI): m/z calculated for [C₁₆H₁₉Cl₃N₂NaO₄]⁺: 431.0303; found 431.0300.

Methyl (R)-2-(2-methoxy-2-oxoethyl)quinazoline-1(2H)-carboxylate (9). A mixture of 5a (20.0 mg, 0.05 mmol, 1 equiv.) and K₂CO₃ (35.0 mg, 0.25 mmol, 5 equiv.; 96:4 er) in anhydrous MeOH (1 mL) was stirred for 1 h at room temperature. Afterwards, H₂O (1 mL) was added, the mixture extracted with CHCl₃ (3 x 3 mL), the organic phase washed with brine (3 x 3 mL) and the crude product was dried over Na₂SO₄. Purification by column chromatography (petrol ether/EtOAc 5 : 1) yielded the desired product 9 (11.0 mg, 0.04 mmol, 84%). The enantiomeric ratio was determined as 97 : 3 er by chiral HPLC [Chiralpack AD, hexane/iPrOH (90 : 10), 1.0 mL min⁻¹, λ = 290 nm: t_r (minor): 21.5 min, t_r (major): 25.2 min]. [α]_D²⁰: -18.8 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.72 (bs, 1H), 7.45 (td, J = 7.5, 1.4 Hz, 1H), 7.41–7.36 (td, J = 7.5, 1.2 Hz, 1H), 7.32–7.25 (m, 2H), 6.01–5.88 (bm, 1H), 3.91 (s, 3H), 3.62 (s, 3H), 2.69 (dd, J = 14.5, 5.8 Hz, 1H), 2.63 (dd, J = 14.5, 8.2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 170.1, 154.4, 143.1, 132.4, 131.9, 128.8, 126.3, 126.0, 123.5, 76.7, 54.0, 51.9, 39.1; HRMS (ESI): m/z calculated for [C₁₃H₁₅N₂O₄]⁺: 263.1026; found 263.1031.

Isopropyl (R)-2-(1,2-dihydroquinazolin-2-yl)acetate (10). A mixture of 5a (20.0 mg, 0.05 mmol, 1 equiv.; 92:8 er) and Zn-powder (34.0 mg, 0.05 mmol, 10 equiv.) in NH₄OAc (1.0 M)/THF (1/3; 1 mL) was stirred for 16 h at room temperature. After that time sat. aq. K₂CO₃ solution (1 mL) was added, extracted with CHCl₃ (3 x 3 mL) and dried over Na₂SO₄ to yield the desired product 10 (11.2 mg, 0.048 mmol, 97%). The enantiomeric ratio was determined as 90 : 10 er by chiral HPLC [Chiralpack AD, hexane/iPrOH (90 : 10), 1.0 mL min⁻¹, λ = 280 nm: t_r (major): 8.6 min, t_r (minor): 9.7 min]. [α]_D²⁰: +16.8 (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.25–7.12 (m, 2H), 7.06–7.01 (m, 2H), 6.93 (dd, J = 8.3, 1.6 Hz, 1H), 5.11–4.99 (m, 1H), 5.05 (sept., J = 6.1 Hz, 1H), 4.63 (bs, 1H), 2.88 (dd, J = 16.8, 10.0 Hz, 1H), 2.59 (dd, J = 16.8, 3.2 Hz, 1H), 1.25 (d, J = 6.3 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 171.2, 146.7, 140.5,

128.6, 125.7, 125.0, 123.4, 123.2, 68.6, 49.0, 44.1, 21.8; HRMS (APCI): m/z calculated for [C₁₃H₁₆N₂O₂]⁺ m/z: 233.1285, found 233.1290.

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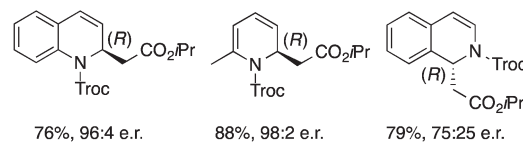
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Notes and references

- (a) P. Mátyus and P. Tapolcsányi, in *Asymmetric Synthesis of Nitrogen Heterocycles*, ed. J. Royer, Wiley-VCH, Weinheim, 2009, p. 293; (b) K. A. Rinderspacher, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and J. A. Joule, Elsevier, Amsterdam, 2015, vol. 27, p. 393.
- S. Chou, *Curr. Opin. Infect. Dis.*, 2015, **28**, 293.
- K. Nepali, S. Sharma, R. Ojha and K. L. Dhar, *Med. Chem. Res.*, 2012, **22**, 1.
- K. Tamaki, K. Tanzawa, S. Kurihara, T. Oikawa, S. Monma, K. Shmada and Y. Sugimura, *Chem. Pharm. Bull.*, 1995, **43**, 1883.
- See for examples: (a) M.-C. Fernandez, A. Escribano, A. I. Mateo, S. Parthasarathy, E. M. Martin de la Nava, X. Wang, S. L. Cockerham, T. P. Beyer, R. J. Schmidt, G. Cao, Y. Zhang, T. M. Jones, A. Borel, S. A. Sweetana, E. A. Cannady, G. Stephenson, S. Frank and N. B. Mantlo, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3056; (b) H. Kubota, Y. Nakamura, T. Higashijima, Y. Yamamoto, K. Oka and S. Igarashi, *U.S. Pat. Appl. Publ.*, US20070032485A120070208, 2007.
- M. Bell, G. Cao, A. Escribano, M. Fernandez, P. Lander, N. Mantlo, E. Martin de la Nava, A. Mateo Herranz, D. Mayhugh and X. Wang, *U.S. Pat. Appl. Publ.*, US2007013526A120070726, 2007.
- C. R. Bourne, E. W. Barrow, R. A. Bunce, P. C. Bourne, K. D. Berlin and W. W. Barrow, *Antimicrob. Agents Chemother.*, 2010, **54**, 3825.
- For some reviews on asymmetric dearomatizations, see: (a) M. Ahamed and M. H. Todd, *Eur. J. Org. Chem.*, 2010, 5935; (b) C.-X. Zhuo, W. Zhan and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662.
- A recent review on asymmetric hydrogenation of azarenes: D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557.
- For some recent organocatalytic and dual catalytic examples, see: (a) L. Mengozzi, A. Guanlandi and P. G. Cozzi, *Chem. Sci.*, 2014, **5**, 3915; (b) F. Berti, F. Malossi, F. Marchetti and M. Pineschi, *Chem. Commun.*, 2015, **51**, 13694; (c) S. Sun, Y. Mao, H. Lou and L. Liu, *Chem. Commun.*, 2015, **51**, 10691; (d) C. M. R. Volla, E. Fava, I. Atoderesei and M. Rueping, *Chem. Commun.*, 2015, **51**, 15788.



- 11 (a) Z.-P. Yang, Q.-F. Wu and S.-L. You, *Angew. Chem., Int. Ed.*, 2014, **53**, 6986. For a review on allylic dearomatizations, see: (b) C.-X. Zhuo, C. Zheng and S.-L. You, *Acc. Chem. Res.*, 2014, **47**, 2558.
- 12 For the initial non-asymmetric studies: (a) S. Beckendorf, S. Asmus, C. Mück-Lichtenfeld and O. García Mancheño, *Chem. – Eur. J.*, 2013, **19**, 1581; (b) S. Asmus, S. Beckendorf, M. Zurro, C. Mück-Lichtenfeld and O. García Mancheño, *Chem. – Asian J.*, 2014, **9**, 2178.
- 13 See reviews: (a) S. Beckendorf, S. Asmus and O. García Mancheño, *ChemCatChem*, 2012, **4**, 926; (b) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518; (c) K. Brak and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2013, **52**, 534; (d) T. J. Auvil, A. G. Schafer and A. E. Mattson, *Eur. J. Org. Chem.*, 2014, 2633.
- 14 (a) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld and O. García Mancheño, *J. Am. Chem. Soc.*, 2014, **136**, 13999; (b) O. García Mancheño, S. Asmus, M. Zurro and T. Fischer, *Angew. Chem., Int. Ed.*, 2015, **54**, 8823; (c) M. Zurro, S. Asmus, J. Bamberger, S. Beckendorf and O. García Mancheño, *Chem. – Eur. J.*, 2016, **22**, 3785–3793.
- 15 (a) A. Reissert, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 1603; (b) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511.
- 16 M. S. Taylor, N. Tokunaga and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 6700.
- 17 V. Kumar and S. Mukherjee, *Chem. Commun.*, 2013, **49**, 11203.
- 18 V. Benedek, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967.
- 19 Assuming the same behaviour, the absolute configuration (*R*) was assigned by comparison with the one obtained with (*R,R*)-**1a** as the catalyst for the related mono-azarene quinolines, pyridines and isoquinolines. See ref. 14.



- 20 The reaction with other diazaarenes such as 6-membered ring pyrazine and 5-bromopyrimidine, or five-membered derivatives *N*-methyl imidazole and *N*-methyl pyrazole proceeded; however the products showed a high instability and they could not be isolated pure.
- 21 The reduction of **5a** with $\text{Et}_3\text{SiH/TFA}$ or the $\text{H}_2\text{-Pd/C}$ system under different conditions did not occur or lead to decomposition products.
- 22 For the reduction of imines with the boric acid-activated NaBH_4 system, see for example: B. T. Cho and S. K. Kang, *Tetrahedron*, 2005, **61**, 5725.

