Asymmetric Catalysis

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Highly Enantioselective Nucleophilic Dearomatization of Pyridines by Anion-Binding Catalysis**

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Abstract: *The asymmetric dearomatization of N-heterocycles is an important synthetic method to gain bioactive and synthetically valuable chiral heterocycles. However, the catalytic enantio- and regioselective dearomatization of the simplest six-membered-ring N-heteroarenes, the pyridines, is still very challenging. The first anion-binding-catalyzed, highly enantioselective nucleophilic dearomatization of pyridines with triazole-based H-bond donor catalysts is presented. Contrary to other more common NH-based H-bond donors, this type of organocatalyst shows a prominent higher C2-regioselectivity and is able to promote high enantioinductions via formation of a close chiral anion-pair complex with a preformed N-acyl pyridinium ionic intermediate. This method offers a straightforward and useful synthetic approach to chiral N-heterocycles from abundant and readily available pyridines.*

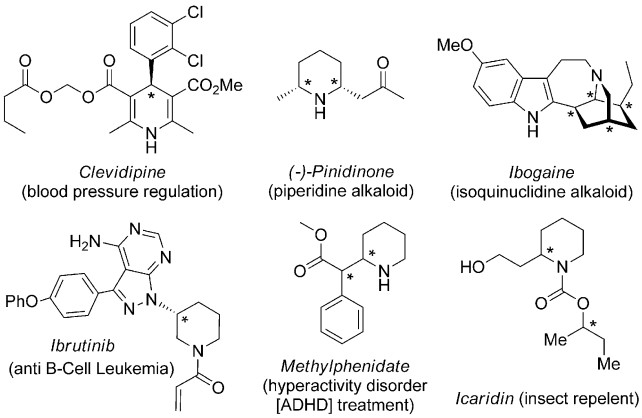

Figure 1. Representative drugs and bioactive pyridine-derived heterocycles.

Pyridine derivatives, and especially the more diversified and complex partial and fully saturated chiral N-heterocycles, constitute an important class of compounds widely present in naturally occurring and synthetic substances with a broad bioactive spectrum (Figure 1).[1] For example, Clevidipine,[2] with a 1,4-dihydropyridine backbone analogous to NADH, is one of the top-selling drugs for blood pressure regulation. On the other hand, numerous types of natural alkaloid structures are derived from the pyridine moiety, such as (−)-pinidinone or ibogaine with a piperidine and isoquinuclidine skeleton, respectively.[3] Among further applications, the tetrahydropyridine (piperidine) structures are known as anti-cancer agents (for example ibrutinib),[4] used for the treatment of many diseases such as hyperactivity disorders (e.g. methylphenidate)[5] or even as insect repellents (for example icaridin).[6]

Despite the great importance of these type of N-heterocycles, there is still a need for simple, mild, and direct synthetic methods for their preparation. Considering the abundance of readily available aromatic systems, the most efficient and fast approach to obtain a broad variety of substituted enantioenriched six-membered-ring N-heterocyclic skeletons is the direct asymmetric dearomatization reaction.[7] Several approaches for the dearomatization of N-heteroarenes have been developed. Besides metal- and organocatalyzed hydrogenative reactions,[8] the main method for inducing chirality is based on nucleophilic additions to a pyridinium salt, either preformed or formed in situ. The asymmetric induction is then achieved by either using a chiral auxiliary group at the nitrogen atom (R* = chiral RCO, R; method A)[9] or a catalytic chiral transition-metal complex (L*M, L* = chiral ligand; method B)[10] (Scheme 1).

However, efficient catalytic enantioselective processes for pyridines, the simplest six-membered-ring N-heteroarenes, are still highly challenging and to date are only based on transition-metal catalysis.[7,10] This can be attributed to the fact that: 1) in pyridines the aromaticity of the entire system will be broken, whereas in other extended systems such as quinolines or isoquinolines the reaction is energetically less-demanding because the aromaticity is partially retained in the other benzene ring; 2) the control of regioselectivity can also be very difficult since both the C4 and C2 positions of the pyridine are prone to nucleophilic additions and a preferential C4 addition is often observed; and 3) the transition-metal catalyst may become deactivated upon a coordination to the pyridine substrates or the products.

Following our research program on triazole-based H-bond donors[11,12] and the recent advances in anion-binding catalysis,[13] we decided to explore this type of organocatalysis for the asymmetric nucleophilic dearomatization reaction of simple pyridines. Thus, we envisioned an effective chiral transfer to the final dihydropyridine product from the in situ

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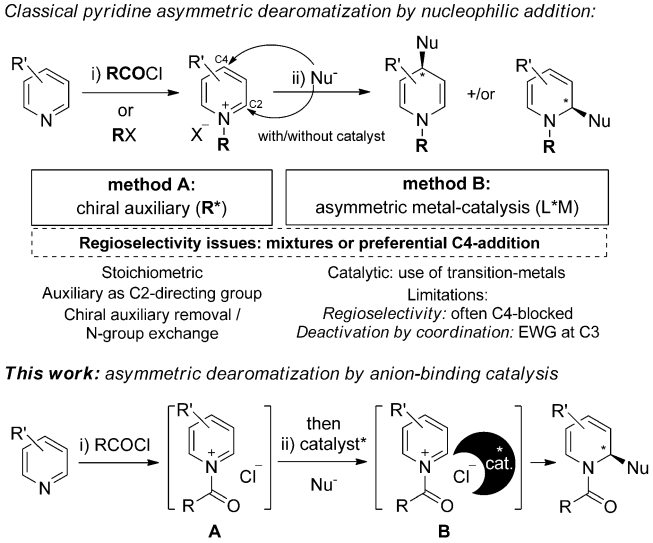


Scheme 1. Asymmetric dearomatization of pyridines by nucleophilic addition.

formed chiral contact ion-pair **B** formed between the ionic intermediate of type-**A** and the catalyst–anion complex (Scheme 1, bottom). Herein, we are pleased to present a new anion-binding organocatalytic approach for the highly enantioselective dearomatization of pyridines with silyl ketene acetals.

2-Picoline (**3a**) was chosen as model substrate for our studies. The dearomatization of **3a** by the one-pot in situ formation of the *N*-Troc pyridinium chloride salt followed by nucleophilic addition of silyl ketene acetal **4** in the presence of various chiral H-donor catalysts was initially explored (Table 1).[14] Thus, our recently developed C–H-based hydrogen-bond-donor catalysts **1a–c**[11c] and the more traditional N–H-based H-donors such as Jacobsen's thiourea catalyst **2a**,[15] squaramide **2b**,[16] or bifunctional thiourea–cinchona alkaloid **2c**[17] were tested (Figure 2).

In our first attempts, the active ionic pyridinium substrate was preformed in situ at 0 °C in MTBE for 30 min, then the

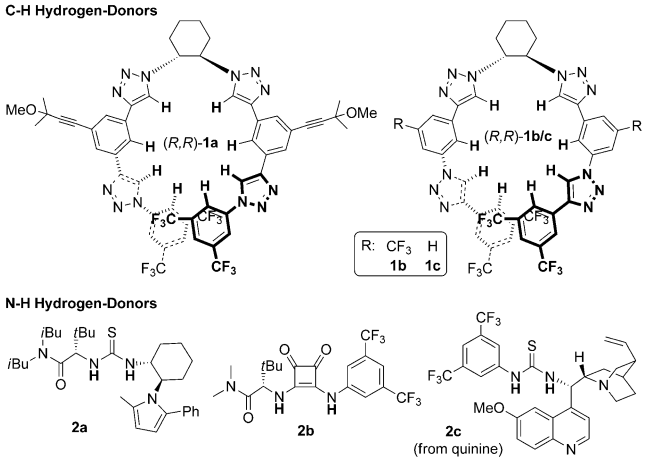
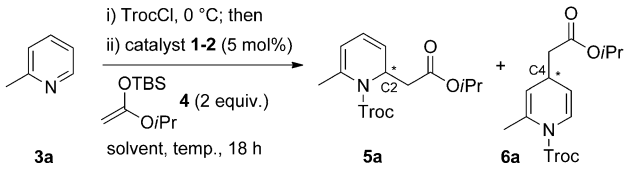


Figure 2. Hydrogen donor catalysts tested in this study.

Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Solv.	*T* [°C]	Yield [%][b]	**5a**:**6a**[c]	**5a**, e.r.[d]
1	(*R,R*)-**1a**	MTBE	−78	87	92:8	97:3
2	(*S,S*)-**1a**	MTBE	−78	87	92:8	4:96
3	(*R,R*)-**1b**	MTBE	−78	89	91:9	83:16
4	(*R,R*)-**1c**	MTBE	−78	62	91:9	50:50
5	**2a**	MTBE	−78	66	11:89[e]	57:43
6	**2b**	MTBE	−78	26	14:86	54:46
7	**2c**	MTBE	−78	21	17:83	52:48
8	–	MTBE	−78→RT	68	32:68	50:50
9	(*R,R*)-**1a**	MTBE	−78→RT	88	91:9	96:4
10	(*R,R*)-**1a**	THF	−78→RT	60	33:67	94:6
11	(*R,R*)-**1a**	Et_2O	−78→RT	87	92:8	97:3
12	(*R,R*)-**1a**	Et_2O	−78	91	94:6[f]	98:2
13	(*R,R*)-**1a**	Et_2O	−40	84	83:17	n.d.
14	(*R,R*)-**1a**	Et_2O	RT	92	67:33	n.d.

[a] Conditions: i) **3a** (1 equiv) and TrocCl (1 equiv) in the appropriate solvent at 0 °C, 30 min; ii) at the corresponding temperature, catalyst (5 mol %) and **4** (2 equiv) were added and stirred for 18 h. [b] Yield of isolated product. [c] Isomeric ratios determined by ^{1}H NMR spectroscopy. [d] Enantiomeric ratios determined by chiral-phase HPLC using a Daicel Chiralcel OJ-H column. [e] **6a** was obtained as a racemate. [f] **6a** presented a 54:46 e.r. n.d. = not determined.

catalyst and nucleophile **4** were added at −78 °C and the reaction was carried out at this temperature for 18 h. The use of 5 mol % of a H-donor catalyst **1** or **2** was translated in good conversions to the dearomatized products **5** and/or **6**. Interestingly, the tetrakistriazole **1a** was superior in terms of reactivity, regio- and enantioselectivity compared to the NH-based thiourea or squaramide catalysts **2** (Table 1, entries 1–7), leading to a highly selective C2 addition[18] (for example, **5:6** ratio 92:8 (**1a**) vs. 11:89 (**2a**); entries 1 and 5, respectively). It is important to mention that a background reaction was observed in the absence of a catalyst, providing the 1,4-dihydropyridine **6** as the major product (entry 8). From the three C–H-based catalysts **1** tested, (*R,R*)-**1a** provided the best results leading to the 1,2-dihydropyridine **5a** in an excellent 97:3 e.r. (entry 1). Moreover, the enantiomer could also be obtained in a high enantiomeric ratio (4:96 e.r.) when using the enantiomeric catalyst (*S,S*)-**1a** (entry 2). (*R,R*)-**1a** was then chosen as optimal catalyst for further studies. A similar high enantiomeric induction was obtained when the reaction (initial addition at −78 °C) was allowed to slowly reach room temperature overnight (96:4 e.r., entry 9). Diethylether proved to be slightly superior with respect to MTBE (98:2 e.r., entry 12). Other solvents (see the Supporting Information) such as THF were also tested, providing **5a** in similar excellent enantiopurity but with an important loss of regioselectivity (**5a:6a** = 33:67, entry 11). Finally, when the reaction was conducted at higher temperatures (−40 °C or RT, entries 13 and 14), again lower regioselectivities towards **5a** were observed, which is most probably due to a strong competition with the non-selective background process.

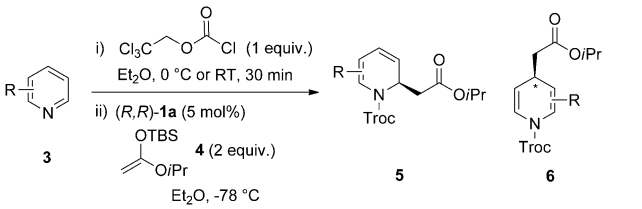
Therefore, the reactions were preferentially carried out at −78 °C.

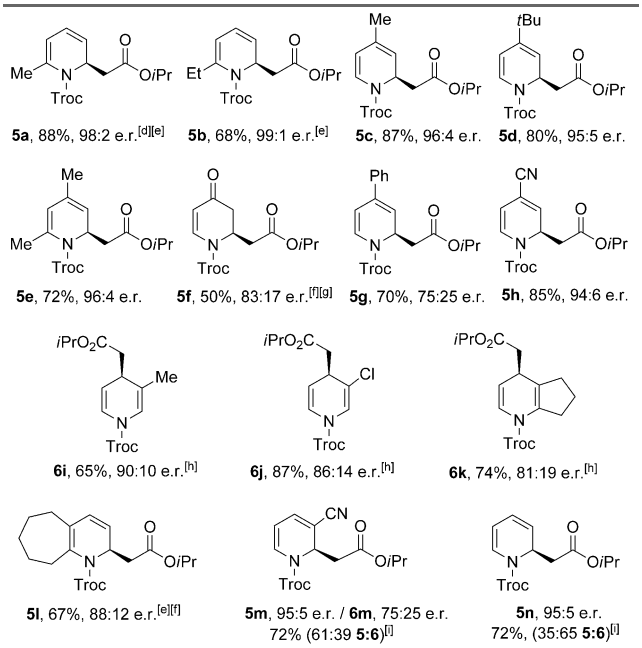
With the optimized conditions in hand (**1a** (5 mol %) as H-donor catalyst in Et_2O at −78 °C), the scope of the reaction with different substituted pyridines was next explored (Table 2). First of all, the reaction could be scaled up to 2 mmol with the model substrate **3a** without detriment on the yield or enantioselectivity (88 %, 98:2 e.r.). Moreover, the catalyst **1a** could be re-isolated in a 95 % yield and reused, showing the same reactivity and regio- and enantioselectivity.[19] The simple change from 2-picoline to 2-ethylpyridine (**3b**) as a substrate led to an improved enantiomeric ratio of 99:1. Other alkyl groups such as methyl or *tert*-butyl in the 2- and/or 4-position, as well as electron withdrawing groups such as 4-cyano, were well tolerated, providing 1,2-dihydropyridines **5c–e** and **5g** in similar high enantioselectivities (94:6–97:3 e.r.). On the other hand, 4-methoxypyridine showed a lower reactivity at −78 °C, therefore it was necessary to carry out the reaction at −60 °C in order to obtain an acceptable enantioinduction and conversion into the corresponding hydroxy derivative **5f** (50 %, 83:17 e.r.). Furthermore, the use of aromatic substituted substrates, such as a 4-phenyl, was translated on a less efficient chiral transfer, leading to **5g** in 75:25 e.r. and a good 70 % yield.

Unexpectedly, in the cases of C3-substituted pyridines with a group such as methyl, chloro, or a 2,3-fused cyclopentane ring, the regioselectivity was reversed towards the 1,4-dihydropyridines **6i–k**.[20–22] The enantiomeric ratios obtained were comparably high (up to 90:10 e.r.). This is surprising considering that the nucleophilic addition is now taking place in a further position to the chiral ion pair that should be close to the positively charged nitrogen atom of the ionic intermediate. Furthermore, the normal C2 selectivity was recovered when having a larger and less bulky fused ring such as 1,2-cycloheptane, leading to **5l** in a good 88:12 e.r. at −60 °C. The regioselectivity was lower when an electron-withdrawing, less-bulky substituent such as a nitrile was placed in the C3 position (61:39, **5m:6m**). Nonetheless, the high enantioinductions were preserved, especially for the 1,2-dihydropyridine **5m** (95:5 e.r.). Lastly, this method was also explored for the most challenging case, the non-substituted pyridine. The reaction proceeded smoothly and with high enantioselectivity for the C2 addition product **5n** (95:5 e.r.), though a C2/C4 competitive addition was observed.

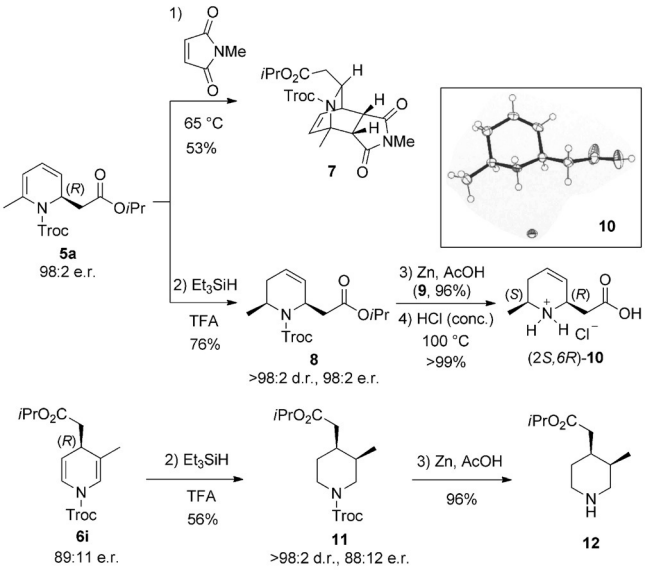
Finally, the utility of this method was demonstrated by the derivatization of the 1,2-dihydropyridine **5a** into the isoquinuclidine derivative **7** as single isomer by a Diels–Alder reaction with N-methyl maleimide, and the chiral β-amino-acid (2*S*,6*R*)-**10** by partial diastereoselective hydrogenation, following by deprotection of the Troc-group and ester hydrolysis (Scheme 2, top). Compound **10** was crystallized and its structure analyzed by X-ray analysis,[23] providing the absolute configuration (*R*) at the new stereocenter formed during the dearomatization reaction. Additionally, the NH-free δ-aminoester **12** was prepared by a similar initial two-step

Table 2: Scope of the reaction.[a–c]





[a] Conditions: i) **3** (1.0 equiv) and TrocCl (1.0 equiv) in Et_2O 30 min at 0 °C or RT; then −78 °C; ii) addition of (*R,R*)-**1a** (5 mol %) and **4** (2 equiv) (18–24 h at −78 °C). [b] Yields of isolated products. [c] Enantiomeric ratios determined by chiral-phase HPLC using Daicel Chiralcel OJ-H and OD-H columns. [d] 2 mmol scale. [e] Observed **5:6** ratio of 94:6 by NMR spectrum of the crude product. [f] Reaction at −60 °C for 48 h. [g] Product of the reaction with 4-methoxy pyridine. [h] Traces of the regioisomer **5** were detected by HPLC at $\lambda = 290–300$ nm. [i] NMR ratios of inseparable mixture of regioisomers.



Scheme 2. Derivatization of the chiral dihydropyridines.

synthetic sequence from the 1,4-dihydropyridine **6i** (Scheme 2, below).[24]

In conclusion, the first highly enantioselective nucleophilic dearomatization of simple pyridines using an anion-binding organocatalysis approach has been developed. Tetrakistriazole-based H-bond donor catalysts were superior to other known N–H-bond based hydrogen donors, leading preferentially to 1,2-dihydropyridines with up to 99:1 e.r. It has also been shown that this method allows rapid access to value added substituted chiral N-heterocycles such as isoquinuclidine, piperidine, or amino acid derivatives.

Experimental Section

Representative example: 1,2-Dihydropyridine (*R*)-**5a**: 2-Picoline (198 μL, 2.0 mmol, 1.0 equiv) was dissolved in Et_2O (0.1–0.05 M) and TrocCl (275 μL, 2.0 mmol, 1.0 equiv) was added at 0 °C. The resulting mixture was stirred for 30 min and cooled to −78 °C. Then, catalyst **1a** (112.1 mg, 0.10 mmol, 5 mol%) and silyl ketene acetal **4** (1.0 mL, 4.0 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 18 h at −78 °C. The desired product **5a** (649.7 mg, 1.75 mmol, 88%) was isolated by flash column chromatography (pentane/EtOAc, 40:1→20:1). The enantiomeric ratio of 98:2 was determined by chiral HPLC (Chiralcel OJ-H, heptane/*i*PrOH (98:2) 1.0 mL min^{-1}, $\lambda = 300$ nm): *tr* (minor): 6.0 min, *tr* (major): 6.9 min.). $[\alpha]_{589}^{20}$: −76.0 (c 0.3, $CHCl_3$). ^{1}H NMR (600 MHz, [D$_6$]acetone) $\delta = 5.99$ (ddt, $J = 9.2$, 5.2, 0.7 Hz, 1H), 5.83 (ddt, $J = 9.3$, 5.9, 0.9 Hz, 1H), 5.62 (dt, $J = 5.3$, 1.2 Hz, 1H), 5.27 (td, $J = 7.4$, 5.9 Hz, 1H), 5.04 (d, $J = 12.2$ Hz, 1H), 4.93 (q, $J = 6.3$ Hz, 1H), 4.81 (d, $J = 12.2$ Hz, 1H), 2.44 (dd, $J = 7.3$, 1.3 Hz, 2H), 2.24 (s, 3H), 1.21 ppm (dd, $J = 6.3$, 1.0 Hz, 6H); ^{13}C NMR (150 MHz, [D$_6$]acetone) $\delta = 169.9$, 150.9, 123.8, 113.6, 113.2, 112.1, 110.9, 96.3, 75.9, 68.4, 50.9, 42.8, 37.4, 22.1, 22.0 ppm; HRMS: *m*/*z* calculated for $[C_{14}H_{18}Cl_3NO_4Na]^+$: 392.0194, found: 392.0194.

Keywords: anion-binding catalysis · dearomatization · enantioselectivity · pyridine · triazoles

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Angew. Chem. **2015**, *127*, 8947–8951

[1] See for example: P. Kiuru, J. Yli-Kauhaluoma, *Pyridine and its Derivatives* in *Heterocycles in Natural Product Synthesis* (Eds.: K. C. Majumdar, S. K. Chattopadhyay), Wiley-VCH, Weinheim, **2011**, Chap. 8, pp. 267–297; and references cited therein.

[2] a) M. Nordlander, P. O. Sjoquist, H. Ericsson, L. Ryden, *Cardiovasc. Drug Rev.* **2004**, *22*, 227–250; b) E. D. Deeks, G. M. Keating, S. J. Keam, *Am. J. Cardiovasc. Drugs* **2009**, *9*, 117–134, and references therein.

[3] See for example: Pinidinone: a) M. Kavala, F. Mathia, J. Kozissek, P. Szolcsanyi, *J. Nat. Prod.* **2011**, *74*, 803; b) M. J. Munchhof, A. I. Mayers, *J. Am. Chem. Soc.* **1995**, *117*, 5399; Ibogaine: c) Chapter 1. Ibogaine: A review: K. R. Alper, *The Alkaloids*, *Vol. 56*, Academic Press, San Diego, **2001**; d) M.-M. Janot, R. Goutarel, US patent US2813873, **1957**.

[4] a) L. Honigberg, E. Verner, Z. Pan, US patent US2008/0108636 (A1), **2008**; b) I. Sagiv-Barfi, H. E. K. Kohrt, D. K. Czerwinski, P. P. Ng, B. Y. Chang, R. Levy, *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E966–E972, and references therein.

[5] See for example: a) D. D. Daly, R. E. Yoss, *Proc. Staff Meet. Mayo. Clin.* **1956**, *31*, 620–626; b) M. J. Battmann, P. J. Percel, D. L. Hensley, K. S. Vishnupad, G. M. Venkatesh, US patent US6344215 (B1), **2002**.

[6] See for example: a) N. Scheinfeld, *J. Drugs Dermatol.* **2004**, *3*, 59–60; b) T. M. Katz, J. H. Miller, A. A. Herbert, *J. Am. Acad. Dermatol.* **2008**, *58*, 865–871.

[7] Review on catalytic asymmetric dearomatization reactions: a) C. Zhuo, W. Zhang, S. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686; *Angew. Chem.* **2012**, *124*, 12834–12858; Recent review on dearomatization of heteroarenes: b) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807–4815.

[8] Reviews on asymmetric hydrogenation of heteroarenes: a) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171–4175; b) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366; c) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2257–2590, and references therein.

[9] Selected examples: a) D. L. Comins, H. Hong, J. M. Salvador, *J. Org. Chem.* **1991**, *56*, 7197–7199; b) D. L. Comins, S. P. Joseph, R. R. Goehring, *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728; c) T. Focken, A. B. Charette, *Org. Lett.* **2006**, *8*, 2985–2988, and references therein.

[10] Selected examples: a) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809; b) Z. Sun, S. Yu, Z. Ding, D. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 9300–9301; c) M. Á. Fernández-Ibáñez, B. Maciá, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2009**, *48*, 9339–9341; *Angew. Chem.* **2009**, *121*, 9503–9505; d) C. Nadeau, S. Aly, K. Belyk, *J. Am. Chem. Soc.* **2011**, *133*, 2878–2880; e) Z.-P. Yang, Q.-F. Wu, A.-L. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 6986–6989; *Angew. Chem.* **2014**, *126*, 7106–7109.

[11] a) S. Beckendorf, S. Asmus, C. Mück-Lichtenfeld, O. García Mancheño, *Chem. Eur. J.* **2013**, *19*, 1581–1585; b) S. Asmus, S. Beckendorf, M. Zurro, C. Mück-Lichtenfeld, R. Fröhlich, O. García Mancheño, *Chem. Asian J.* **2014**, *9*, 2178–2186; c) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. García Mancheño, *J. Am. Chem. Soc.* **2014**, *136*, 13999–14002.

[12] Selected examples on triazole and triazolium salt C–H-based H-donors: Triazole anion-binders: a) Y. Li, A. H. Flood, *Angew. Chem. Int. Ed.* **2008**, *47*, 2649–2652; *Angew. Chem.* **2008**, *120*, 2689–2692; b) R. M. Meudtner, S. Hecht, *Angew. Chem. Int. Ed.* **2008**, *47*, 4926–4930; *Angew. Chem.* **2008**, *120*, 5004–5008; c) H. Juwarker, J. M. Lenhardt, D. M. Pham, S. L. Craig, *Angew. Chem. Int. Ed.* **2008**, *47*, 3740–3743; *Angew. Chem.* **2008**, *120*, 3800–3803; Triazolium organocatalysts: d) K. Ohmatsu, M. Kiyokawa, T. Ooi, *J. Am. Chem. Soc.* **2011**, *133*, 1307–1309.

[13] Selected reviews: a) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; b) S. Beckendorf, S. Asmus, O. García Mancheño, *ChemCatChem* **2012**, *4*, 926–936; c) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518–533; *Angew. Chem.* **2013**, *125*, 540–556; d) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561; *Angew. Chem.* **2013**, *125*, 558–588; e) D. Seidel, *Synlett* **2014**, *25*, 783–794.

[14] Pioneer work on anion-binding thiourea-catalyzed dearomatization with silyl ketene acetals: a) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6700–6704; *Angew. Chem.* **2005**, *117*, 6858–6862; For a siladienol-catalyzed example, see: b) A. G. Schafer, J. M. Wieting, T. J. Fisher, A. E. Mattson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11321–11324; *Angew. Chem.* **2013**, *125*, 11531–11534.

[15] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559.

[16] a) V. Kumar, S. Mukherjee, *Chem. Commun.* **2013**, *49*, 11203–11205; Selected review on squaramide catalysis: b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899.

[17] a) B. Vakulya, S. Varga, A. Csámpi, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; b) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; *Angew. Chem.* **2005**, *117*, 6525–6528;

c) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481 – 4483.
[18] For regioselective 1,2-dearomatization of pyridines, see: A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro, T. J. Marks, *Nat. Chem.* **2014**, *6*, 1100 – 1107, and references therein.
[19] A 2 mmol reaction with the recycled catalyst **1a** led to **5a** in similar good results: 84% yield and 98:2 e.r.
[20] Only traces of 1,2-dihydropyridines **5i–k**, which also present the typically high 91:9–94:6 e.r., could be detected by HPLC. This substrate-dependent change on the regioselectivity is still not well understood. The catalyst provided relatively high stereocontrol in **6i–k** compared to **6a** (54:46 e.r.), which might be attributed to a less efficient but still active action of the catalysts with **3i–k** vs. the mainly competitive achiral background reaction with **3a** towards the C4 addition.
[21] 2,6-Disubstituted pyridines led to no conversion, showing a special preferential selectivity for the 1,2-dearomatization by the **1a** catalyst.
[22] The structure of **6** was assigned by NMR spectroscopy: 1) ^{1}H NMR characteristic signal of the H at the new stereocenter at 3.2–3.6 ppm (vs. aprox. 5.0 ppm in **5** (H in α-position to the N-atom)); 2) 2D-NMR and NOESY experiments on **11** also confirmed this regioisomeric structure.
[23] CCDC 1054813 contains the crystallographic data of (2*S*,6*R*)-**10**. These data are provided free of charge by The Cambridge Crystallographic Data Centre. See also the Supporting Information for the X-ray crystal structure.
[24] The absolute configuration (*R*) in compound **6** was determined by derivatization of 3-ethylpyridine and comparison of the $[\alpha]_D$ value of a known compound (see the Supporting Information).

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