

Asymmetric Catalysis

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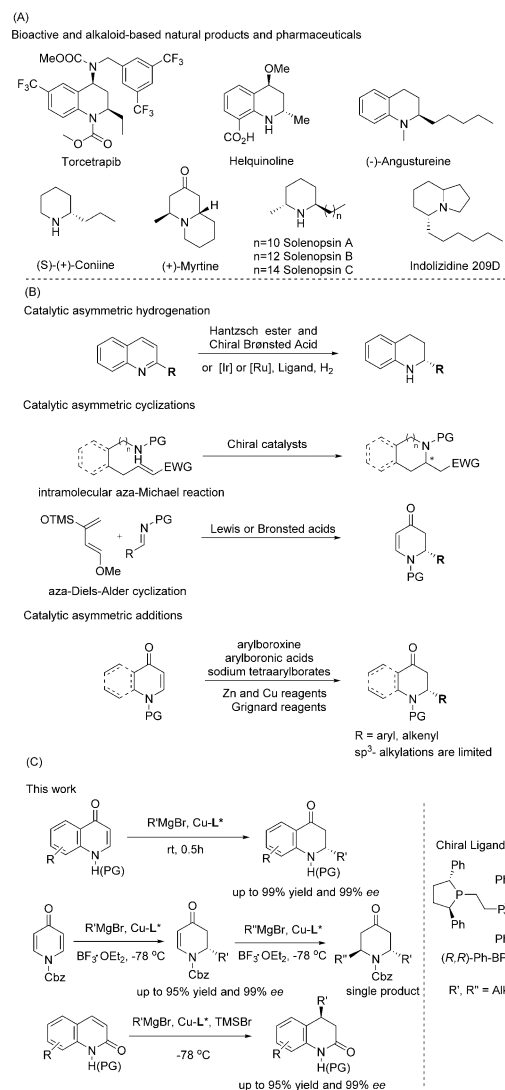
Highly Enantioselective Catalytic Addition of Grignard Reagents to N-Heterocyclic Acceptors

Yafei Guo and Syuzanna R. Harutyunyan*

Abstract: General methods to prepare chiral N-heterocyclic molecular scaffolds are greatly sought after because of their significance in medicinal chemistry. Described here is the first general catalytic methodology to access a wide variety of chiral 2- and 4-substituted tetrahydro-quinolones, dihydro-4-pyridones, and piperidones with excellent yields and enantioselectivities, utilizing a single catalyst system.

Optically active piperidine and tetrahydroquinoline derivatives are ubiquitous structural motifs in alkaloid-based natural products, and bioactive and pharmaceutical compounds. Some examples to be highlighted include *Torcetrapib*, a drug used to treat elevated cholesterol levels, the antibiotic *Helquinoline*, as well as various alkaloids such as the *Angustureine*, *Coniine*, *Myrtine*, *Solenopsin* series and *Indolizidine* (Scheme 1A).^[1] Accordingly, chiral piperidine and tetrahydroquinoline derivatives represent important synthetic targets. General asymmetric synthetic routes for their synthesis rely on several strategic approaches (Scheme 1B). Some of the most developed routes to chiral substituted tetrahydroquinolines make use of catalytic asymmetric hydrogenation of quinoline derivatives using chiral transition-metal complexes and transfer hydrogenations by chiral Brønsted acids with Hantzsch esters.^[2] Efficient catalytic asymmetric synthesis to access chiral hydroquinoline, quinolone, and piperidone derivatives using intramolecular aza-Michael and aza-Diels–Alder reactions, catalyzed by Lewis or Brønsted acids, have been also explored.^[3]

Other potential alternative N-heterocyclic precursors for the synthesis of chiral piperidine and tetrahydroquinoline derivatives include piperidones, dihydropyridones, and quinolones, which in addition are often found as part of more complex biologically active compounds.^[4] A common strategy for accessing these precursors is the asymmetric conjugate addition of organometallics to N-heterocyclic acceptors using chiral auxiliaries.^[5] However, catalytic enantioselective methodologies for conjugate additions to, for example quinolone, pyridone, dihydropyridone, and acylpyridinium salts, would



Scheme 1. A) Examples of pharmaceuticals and natural products featuring chiral an N-heterocyclic core. B) State of the art. C) This work.

constitute more attractive routes. Several such methods for additions of organometallics to 4-quinolones and dihydropyridone have been developed to date, with the most successful examples focusing on arylations.^[6] In contrast, for asymmetric alkylations there are only a few reports which make use of dihydropyridone^[6f,g] and an acylpyridinium salt.^[1a,7,8b] These alkylation methods suffer from limited product scope with either low yields or moderate enantioselectivities. Furthermore, catalytic asymmetric alkylation of 4-quinolones and catalytic asymmetric conjugate additions, in general, to 2-quinolones as well as 4-pyridone^[8] are unknown. In pursuit

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of a catalytic asymmetric approach to a wide variety of chiral N-heterocyclic compounds we were interested in developing a single catalytic system capable of harnessing the reactivity of various N-heterocyclic acceptors.

Herein, we describe the first general protocol for catalytic asymmetric addition of various Grignard reagents to a wide variety of N-heterocyclic acceptors with excellent yields and enantioselectivities (Scheme 1C), and it requires a single catalytic system based on a copper salt and chiral diphosphine ligand.

Our initial studies focused on the development of an efficient catalytic methodology for the alkylation of 4-quinolones (Table 1). To compensate for the relatively low reactivity of the 4-quinolone acceptor, we decided to take advantage of the high reactivity of Grignard reagents. For the screening of catalytic systems and reaction conditions we chose the addition of EtMgBr to the carboxybenzyl-protected (Cbz) 4-quinolone **1a** as a model reaction. Addition of EtMgBr in the absence of any catalyst did not provide substrate conversion, even at room temperature (entry 1). First we set out to identify promising chiral catalysts, using 5 mol% of CuBr·SMe₂ and 6 mol% of various chiral

diphosphine (**L1–L5**) and phosphoramidite (**L6**) ligands. To our delight, using the chiral diphosphine ligand **L1**, developed by Pilkington et al.,^[9] the reaction proceeded to completion in 12 hours at –78 °C, providing the isolated final product **2a** in 99% yield and with 99% of enantiomeric excess. Optimization of the reaction temperature (entries 2–5) allowed us to establish highly practical conditions in which the addition product can be obtained at room temperature in only 20–30 minutes with a yield and enantiomeric purity of 98% (entry 5). This result is remarkable in its own right, as it represents the first example of highly enantioselective catalytic conjugate addition of Grignard reagents at room temperature.^[10] Further ligand screening revealed that neither of the other diphosphine-type ligands (**L2–L5**) nor the phosphoramidite-type ligand **L6** work for this chemistry both in terms of yield and enantioselectivity (entries 6–10). This discovery is rather surprising, as all of these ligands are normally very efficient in Grignard additions to more conventional Michael acceptors.^[11]

Based on these results we adopted the following optimized reaction conditions for further substrate scope studies: CuBr·SMe₂ (5 mol%), (*R,R*)-**L1** (6 mol%), and Grignard reagent (2.0 equiv) in CH₂Cl₂ for 30 minutes at room temperature.

Next, we evaluated EtMgBr with quinolones featuring various substituents at the N atom (Scheme 2). We found that quinolones with electron-withdrawing groups such as Cbz and Boc are well tolerated and give the corresponding products (**2a** and **2b**) with excellent yields and enantiomeric excess. However, for less-reactive Bn- and Me-protected quinolones the addition products **2c** and **2d** can only be isolated in the presence of a Lewis acid (TMSBr) with good yields and moderate 42–43% *ee*. Importantly, the addition of EtMgBr to the unprotected quinolone substrate in the presence of TMSBr provided the corresponding product **2e** with 52% yield and 96% *ee*.

Having established the effect of the substituents at the nitrogen atom of the quinolone we explored the scope of Grignard reagents with **1a** (Scheme 2). We were pleased to find that our catalytic system enables the addition of a wide variety of alkyl Grignard reagents, including linear, α -, β -, and γ -substituted reagents, as well as functionalized PhMgBr and *p*TolMgBr, providing products (**2f–n**) all with excellent results. This scope even extended to the markedly less reactive MeMgBr, for which **2o** was obtained with 93% yield and 97% enantiomeric excess.

Subsequently we examined the scope with respect to the N-Cbz-4-quinolone substrates and found that substrates bearing functional groups such as Me, Br, CF₃, ether, amide, or ester at the 5, 6, and 7-positions, were all converted into the corresponding final products (**2p–v**) successfully (Scheme 2). In all cases, our optimized system afforded the products in excellent yields (66% to 99%) and enantioselectivities (*ees* 94% to 99%). However, when 2-Me-N-Cbz-4-quinolone was used as a substrate, a lack of reactivity prevented the formation of the addition product **2w** with a quaternary stereocenter.

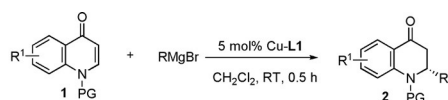
To expand this strategy towards the synthesis of chiral dihydro-pyridones and piperidones, we hypothesised that this

Table 1: Optimization of reaction conditions for the addition of EtMgBr to N-Cbz-4-quinolone (**1a**).^[a]

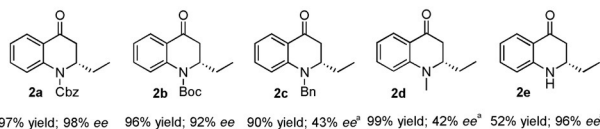
Entry	T [°C]	t [h]	Ligand	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1 ^[d]	RT	2	–	0	0
2	–78	12	L1	99	99
3	–20	2	L1	99	99
4	0	2	L1	99	98
5	RT	0.5	L1	98	98
6	RT	0.5	L2	21	28
7	RT	0.5	L3	78	27
8	RT	0.5	L4	82	57
9	RT	0.5	L5	32	0
10	RT	0.5	L6	71	0

[a] Reaction conditions: N-Cbz-4-quinolone **1a** (0.2 mmol), EtMgBr (2.0 equiv), **L** (6 mol%), and CuBr·SMe₂ (5 mol%) in CH₂Cl₂ (2 mL).

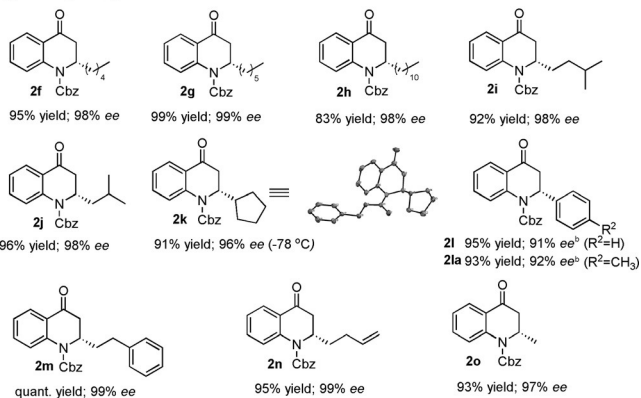
[b] Yields are those for the isolated products. [c] The enantiomeric excess was determined by HPLC on a chiral stationary phase. [d] Reaction without CuBr·SMe₂ and ligand.



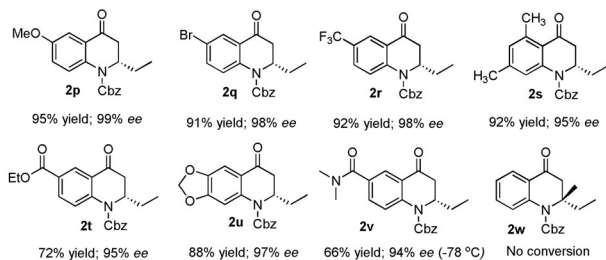
Substituents at N-atom



Grignard reagent scope

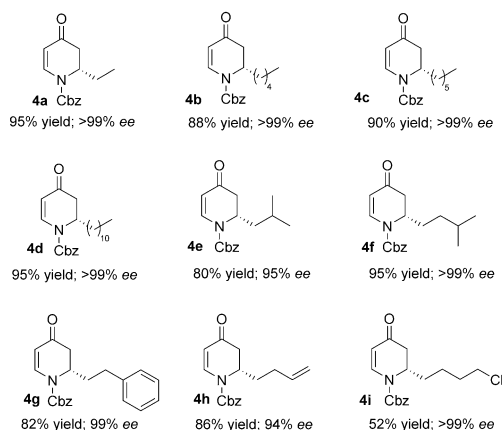
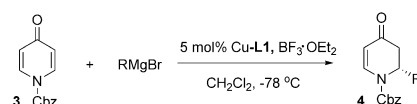


Substituents in the aromatic ring of the substrate



Scheme 2. Scope of the reaction between the *N*-Cbz-4-quinolones **1** and organomagnesium reagents. Reaction conditions: *N*-Cbz-4-quinolones **1** (0.2 mmol), EtMgBr (2.0 equiv), **L1** (6 mol%), and CuBr·SMe₂ (5 mol%) in CH₂Cl₂ (2 mL) at room temperature for 0.5 h. [a] Reactions with the quinolones **1c–e** were carried out in the presence of TMSBr (2.0 equiv) at –78 °C for 12 h. Absolute configuration of **2k** was established by X-ray crystallography.^[14] [b] PhMgBr and *p*TolMgBr were added slowly by a syringe pump in 2 h at 0 °C.

protocol could also enable addition reactions to *N*-Cbz-4-pyridone (**3**; Scheme 3). This substrate is more challenging for applications in catalysis as its aromatic character reduces the reactivity towards nucleophilic additions. As a result, pyridones have been hardly explored in asymmetric catalysis,^[8] even though there is major potential in the application of these substrates in chemical synthesis: after the initial conjugate addition reaction the resulting chiral *N*-heterocyclic product, with remaining Michael acceptor functionality, can subsequently undergo further stereoselective functionalizations to provide 2,6-substituted chiral pyridines, which can be useful for natural product synthesis. We initially evaluated the reactivity of **3** towards nucleophilic addition of EtMgBr using the reaction conditions optimized for *N*-Cbz-4-quinolones (Table 1, entry 2). Unfortunately the corresponding addition product **4a** was not obtained, but instead the side products derived from the addition of EtMgBr to the

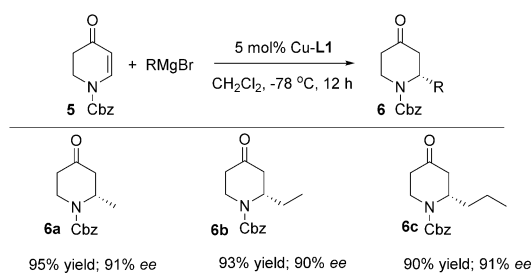


Scheme 3. Scope of the reaction of *N*-Cbz-4-pyridone (**3**) with organomagnesium reagents. Reaction conditions: **3** (0.2 mmol), Grignard reagents (2.0 equiv), **L1** (6 mol%), BF₃·OEt₂ (2.0 equiv), and CuBr·SMe₂ (5 mol%) in CH₂Cl₂ (2 mL) at –78 °C for 12 h.

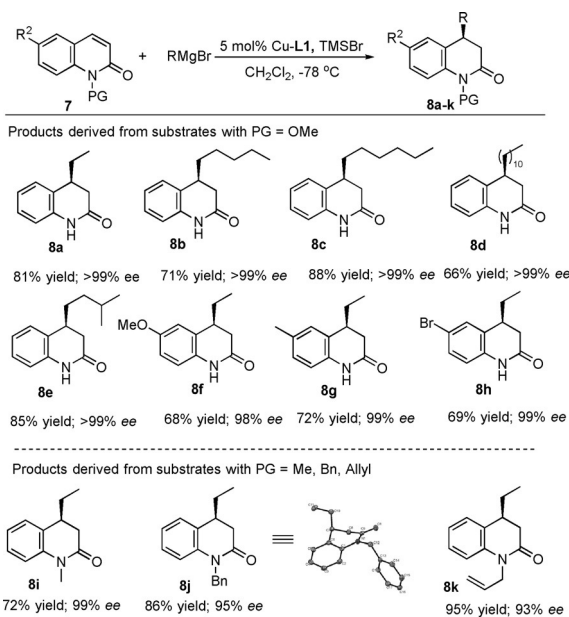
carboxybenzyl moiety were found.^[12] To steer the chemoselectivity of the reaction towards **4a**, we decided to introduce Lewis acids.^[8a,b] With BF₃·OEt₂ as the Lewis acid the best possible results, with 95% yield and more than 99% enantiomeric purity, were obtained (Scheme 3).^[13] With these reaction conditions we assessed the scope with respect to the organomagnesium reagents for this reaction system. A number of chiral 2-substituted 2,3-dihydro-4-pyridone products derived from the addition of linear (**4a–d**), β-, and γ-branched (**4e,f**) and functionalized (**4g–i**) Grignard reagents were synthesized with high yields. In all cases excellent enantioselectivities were observed as well (*ee* values 94 to > 99%).

Although asymmetric conjugate addition of arylboronic acid, and aryl and dialkylzinc nucleophiles to *N*-substituted-2,3-dihydro-4-pyridones has been well explored in recent years^[5,6,f,g] we were interested in investigating the behavior of our catalytic system when applied to these substrates. Given their substantially higher reactivity than **3** we anticipated that Lewis acids would not be needed and that low temperatures would most likely be required to avoid noncatalyzed addition of Grignard reagents. Indeed, quick screening of several Grignard reagents, namely MeMgBr, EtMgBr, and *n*PrMgBr supported this notion and the corresponding chiral 2-substituted 4-piperidones (**6a–c**) were obtained with excellent yields and enantiomeric excesses above 90% (Scheme 4).

Our next quest was to access chiral products derived from additions to *N*-substituted-2-quinolones, which are formally cyclic α,β-conjugated amides and are expected to be less reactive than 4-quinolones (Scheme 5). We were pleased to find that when using 2-quinolones with an OMe protecting group at the *N* atom, the corresponding deprotected products **8a–h** were obtained with excellent enantiomeric excess and chemical yields. However, to reach full conversion and high



Scheme 4. Scope of the reaction of *N*-Cbz-2,3-dihydro-4-pyridone (**5**) with organomagnesium reagents. Reaction conditions: *N*-Cbz-2,3-dihydro-4-pyridone **5** (0.2 mmol), EtMgBr (2.0 equiv), **L1** (6 mol%), and CuBr-SMe₂ (5 mol%) in CH₂Cl₂ (2 mL) at -78 °C for 12 h.



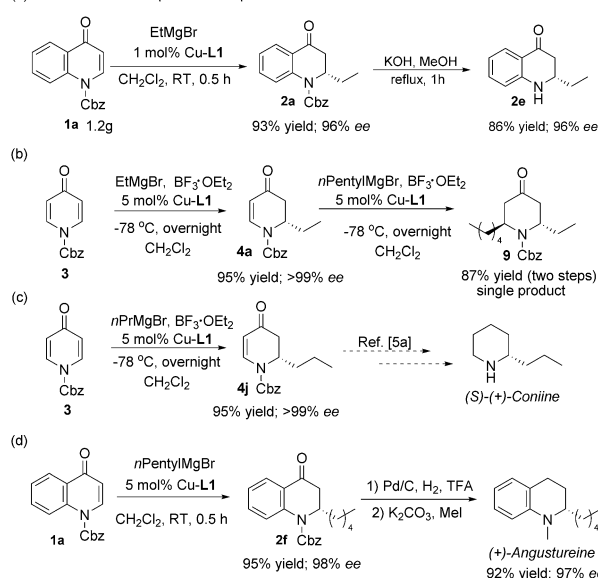
Scheme 5. Scope of conjugate addition reactions of organomagnesium reagents to the *N*-protected 2-quinolones **7**. Reaction conditions: 2-quinolone **7** (0.2 mmol), EtMgBr (2.0 equiv), Ligand **L1** (6 mol%), TMSBr (2.0 equiv), and CuBr-SMe₂ (5 mol%) in CH₂Cl₂ (2 mL) at -78 °C for 12 h. Absolute configuration of **8j** was established by X-ray crystallography.^[14]

yields it is necessary to use a Lewis acid, with TMSBr performing best. Importantly, the methoxy substituent at the N atom is removed upon reaction work up. Using this reaction protocol we obtained a variety of products using various Grignard reagents as well as substrates with different substituents in the aromatic ring. It is noteworthy that this catalytic system tolerates 2-quinolone substrates with various protecting groups, such as Me, Bn, and allyl on N. The products **8i–k**, derived from conjugate addition of EtMgBr to these substrates, were obtained with enantiomeric purities above 93% and yields above 72%.

Finally, to demonstrate the potential applications of our reaction protocol, we carried out a gram-scale reaction as well as several additional transformations, all depicted in Scheme 6.

In summary, we have developed the first general protocol for the alkylation of various classes of N-heterocyclic electro-

(a) Gram-scale and deprotection experiment



Scheme 6. Gram-scale reaction and useful derivatizations.

philes with organomagnesium reagents, utilizing one catalytic system based on a Cu^I complex with (*R,R*)-Ph-BPE. Alkylation of 2-quinolones, 4-quinolones, and 4-pyridones provides easy access to various derivatives of chiral 2- and 4-substituted tetrahydroquinolones and dihydro-4-pyridones in excellent yields and enantioselectivities. Significantly, addition reactions to *N*-substituted-4-quinolones can be carried out at room temperature, while consecutive alkylation of pyridone and the resulting 2,3-dihydro-4-pyridones allows convenient catalytic access to 2,6-substituted diastereomerically and enantiomerically pure piperidones. We anticipate that this methodology will be a valuable synthetic tool and find practical application in the synthesis of complex building blocks and natural and pharmaceutical compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · asymmetric catalysis · copper · Grignard reagent · Michael addition

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Angew. Chem. **2019**, *131*, 13084–13088

- [1] For reviews and selected examples, see: a) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642–2713; b) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157–7259; c) R. A. Saporito, H. M. Garraffo, M. A. Donnelly, A. L. Edwards, J. T. Longino, J. W. Daly, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 8045–8050.
- [2] For selected examples of catalytic asymmetric hydrogenation, see: a) W. B. Wang, S. M. Lu, P. Y. Yang, X. W. Han, Y. G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537; b) T. Wang, L. G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q. H. Fan, J. Xiang, Z. X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891; c) N. Mršić, L. Lefort, J. A. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081–1089; d) J. Wen, R. Tan, S. Liu, Q. Zhao, X. Zhang, *Chem. Sci.* **2016**, *7*, 3047–3051; e) X. F. Tu, L. Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 11346–11349; *Angew. Chem.* **2012**, *124*, 11508–11511; f) Q. S. Guo, D. M. Du, J. Xu, *Angew. Chem. Int. Ed.* **2008**, *47*, 759–762; *Angew. Chem.* **2008**, *120*, 771–774; g) M. Rueping, A. P. Antonchick, T. A. Theissmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686; *Angew. Chem.* **2006**, *118*, 3765–3768.
- [3] For selected examples of asymmetric cyclization reactions, see: a) Y. M. Sun, P. Gu, Y. N. Gao, Q. Xu, M. Shi, *Chem. Commun.* **2016**, *52*, 6942–6945; b) K. Saito, Y. Moriya, T. Akiyama, *Org. Lett.* **2015**, *17*, 3202–3205; c) X. Liu, Y. Lu, *Org. Lett.* **2010**, *12*, 5592–5595; d) S. Kobayashi, S. Komiyama, H. Ishitani, *Angew. Chem. Int. Ed.* **1998**, *37*, 979–981; *Angew. Chem.* **1998**, *110*, 1026–1028; e) K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588; *Angew. Chem.* **2000**, *112*, 3702–3733; f) N. Kandedu, I. Abrunhosa-Thomas, Y. Troin, *Org. Chem. Front.* **2017**, *4*, 1655–1704; g) M. Sánchez-Roselló, J. L. Aceña, A. Simón-Fuentes, C. del Pozo, *Chem. Soc. Rev.* **2014**, *43*, 7430–7453.
- [4] a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446; b) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166–187; c) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031–15070; d) M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953–2989.
- [5] For selected examples of asymmetric conjugate addition reactions by using chiral auxiliaries, see: a) R. S. Al-awar, S. P. Joseph, D. L. Comins, *J. Org. Chem.* **1993**, *58*, 7732–7739; b) D. L. Comins, X. Chen, L. A. Morgan, *J. Org. Chem.* **1997**, *62*, 7435–7438; c) D. L. Comins, Y. M. Zhang, S. P. Joseph, *Org. Lett.* **1999**, *1*, 657–659; d) D. L. Comins, Y. M. Zhang, X. Zheng, *Chem. Commun.* **1998**, 2509–2510; e) D. L. Comins, C. A. Brooks, R. S. Al-awar, R. R. Goehring, *Org. Lett.* **1999**, *1*, 229–232.
- [6] For selected examples of catalytic asymmetric conjugate additions to quinolones and dihydropyridones: a) R. Shintani, N. Tokunaga, H. Doi, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 6240–6241; b) R. Shintani, T. Yamagami, T. Kimura, T. Hayashi, *Org. Lett.* **2005**, *7*, 5317–5319; c) D. Müller, A. Alexakis, *Org. Lett.* **2012**, *14*, 1842–1845; d) R. B. Jagt, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 2433–2435; e) Q. Xu, R. Zhang, T. Zhang, M. Shi, *J. Org. Chem.* **2010**, *75*, 3935–3937; f) R. Sebesta, M. G. Pizzuti, A. J. Boersma, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2005**, 1711–1713; g) M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2008**, *6*, 3464–3466.
- [7] a) M. Á. Fernández-Ibáñez, B. Macia, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2009**, *48*, 9339–9341; *Angew. Chem.* **2009**, *121*, 9503–9505; b) F. W. Hartrampf, T. Furukawa, D. Trauner, *Angew. Chem. Int. Ed.* **2017**, *56*, 893–896; *Angew. Chem.* **2017**, *129*, 912–915; c) W. Shao, Y. Wang, Z. P. Yang, X. Zhang, S. L. You, *Chem. Asian J.* **2018**, *13*, 1103–1107.
- [8] 4-Pyridones have been explored in addition reactions with various organometallics only for non-asymmetric reactions (see the references below). In reference (b) however one example of catalytic asymmetric addition was reported for the addition of Et₂Zn to 4-pyridone, furnishing the final product with 82% ee. a) F. Guo, R. C. Dhakal, R. K. Dieter, *J. Org. Chem.* **2013**, *78*, 8451–8464; b) R. K. Dieter, F. Guo, *J. Org. Chem.* **2009**, *74*, 3843–3848.
- [9] C. J. Pilkington, A. Zanotti-Gerosa, *Org. Lett.* **2003**, *5*, 1273–1275.
- [10] G. P. Howell, *Org. Process Res. Dev.* **2012**, *16*, 1258–1272.
- [11] a) A. Alexakis, J. E. Backvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796–2823; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844; c) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824–2852.
- [12] For the optimization data see the Supporting Information.
- [13] In contrast with 4-quinolone, this reaction does not work at room temperature because of compatibility issues between BF₃·OEt₂ and the Grignard reagent at this temperature. For effect of Lewis acids in asymmetric catalysis and their compatibility with Grignard reagents, see: a) J. Rong, R. Oost, A. Desmarchelier, A. J. Minnaard, S. R. Harutyunyan, *Angew. Chem. Int. Ed.* **2015**, *54*, 3038–3042; *Angew. Chem.* **2015**, *127*, 3081–3085; b) R. P. Jumde, F. Lanza, M. J. Veenstra, S. R. Harutyunyan, *Science* **2016**, *352*, 433–437; c) M. Rodríguez-Fernández, X. Yan, J. F. Collados, P. B. White, S. R. Harutyunyan, *J. Am. Chem. Soc.* **2017**, *139*, 14224–14231; d) R. P. Jumde, F. Lanza, T. Pellegrini, S. R. Harutyunyan, *Nat. Commun.* **2017**, *8*, 2058.
- [14] CCDC 1942935 (**2k**) and 1942936 (**8j**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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