Enantioselective Reactions

Deutsche Ausgabe: DOI: 10.1002/ange.201509967
Internationale Ausgabe: DOI: 10.1002/anie.201509967

Combining Organocatalysis with Central-to-Axial Chirality Conversion: Atroposelective Hantzsch-Type Synthesis of 4-Arylpyridines

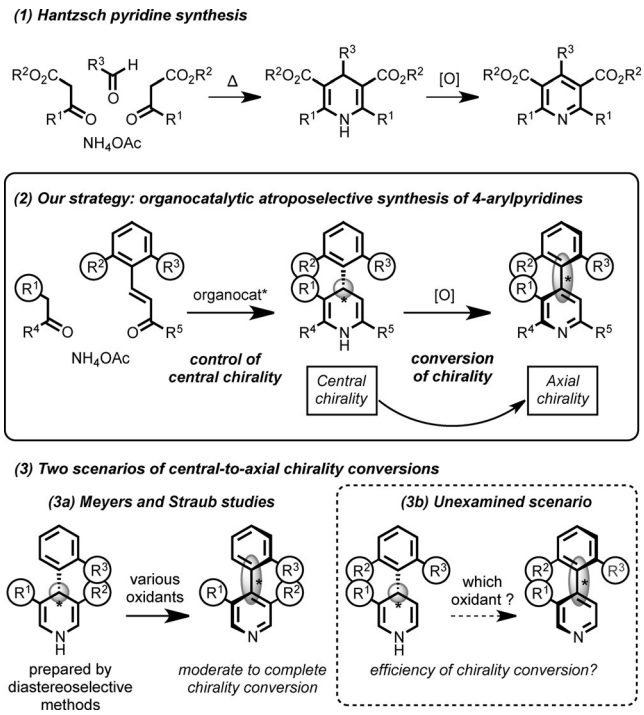
Ophélie Quinonero, Marion Jean, Nicolas Vanthuyne, Christian Roussel, Damien Bonne, Thierry Constantieux, Cyril Bressy, Xavier Bugaut,* and Jean Rodriguez**

Abstract: *Suitably substituted enantioenriched 4-aryl-1,4-dihydro-pyridines prepared by an organocatalytic enantioselective Michael addition were oxidized with MnO_2 into axially chiral 4-arylpyridines with central-to-axial chirality conversion. Moderate to complete percentages (cp) were observed, and a model for the conversion of chirality is discussed.*

In view of the importance of atropisomerism in natural product chemistry,[1] drug discovery,[2] and catalyst design,[3] the stereoselective access to enantioenriched biaryls has been the focus of numerous studies.[4] Despite the tremendous development of enantioselective organocatalysis over the past fifteen years,[5] the majority of methodologies in this field focused on the control of central chirality, whereas synthetic approaches targeting axially chiral biaryls have started to emerge only recently.[6–9]

Chirality conversions represent a fascinating class of chemical processes consisting of the destruction of a stereogenic element on a molecule and the simultaneous installation of another stereogenic element of a different nature.[10] First hypothesized in 1955 by Berson,[11] the feasibility of central-to-axial chirality conversion in biarylic systems was elegantly demonstrated by Meyers almost 30 years later.[12] Since then, chirality conversion has found only a limited number of applications in comparison to its potential.[10,13]

In 1881, Hantzsch developed a multicomponent, two-step synthesis of pyridines consisting of the condensation of two equivalents of a β-ketoester with an aldehyde and ammonium acetate, followed by the oxidation of the intermediate 1,4-dihydropyridine [Scheme 1.1].[14] The pyridine ring is among the most encountered scaffolds in bioactive molecules,[15] but, despite promising biological activities,[16] atropisomeric 4-arylpyridines have received less attention because there is a lack of enantioselective synthetic approaches to prepare them. Indeed, the only pre-existing catalytic enantioselective method for the synthesis of this structural motif, a Suzuki–Miyaura cross-coupling, culminated in 42% *ee*.[17]



Scheme 1. Rationale for the development of an atroposelective Hantzsch-type synthesis of 4-arylpyridines.

To address this issue, we envision a stepwise strategy combining an organocatalytic enantioselective Michael-addition-initiated synthesis of 4-aryl-1,4-dihydropyridines,[18,19] followed by a central-to-axial chirality conversion through an oxidative aromatization [Scheme 1.2]. To achieve this goal, two main challenges had to be solved: i) the selection of suitable substrates, especially a Michael acceptor that allows a compromise between reactivity and selectivity in the organocatalytic Michael addition, and the steric hindrance required to reach high enough barriers to rotation to maintain the integrity of the chiral axis; ii) the development of oxidation conditions that preserve the enantiopurity during the aromatization. In both previous diastereoselective approaches to 4-arylpyridine atropisomers by chirality conversion,[12,13b] the target products bear two substituents *ortho* to the chiral axis on the pyridine ring and one on the other aryl group [Scheme 1.3a,], whereas the present complemen-

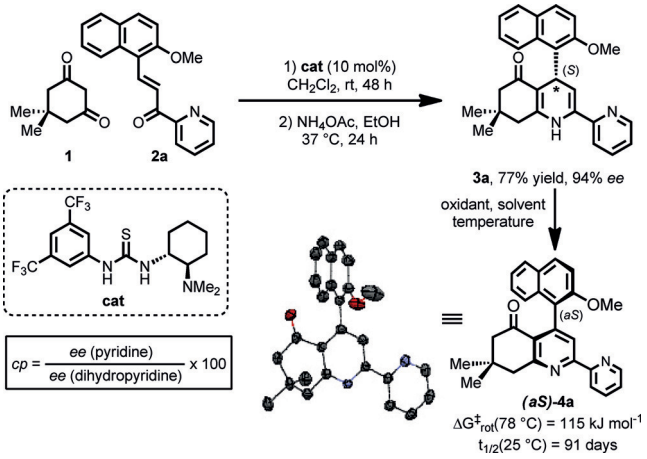
[*] O. Quinonero, M. Jean, Dr. N. Vanthuyne, Prof. Dr. C. Roussel, Dr. D. Bonne, Prof. Dr. T. Constantieux, Prof.Dr. C. Bressy, Dr. X. Bugaut, Prof. Dr. J. Rodriguez
Aix Marseille Université
Centrale Marseille, CNRS, iSm2 UMR 7313
13397 Marseille (France)
E-mail: cyril.bressy@univ-amu.fr
xavier.bugaut@univ-amu.fr
jean.rodriguez@univ-amu.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509967.

tary scenario with a single substitution on the pyridine ring has remained unstudied [Scheme 1.3b]. This structural difference is expected to strongly influence the conversion of the chiral information during the aromatization process. Herein, we disclose how the two aforementioned challenges were addressed to develop the first organocatalysis-based synthesis of axially chiral 4-arylpyridines with up to 94% *ee*.

Our initial investigations focused on the potential use of β-aryl-2-enoylpyridines as suitable electron-poor olefins for the enantioselective Michael addition (Table 1).[20] Despite its

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



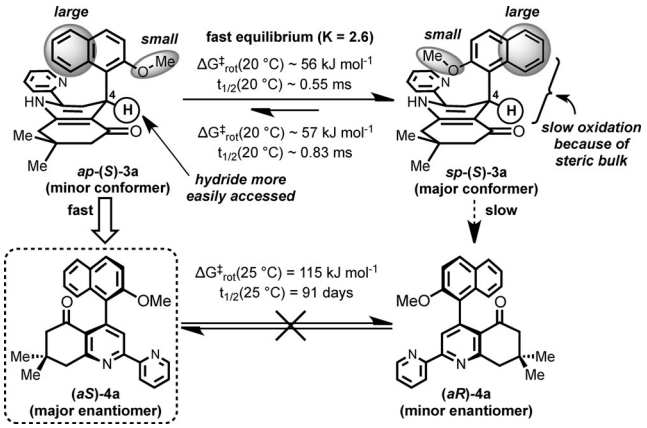
Entry	Oxidant, solvent, temperature[a]	*ee*[b] **3a** [%]	Yield[c] **4a** [%]	*ee*[b] **4a** [%]	*cp* [%]
1	DDQ, CH_2Cl_2, 25 °C	84	19	8	10
2	DDQ, CH_2Cl_2, −78 °C	88	35	2	2
3	$NOBF_4$, CH_3CN, 25 °C	86	62	8	9
4	MnO_2,[d] $CHCl_3$, 20 °C	94	59	78	83
5	**MnO_2,[e] C_6H_{12}, 20 °C**	**94–95**	**60–68[f] (46)[g]**	**82–86[f] (99)[g]**	**86–91**

[a] See the Supporting Information for the reaction conditions. [b] Enantiomeric excesses (*ee*) were determined by HPLC analysis on chiral stationary phase. [c] Yield of purified product. [d] 40 equiv. [e] 20 equiv. [f] Range obtained from four independent reactions. [g] After crystallization of the final product from Et_2O. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

high steric hindrance, the combination of derivative **2a** with dimedone (**1**) in the presence of various bifunctional organocatalysts enabled the exclusive formation of the expected 4-aryl-1,4-dihydropyridine **3a**, after the treatment of the intermediate Michael adduct with ammonium acetate in ethanol. All of the bifunctional catalysts that were screened afforded **3a** in similar yields, with the (*R*,*R*)-Takemoto thiourea catalyst performing best.[21,22] These results were preserved upon scale-up: 1,4-dihydropyridine **3a** was prepared on more than 2.5-mmol scale in 77% yield over the two steps and with 94% *ee*.

We then studied the behavior of 1,4-dihydropyridine **3a** in the presence of different oxidants (Table 1). As suspected, the oxidative methods used in previous conversions of chirality could not be directly applied to the preparation of enantioenriched **4a**. Indeed, the initial attempt to aromatize **3a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature, as described by Meyers,[12] afforded **4a** in low yield and as a virtually racemic product with a conversion percentage (*cp*) lower than 10% (entry 1). At this point, we verified that the barrier to rotation of the chiral axis was high enough to prevent the racemization of product **4a** during the reaction or its purification: indeed, with $\Delta G^{\ddagger}_{rot} = 115\ kJ\,mol^{-1}$ at 78 °C, the half-life of rotation is higher than 90 days at 25 °C (assuming that $\Delta G^{\ddagger}_{rot}$ is independent of the temperature).[21] Adding the oxidant at −78 °C had no positive impact on the outcome of the reaction (entry 2). Nitrosonium tetrafluoroborate $NOBF_4$ was also inefficient at converting the chiral information (entry 3).[13b] Pleasingly, when excess activated manganese dioxide MnO_2 was used in $CHCl_3$,[13b] pyridine **4a** was obtained with a promising yield and a *cp* of 83% (entry 4). A thorough optimization of the oxidation step was then carried out:[21] when **3a** was treated with 20 equivalents of MnO_2 in cyclohexane at 20 °C, the enantioenriched 4-arylpyridine **4a** was reproducibly isolated in around 65% yield with an enantiomeric excess of 82–86%, meaning that the chiral information was converted with 86–91% efficiency (entry 5). Fortunately, a crystallization from Et_2O at low temperature delivered 4-arylpyridine **4a** as a virtually enantiopure product (99% *ee*) in reasonable yield.[21] In accordance with the literature precedents, an (*S*) configuration was attributed to the stereogenic center of **3a**,[20a,21] and the absolute configuration of product **4a** chiral axis was determined as being (*aS*) by X-ray diffraction analysis (Table 1).[23]

1,4-Dihydropyridines are known to exist predominantly as boat conformers, with the more bulky substituent on position 4 in pseudo-axial position (Scheme 2).[13b] In the case of



Scheme 2. Proposed model for the conversion of chirality.

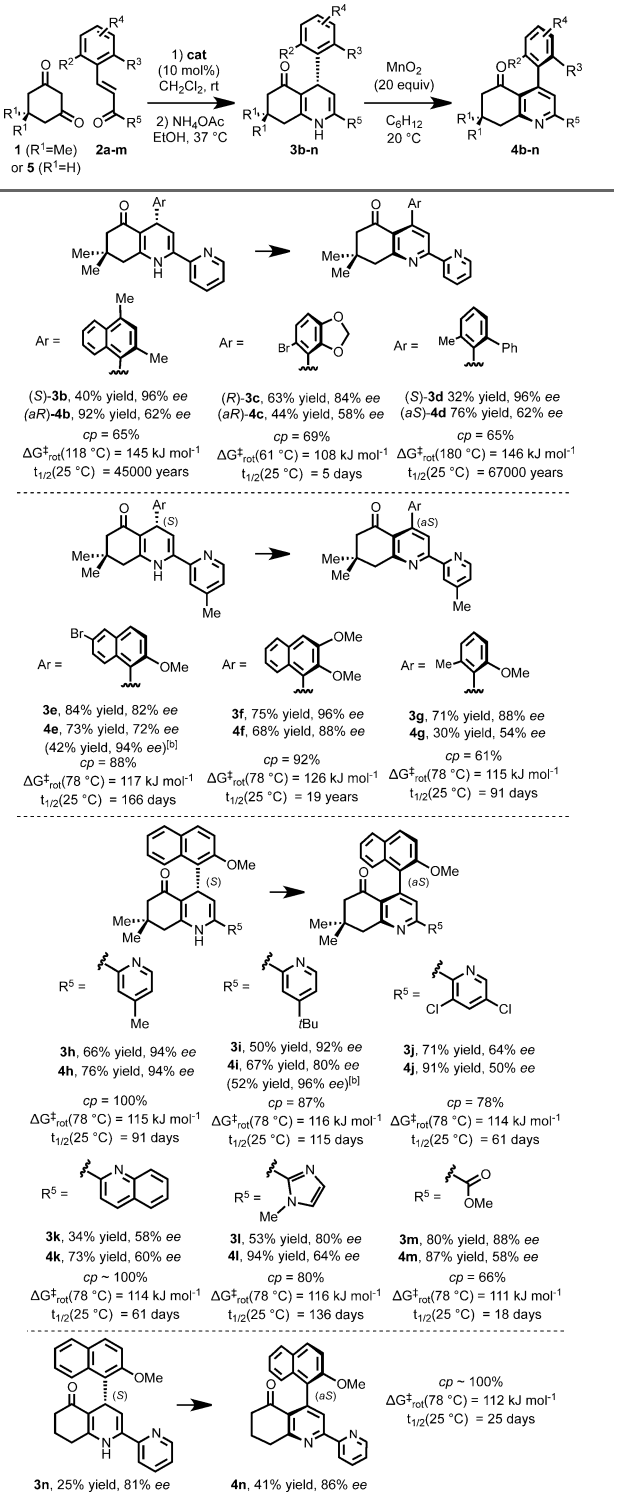
compound **(*S*)-3a**, the steric bulk around this bond in the axial orientation slows down its rotation and complicated the characterization of the product. Performing the NMR analyses at more than 80 °C accelerated this rotation and allowed recording of NMR spectra suitable for the description of the product.[21] In contrast, a gradual decrease of the temperature allowed distinguishing clearly the spectra of the major rotamer ***sp*-(*S*)-3a**, for which the bulky aromatic group is

positioned away from the crowded dihydropyridine ring, and the minor one ***ap-(S)*-3a**, in a roughly 2.6:1 ratio. Their oxidations result in the formation of both enantiomers of 4-arylpyridine, **(*aR*)-4a** and **(*aS*)-4a**, respectively. By application of the Eyring equation, barriers to rotation $\Delta G^{\ddagger}_{rot}$(20 °C) to interconvert rotamers ***sp-(S)*-3a** and ***ap-(S)*-3a** could be estimated to 56–57 kJ mol^{-1}. This value corresponds to a half-life $t_{1/2}$(20 °C) of less than 1 ms, indicating that the rotation of the hindered bond is fast in comparison with the kinetics of the oxidation.[21] Consistent with other reports,[12,13b] our observations point towards a scenario where the two conformers are in fast equilibrium and the chirality conversion depends on the ability of the oxidant to efficiently discriminate between the two conformers. Moreover, the absolute configuration of **4a** indicates that the oxidation preferentially occurs for the less stable conformer ***ap*-(*S*)-3a**, presumably because of greater accessibility to the hydride on position 4 of the 1,4-dihydropyridine.

To complete our study, we set on exploring the scope and limitations of the atroposelective Hantzsch-type synthesis of axially chiral 4-arylpyridines (Table 2). The absolute configurations of the products **4b–n** were attributed by correlation to the one of ***(aS)*-4a**, in accordance with the model proposed in Scheme 2 and the interference values of the substituents.[24] Our strategy could be successfully applied to the synthesis of several enantioenriched 4-arylpyridines **4b–g** bearing diverse 2-substituted naphthyl and 2,6-disubstituted phenyl motifs, with methyl, phenyl, and alkoxy groups, or a bromine atom as blocking substituents, with moderate to complete conversion percentages. Moreover, variations on the substitution pattern of the 2-pyridyl group with additional electron-donating or electron-withdrawing groups, along with its replacement by a quinolinyl unit, were possible. The enantioselectivities of the organocatalytic Michael addition varied, but conversion percentages remained high (from 78% to 100%) for **4h–k**, and product **4h** was even obtained with an enantiomeric excess of 94%. Further structural diversity was introduced with Michael acceptors bearing either an *N*-methylimidazole ring or an ester function, leading to 2-functionalized-4-arylpyridines **4l** and **4m**, with a slightly decreased efficiency of the chirality conversion. Finally, dimedone can also be replaced by cyclohexa-1,3-dione (**5**), with lower yields but a complete chirality conversion during the preparation of **4n**. As for the standard substrate, crystallization from Et_2O allows improving the enantiomeric excesses of the products, and this method was exemplified on compounds **4e** and **4i**, whose enantiomeric excesses could be increased from 72% to 94% and 80% to 96%, respectively.

In conclusion, we developed an enantioselective synthesis of axially chiral 4-arylpyridines with up to 94% *ee*. The synthetic route combines an organocatalytic synthesis of 4-aryl-1,4-dihydropyridines with an oxidative conversion of chirality. In view of the numerous enantioselective organocatalytic transformations that deliver partially saturated carbo- or heterocycles bearing stereogenic centers,[25] further efforts will be directed towards the implementation of the present strategy on other families of chiral biaryls. More detailed studies on the structural factors that influence the

Table 2: Substrate scope for the atroposelective synthesis of 4-arylpyridines **4b–n**.[a]



[a] Yield of isolated pure 1,4-dihydropyridines **3b–n** (over two steps) and pyridines **4b–n** after purification by flash chromatography. Enantiomeric excesses (*ee*) were determined by HPLC analysis on chiral stationary phase. For the determination of barriers to rotation $\Delta G^{\ddagger}$ and half-lives $t_{1/2}$, see the Supporting Information. [b] Yields and enantiomeric excesses between brackets refer to the results obtained after crystallization from Et_2O.

chirality conversion, especially the unique behavior of MnO_2 as the oxidant, will be conducted.

Acknowledgements

We warmly thank Roseline Rosas for VT NMR experiments, Michel Giorgi for X-ray diffraction analyzes, and the whole team of the Spectropole (http://www.spectropole.fr). Financial support from Aix Marseille Université, Centrale Marseille, the CNRS and the Agence Nationale de la Recherche (ANR-13-BS07-0005, scholarship for O.Q.) is acknowledged.

Keywords: atropisomers · chiral conversion · enantioselectivity · organocatalysis · pyridines

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 1401 – 1405
Angew. Chem. **2016**, *128*, 1423 – 1427

[1] a) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; b) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; c) A. Zask, J. Murphy, G. A. Ellestad, *Chirality* **2013**, *25*, 265; d) J. E. Smyth, N. M. Butler, P. A. Keller, *Nat. Prod. Rep.* **2015**, *32*, 1562.

[2] a) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem. Int. Ed.* **2009**, *48*, 6398; *Angew. Chem.* **2009**, *121*, 6516; b) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, *54*, 7005.

[3] a) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345; b) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047.

[4] For reviews, see: a) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; *Angew. Chem.* **2005**, *117*, 5518; b) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418.

[5] a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; b) B. List, K. Maruoka, *Asymmetric Organocatalysis*, Thieme, Stuttgart, **2012**; c) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, Vol. 3* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.

[6] (Dynamic) kinetic resolution of pre-existing biaryls: a) J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251; b) J. L. Gustafson, D. Lim, K. T. Barrett, S. J. Miller, *Angew. Chem. Int. Ed.* **2011**, *50*, 5125; *Angew. Chem.* **2011**, *123*, 5231; c) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964; d) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *Chem. Sci.* **2013**, *4*, 4235; e) S. Shirakawa, X. Wu, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 14200; *Angew. Chem.* **2013**, *125*, 14450; f) D.-J. Cheng, L. Yan, S.-K. Tian, M.-Y. Wu, L.-X. Wang, Z.-L. Fan, S.-C. Zheng, X.-Y. Liu, B. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 3684; *Angew. Chem.* **2014**, *126*, 3758; g) S. Lu, S. B. Poh, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 11041; *Angew. Chem.* **2014**, *126*, 11221; h) G. Ma, J. Deng, M. P. Sibi, *Angew. Chem. Int. Ed.* **2014**, *53*, 11818; *Angew. Chem.* **2014**, *126*, 12012; i) R. J. Armstrong, M. D. Smith, *Angew. Chem. Int. Ed.* **2014**, *53*, 12822; *Angew. Chem.* **2014**, *126*, 13036; j) R. Miyaji, K. Asano, S. Matsubara, *J. Am. Chem. Soc.* **2015**, *137*, 6766.

[7] Benzidine rearrangements: a) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess, L. Kürti, *J. Am. Chem. Soc.* **2013**, *135*, 7414; b) C. K. De, F. Pesciaioli, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 9293; *Angew. Chem.* **2013**, *125*, 9463.

[8] Construction of one aromatic ring: a) M. Terada, K. Dan, *Chem. Commun.* **2012**, *48*, 5781; b) A. Link, C. Sparr, *Angew. Chem. Int. Ed.* **2014**, *53*, 5458; *Angew. Chem.* **2014**, *126*, 5562; c) for a Highlight, see: O. Quinonero, C. Bressy, X. Bugaut, *Angew. Chem. Int. Ed.* **2014**, *53*, 10861; *Angew. Chem.* **2014**, *126*, 11039; d) During the preparation of our manuscript, results on the NHC-catalyzed synthesis of axially chiral 2-formylbiaryls have been disclosed: L. Candish, A. Levens, D. W. Lupton, *Chem. Sci.* **2015**, *6*, 2366.

[9] For reviews, see: a) G. Bencivenni, *Synlett* **2015**, 1915; b) S. Shirakawa, S. Liu, S. Kaneko, *Chem. Asian J.* **2015**, DOI: 10.1002/asia.201500951.

[10] Chirality (inter)conversion differs from chirality transfer, in that the latter one represents transformations where the stereogenic element that is created and the one that is destroyed are of the same nature. We consider conversion as a more suitable term than interconversion because the latter one would imply a reversible process. For further details, see: C. Wolf, in *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, RSC, Cambridge, **2008**, pp. 233 – 271.

[11] J. A. Berson, E. Brown, *J. Am. Chem. Soc.* **1955**, *77*, 450.

[12] A. I. Meyers, D. G. Wettlaufer, *J. Am. Chem. Soc.* **1984**, *106*, 1135.

[13] For other occurrences of this strategy in the synthesis of chiral biaryls, see: a) M. Shindo, K. Koga, K. Tomioka, *J. Am. Chem. Soc.* **1992**, *114*, 8732; b) A. Straub, A. Goehrt, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2662; *Angew. Chem.* **1996**, *108*, 2832; c) T. Hattori, M. Date, K. Sakurai, N. Morohashi, H. Kosugi, S. Miyano, *Tetrahedron Lett.* **2001**, *42*, 8035; d) Y. Nishii, K. Wakasugi, K. Koga, Y. Tanabe, *J. Am. Chem. Soc.* **2004**, *126*, 5358; e) Y. Liu, K. Lu, M. Dai, K. Wang, W. Wu, J. Chen, J. Quan, Z. Yang, *Org. Lett.* **2007**, *9*, 805; f) F. Guo, L. C. Konkol, R. J. Thomson, *J. Am. Chem. Soc.* **2011**, *133*, 18; g) L. C. Konkol, F. Guo, A. A. Sarjeant, R. J. Thomson, *Angew. Chem. Int. Ed.* **2011**, *50*, 9931; *Angew. Chem.* **2011**, *123*, 10105; h) F. Prause, B. Arensmeyer, B. Frohlich, M. Breuning, *Catal. Sci. Technol.* **2015**, *5*, 2215.

[14] a) A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637; b) J.-J. Vanden Eynde, A. Mayence, *Molecules* **2003**, *8*, 381; c) J.-J. Xia, G.-W. Wang, *Synthesis* **2005**, 2379; d) F. Liéby-Muller, C. Allais, T. Constantieux, J. Rodriguez, *Chem. Commun.* **2008**, 4207; e) For a review on the metal-free multicomponent synthesis of pyridines, see: C. Allais, J.-M. Grassot, J. Rodriguez, T. Constantieux, *Chem. Rev.* **2014**, *114*, 10829.

[15] Pyridine is the second most frequent heterocycle in FDA-approved drugs. See: E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[16] Axially chiral 4-arylpyridines exhibit diverse biological activities, see: a) G. Bringmann, Y. Reichert, V. V. Kane, *Tetrahedron* **2004**, *60*, 3539, and references therein; b) K. R. Fandrick, W. Li, Y. Zhang, W. Tang, J. Gao, S. Rodriguez, N. D. Patel, D. C. Reeves, J.-P. Wu, S. Sanyal, N. Gonnella, B. Qu, N. Haddad, J. C. Lorenz, K. Sidhu, J. Wang, S. Ma, N. Grinberg, H. Lee, Y. Tsantrizos, M.-A. Poupart, C. A. Busacca, N. K. Yee, B. Z. Lu, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2015**, *54*, 7144; *Angew. Chem.* **2015**, *127*, 7250, and references therein.

[17] a) T. J. Donohoe, C. R. Jones, A. F. Kornahrens, L. C. A. Barbosa, L. J. Walport, M. R. Tatton, M. O'Hagan, A. H. Rathi, D. B. Baker, *J. Org. Chem.* **2013**, *78*, 12338 – 12350; b) A Pd-catalyzed synthesis of moderately to highly enantioenriched 4-aryl-2-quinolinones was also reported: T. Shibuya, Y. Shibata, K. Noguchi, K. Tanaka, *Angew. Chem. Int. Ed.* **2011**, *50*, 3963; *Angew. Chem.* **2011**, *123*, 4049.

[18] For seminal studies, see: a) J. Moreau, A. Duboc, C. Hubert, J.-P. Hurvois, J.-L. Renaud, *Tetrahedron Lett.* **2007**, *48*, 8647; b) P. T. Franke, R. L. Johansen, S. Bertelsen, K. A. Jørgensen, *Chem. Asian J.* **2008**, *3*, 216; c) J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao, L.-

Z. Gong, *Angew. Chem. Int. Ed.* **2008**, *47*, 2458; *Angew. Chem.* **2008**, *120*, 2492; d) For a review, see: H. Thu Pham, I. Chataigner, J.-L. Renaud, *Curr. Org. Chem.* **2012**, *16*, 1754.

[19] Our group has also contributed to this field by preparing different families of enantioenriched polyhydropyridines. See: a) M. M. Sanchez Duque, O. Baslé, Y. Génisson, J.-C. Plaquevent, X. Bugaut, T. Constantieux, J. Rodriguez, *Angew. Chem. Int. Ed.* **2013**, *52*, 14143; *Angew. Chem.* **2013**, *125*, 14393; b) H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Adv. Synth. Catal.* **2014**, *356*, 851; c) Y. Dudognon, H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Chem. Commun.* **2015**, *51*, 1980.

[20] a) N. Molleti, S. Allu, S. K. Ray, V. K. Singh, *Tetrahedron Lett.* **2013**, *54*, 3241; b) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2014**, *114*, 6081.

[21] See the Supporting Information for further details.

[22] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[23] CCDC 1056472 contains the supplementary crystallographic data for product **(*aS*)-4a**, available free of charge from The Cambridge Crystallographic Data Centre.

[24] a) G. Bott, L. D. Field, S. Sternhell, *J. Am. Chem. Soc.* **1980**, *102*, 5618; Further chiroptic studies will aim at securing the absolute configurations of all products **4b**–**k**. For more recent related studies, see: b) N. Vanthuyne, F. Andreoli, S. Fernandez, M. Roman, C. Roussel, *Lett. Org. Chem.* **2005**, *2*, 433; c) C. Roussel, N. Vanthuyne, M. Bouchekara, A. Djafri, J. Elguero, I. Alkorta, *J. Org. Chem.* **2008**, *73*, 403; d) R. Ruzziconi, S. Spizzichino, L. Lunazzi, A. Mazzanti, M. Schlosser, *Chem. Eur. J.* **2009**, *15*, 2645.

[25] a) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1909; b) X. Bugaut, D. Bonne, Y. Coquerel, J. Rodriguez, T. Constantieux, *Curr. Org. Chem.* **2013**, *17*, 1920; c) see also Reference [18d].

Received: October 26, 2015
Published online: December 14, 2015

