Direct Access to Alkylideneoxindoles via Axially Enantioselective Knoevenagel Condensation

Published Version:
Simone Crotti, N.D.I. (2019). Direct Access to Alkylideneoxindoles via Axially Enantioselective Knoevenagel Condensation. ORGANIC LETTERS, 21(9), 3013-3017 [10.1021/acs.orglett.9b00505].

Availability:
This version is available at: https://hdl.handle.net/11585/690908 since: 2021-02-28

Published:
DOI: http://doi.org/10.1021/acs.orglett.9b00505

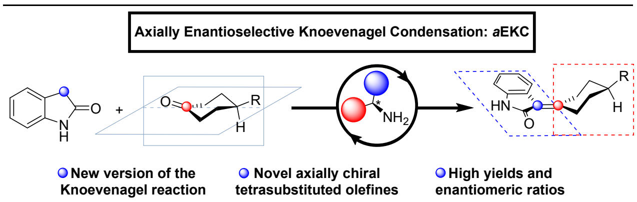
(Article begins on next page)

Direct Access to Alkylideneoxindoles *via* Axially-Enantioselective Knoevenagel Condensation.

Simone Crotti, Nicola Di Iorio, Chiara Artusi, Andrea Mazzanti, Paolo Righi, and Giorgio Bencivenni*

Department of Industrial Chemistry "Toso Montanari" University of Bologna, Viale del Risorgimento 4, 40136, Bologna-I.

Supporting Information Placeholder



ABSTRACT: The organocatalytic axially-enantioselective Knoevenagel condensation between prochiral cyclohexanones and oxindoles is presented. The reaction, promoted by a primary amine, proceeded smoothly and furnished unprecedented examples of novel cyclohexylidene oxindoles displaying axial chirality.

Asymmetric organocatalysis revealed to be an elective platform to perform the synthesis of atropisomers,[1] an important class of chiral molecules bearing a stereogenic axis that originates from the restricted rotation along a single bond.[2] This element of chirality, is the structural feature of many natural and bioactive compounds as well as catalysts or ligands for asymmetric synthesis.[3] An important class of axially chiral compounds is represented by allenes and alkylidenecycloalkanes[4] (Figure 1).

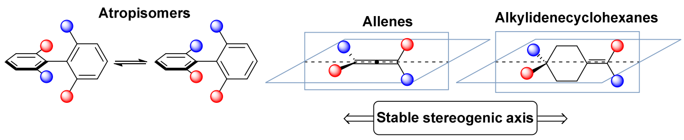


Figure 1. Examples of axially chiral compounds.

Because of their diffusion in Nature, the chemistry of chiral allenes has been largely studied in the past and various catalytic enantioselective synthesis are known.[5] Alkylidenecycloalkanes, despite a few applications as precursors of chiral liquid crystals and in circular dichroism studies,[6,4a] encountered less attention and their catalytic enantioselective syntheses are rare. Previous approaches have been focused on two main strategies: 1) the construction of the double bond by means of Horner-Wadsworth-Emmons (HWE) or Peterson olefination[7] using a stoichiometric amount of chiral reagent or ligands; 2) reduction of prochiral alkylidene cyclohexanone derivatives.[8] An important contribute has been recently proposed by Bernardi who realized the first catalytic synthesis of axially chiral trisubstituted alkylidenes through organocatalyzed Wittig reaction.[9] Despite the straightforward novelty reported, this reaction evidenced in general low enantioselectivities and yields (Figure 2). The Knoevenagel[10] condensation (KC) represents one of the earliest and most important organocatalytic olefination process, however enantioselective versions are rare. The first example, has been recently reported by List who used the KC for the dynamic kinetic resolution of racemic α-branched aldehydes.[11] Surprisingly, to date the use of this venerable transformation for the synthesis of axially chiral olefins remains totally unexplored.

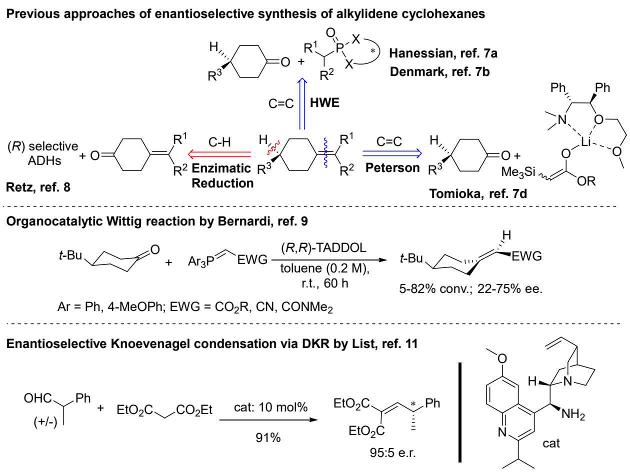
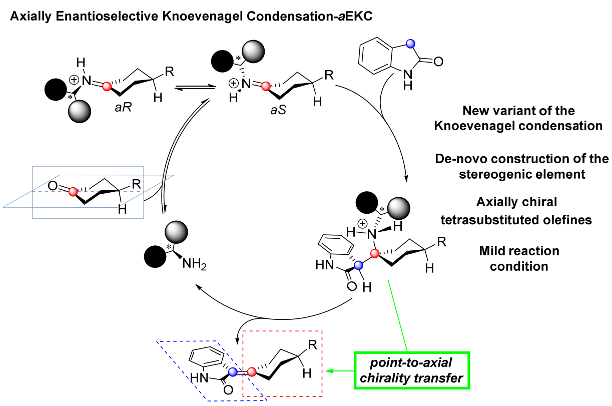


Figure 2. Previous examples of asymmetric olefinations and catalytic enantioselective Knoevenagel condensation.

Our idea is to design a new variant of the Knoevenagel reaction that can assemble together prochiral 4-substituted cyclohexanones and 2-oxindoles realizing the enantioselective generation of a new stereogenic axis in an alkylidene framework (Scheme 1).

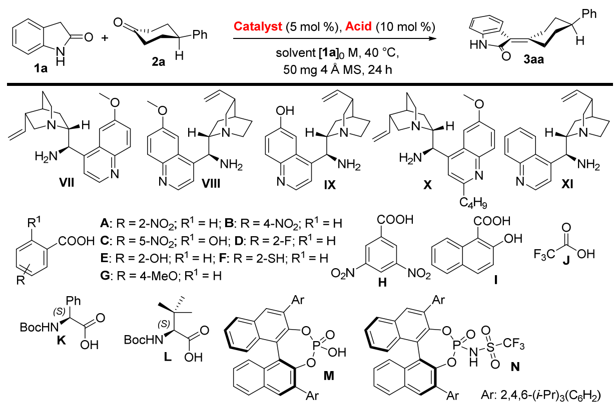
Scheme 1. Strategic plan for the axially enantioselective Knoevenagel condensation (*a*EKC).



We envisioned that a chiral amine can form a pair of diastereomeric iminium ions followed by the alkylation/elimination sequence wherein a point to axial chirality transfer path[12,1f,1k] transforms the 3-alkyl oxindole intermediate into the new axially chiral tetrasubstituted 3-alkylideneoxindoles.[13] The *a*EKC represents a breakthrough in the field of enantioselective olefinations offering a milder, cheaper and easier to handle strategy than the previously reported methodologies which required the use of chiral reagents, stoichiometric amounts of ligands and strong bases. Indeed, in light of the role that many axially chiral compounds cover as drugs and biologically active compounds,[14,3a,3b] the synthesis of novel axially chiral molecules is highly desirable.

We started our investigation by screening various chiral amines as catalysts (Table 1).[15] Cinchona alkaloids primary amines, due to their ease to condense on the carbonyl group of cyclohexanone,[16] catalyzed the *a*EKC in high yield and enantiomeric ratio.

Table 1. Screening of the reaction conditions.[a]



entry	catalyst	acid	solvent (M)	yield (%)[b]	e.r.[c]
1[d]	**VII**	**H**	MeOH (0.1)	55	14:86
2	**VIII**	**H**	MeOH (0.1)	52	85:15
3	**IX**	**H**	MeOH (0.1)	--	--
4	**X**	**H**	MeOH (0.1)	49	14:86
5	**XI**	**H**	MeOH (0.1)	45	83:17
6	**VII**	**H**	toluene (0.1)	63	14:86
7	**VII**	**H**	toluene (0.4)	90	13:87
8	**VII**	**H**	toluene (0.7)	62	14:86
9	**VII**	**H**	toluene (1.0)	64	13:87
10	**VII**	**A**	toluene (0.4)	70	14:86
11	**VII**	**B**	toluene (0.4)	45	12:88
12	**VII**	**C**	toluene (0.4)	62	20:80
13	**VII**	**D**	toluene (0.4)	n.d.	19:81
14	**VII**	**E**	toluene (0.4)	60	14:86
15	**VII**	**F**	toluene (0.4)	n.d.	19:81
16	**VII**	**G**	toluene (0.4)	43	15:85
17	**VII**	**I**	toluene (0.4)	n.d.	22:78
18	**VII**	**J**	toluene (0.4)	----	----
19	**VII**	**K**	toluene (0.4)	12	20:80
20	**VII**	**L**	toluene (0.4)	28	19:81
21	**VII**	**M**	toluene (0.4)	<10	20:80
22	**VII**	**N**	toluene (0.4)	<10	20:80

[a]Reactions were performed on a 0.2 mmol scale using a 1:1 ratio between **1a** and **2a**. [b]Isolated yield. [c]Determined by HPLC using chiral stationary phase. [d]When the reaction was performed without molecular sieves, compound **3aa** was obtained in 8% yield and 59:41 e.r. after 24 hours.

A 5 mol % of 9-epi-NH_2-QDA (**VII**), in combination with 10 mol % of 3,5-dinitrobenzoic acid (**H**), gave **3aa** in 55% yield and 14:86 e.r. With this catalytic combination, we studied different solvents finding an increment of the yield using toluene (entry 6). Despite the reaction was not completely homogeneous, a concentration of 0.4 M was perfect to ensure optimal reactivity and enantiocontrol (entry 7). Higher values were detrimental because of the scarce solubility of oxindole (entries 8-9). The screening of acidic additives (entries 10-21) revealed that benzoic acid derivatives provided better results than trifluoroacetic acid (TFA) and chiral acids (entries 18-22). At the end of these detailed screening[16] 3,5-dinitrobenzoic acid **H** remained the best acidic co-catalyst.

With the optimized conditions the scope and limits of the *a*EKC reaction were studied (Figure 3).

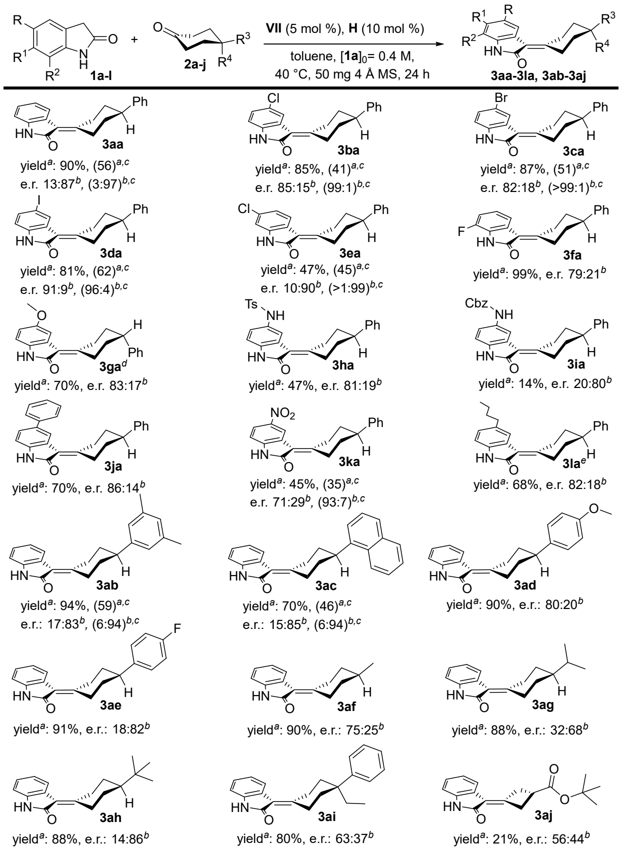
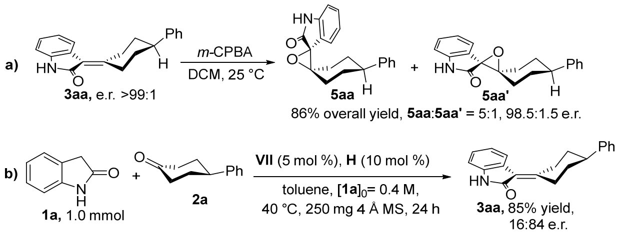


Figure 3. Knoevenagel condensation of oxindoles **1a-l** with prochiral 4-phenylcyclohexanones **2a-j.** The reactions were performed on a 0.2 mmol scale with a 1:1 ratio between **1a-l** and **2a**. [a]Determined via ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. In all cases NMR yields are consistent with isolated yields.[16] [b]Determined by HPLC on chiral stationary phase. [c]Isolated yield and e.r. were determined after filtration of the crude reaction mixture.[17] [d]Catalyst **VIII** was used. [e][**1a**]$_0$= 1.0 M.

The *a*EKC could be performed using oxindoles with different substituents (**3aa-3la**). In general, a good control of the stereochemical outcome is obtained. Various substituents with different electronic properties gave high yields of the corresponding alkylideneoxindole (**3ba-3da, 3fa-3ga**, **3ja**, **3la**) however poor yields can be observed when highly insoluble oxindoles were used (**3ea**, **3ha-3ia**, **3ka**). The presence of a strong electron-withdrawing nitro group was detrimental for both yield and stereocontrol (**3ka**). The scope of several prochiral cyclohexanones **2b-j** was then explored. Good yields and e.r. were obtained for new cyclohexylidene oxindoles **3ab-3aj** with aromatic and aliphatic substituents. In the case of aliphatic cyclohexanones, the size of the substituent was a discriminant factor (not exclusively) for the enantiomeric ratio of the product. The larger the group the higher the enantioselectivity. This is due to the conformational equilibrium of 4-substituted cyclohexanones where the presence of a large group ensures that only one side of the iminium group is effectively accessible by the nucleophile. This is the specific case of ketones **2g** and **2h**. With ketones **2f** and **2i**, the conformational equilibrium is not completely shifted towards the equatorial conformer, and a poor enantiocontrol is observed because both sides of the iminium ion are accessible. The reaction can be extended to cyclobutanones but with poor yield and e.r. (**3aj**) whilst 4-phenylcyclooctanone is not reactive at all. The absolute configuration of **3aa** was determined to be *aR* by means of TD-DFT calculation of the electronic circular dichroism (ECD) spectra.[15] A possible derivatization of the 3-alkylidene oxindole was identified in the epoxidation of the double bond. Enantiopure **3aa** was treated with *m*-CPBA and the resulting epoxide can be isolated in 86% yield as a 5:1 mixture of diastereoisomers **5aa** and **5aa'** and both with a 98.5:1.5 e.r. (Scheme 2a). Furthermore the reproducibility of the *a*EKC was tested in a 1 mmol scale reaction. As showed in Scheme 2b compound **3aa** was obtained in 85% of isolated yeld and 84:16 of e.r.

Scheme 2. Epoxidation of enantiopure 3aa and 1.0 mmol scale reaction.



In order to investigate the reaction mechanism that explains the stereochemical outcome of the reaction, a DFT computational study was performed.[15] The calculations suggest that the reaction pathway follows two distinct events. After the formation of an equilibrium mixture of two diastereomeric axially chiral iminium ions, the reaction proceeds through a selective alkylation of the (*aS*)-iminium ion. The addition of the Re face of the oxindole is favored over the Si face (TS1). The resulting diastereoisomeric intermediate (GS3) undergoes a rate- and stereo-determining E1cb elimination (TS2), as usually occurs for Knoevenagel condensation,[18] promoted by the carboxylate anion furnishing the *aR* product as the major enantiomer (Figure 4), in good agreement with the experimental results.

In conclusion we reported the axially enantioselective Knoevenagel condensation. The process is highly efficient, with a large scope for both ketone and oxindole and furnished a rare example of synthesis of axially chiral 3-alkylideneoxindoles which can be readily functionalized through standard organic procedure. This reaction represents an important application of aminocatalysis for the synthesis of axially chiral oxindoles with possible biological applications. The theoretical study gave an important elucidation on the reaction mechanism which proceeded through an E1cb elimination.

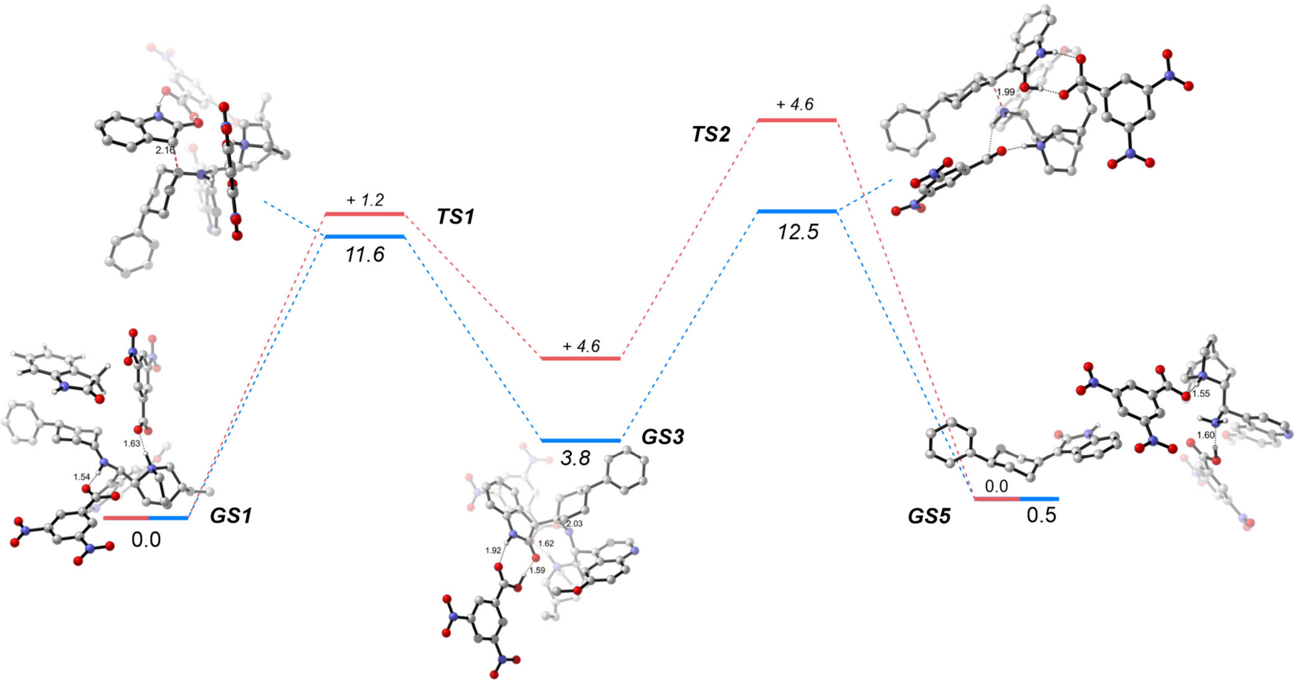


Figure 4. Main steps of the proposed reaction mechanism. Corrected relative free energies ($\Delta\Delta G_{313}$) at the M06-2X/6-311++G(2d,p)/SMD(toluene)//M06-2X/6-31G(d)/SMD(toluene) level of theory. All values are in kcal/mol. Blue: reaction path to the major (*aR*)-product; red: reaction path to the minor (*aS*)-product. Values for the red path are expressed relative to the corresponding values of the blue path. Structures are shown only for the reaction path leading to the major product.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compounds characterization, NMR spectra, HPLC traces, and DFT calculations. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

giorgio.bencivenni2@unibo.it

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The University of Bologna is gratefully acknowledged for financial support.

REFERENCES

(1) (a) Renzi, P. Organocatalytic Synthesis of Axially Chiral Atropisomers. *Org. Biomol. Chem.*, **2017**, *15*, 4506. (b) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534. (c) Bencivenni, G. Organocatalytic Strategies for the Synthesis of Axially Chiral Compounds. *Synlett*, **2015**, *26*, 1915. (d) Shirakawa, S.; Liu, S.; Kaneko, S. Organocatalyzed Asymmetric Synthesis of Axially, Planar, and Helical Chiral Compounds. *Chem.-Asian J.* **2016**, *11*, 330. For representative examples see: (e) Link, A.; Sparr, C. Organocatalytic Atroposelective Aldol Condensation: Synthesis of Axially Chiral Biaryls by Arene Formation. *Angew. Chem. Int. Ed.*, **2014**, *53*, 5458. (f) Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. Highly Atroposelective Synthesis of Arylpyrroles by Catalytic Asymmetric Paal–Knorr Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 1714. (g) Quinonero, O.; Jean, M.; Vanthuyne, N.; Roussel, C.; Bonne, D.; Constantieux, T.; Bressy, C.; Bugaut, X.; Rodriguez, J. Combining Organocatalysis with Central-to-Axial Chirality Conversion: Atroposelective Hantzsch-Type Synthesis of 4-Arylpyridines. *Angew. Chem. Int. Ed.* **2016**, *55*, 1401. (h) Liu, Y.; Tse, Y.-L. S.; Kwong, F. Y.; Yeung, Y.-Y. Accessing Axially Chiral Biaryls via Organocatalytic Enantioselective Dynamic-Kinetic Resolution-Semipinacol Rearrangement. *ACS Catal.* **2017**, *7*, 4435. (i) Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D. Catalytic Enantioselective Synthesis of Atropisomeric Biaryls by a Cation-Directed O-alkylation. *Nat. Chem.* **2017**, *9*, 558. (j) Di Iorio, N.; Righi, P.; Mazzanti, A.; Mancinelli, M.; Ciogli, A.; Bencivenni, G. Remote Control of Axial Chirality: Aminocatalytic Desymmetrization of N-Arylmaleimides via Vinylogous Michael Addition. *J. Am. Chem. Soc.* **2014**, *136*, 10250. (k) Tan, Y.; Jia, S.; Hu, F.; Liu, Y.; Peng, L.; Li, D.; Yan, H. Enantioselective Construction of Vicinal Diaxial Styrenes and Multiaxis System via Organocatalysis. *J. Am. Chem. Soc.* **2018**, *140*, 16893. (l) Zhang, J.-W.; Xu, J.-H.; Cheng, D.-J.; Shi, C.; Liu, X.-Y.; Tan, B. Discovery and Enantiocontrol of Axially Chiral Urazoles via Organocatalytic Tyrosine Click Reaction. *Nat. Commun.* **2016**, *7*, 10677. (m) Raut, V. S.; Jean, M.; Vanthuyne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez, J. Enantioselective Syntheses of Furan Atropisomers by an Oxidative Central-to-Axial Chirality Conversion Strategy. *J. Am. Chem. Soc.* **2017**, *139*, 2140. (n) Li, S.-L.; Yang, C.; Wu, Q.; Zheng, H.-L.; Li, X.; Cheng, J.-P. Atroposelective Catalytic Asymmetric Allylic Alkylation Reaction for Axially Chiral Anilides with Achiral Morita–Baylis–Hillman Carbonates. *J. Am. Chem. Soc.* **2018**, *140*, 12836. (o) Fasëke, V. C.; Sparr, C. Stereoselective Arene-Forming Aldol Condensation: Synthesis of Axially Chiral Aromatic Amides. *Angew. Chem. Int. Ed.* **2016**, *55,* 7261.

(2) (a) Ōki, M. Recent Advances in Atropisomerism. In Topics in Stereochemistry; Vol. 14 (Eds: E. L. Eliel, S. H. Wilen, N. L. Al-

linger), John Wiley and Sons: New York, **2007**, pp 1–81. (b) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. Tropos or Atropos? That is the Question! *Synlett* **2002**, 1561.

(3) (a) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563. (b) Smyth, J. E.; Butler N. M.; Keller, P. A. A Twist of Nature – The Significance of Atropisomers in Biological Systems. *Nat. Prod. Rep.,* **2015**, *32*, 1562. (c) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Non biaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239. (d) Chen, Y.; Yekta, S.; Yudin, A. K. Modified BINOL Ligands in Asymmetric Catalysis. *Chem. Rev.* **2003**, *103*, 3155. (e) Kočovský, P.; Vyskočil, Š.; Smrčina, M. Non-Symmetrically Substituted 1,1'-Binaphthyls in Enantioselective Catalysis. *Chem. Rev*. **2003**, *103*, 3213. (f) Zilate, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal*. **2018**, *8*, 2981. (g) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent Advances and New Concepts for the Synthesis of Axially Stereoenriched Biaryls. *Chem. Soc. Rev*., **2015**, *44*, 3418. (h) Dai, W.-M.; Yeung, K. K. Y.; Liu, J.-T.; Zhang, Y.; Williams, I. D. A Novel Class of Nonbiaryl Atropisomeric P,O-Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation. *Org. Lett.* **2002**, 4, 1615.

(4) (a) Eliel, E. L.; Wilen, S. H. in Stereochemistry of Organic Compounds, John Wiley-Interscience: New-York, 1994. (b) Testa, B. Principles of Organic Stereochemistry. In Studies in Organic Chemistry; Vol. 6 (Ed: P. G. Gassman), Dekker: New-York, 1979.

(5) (a) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem. Int. Ed.,* **2012**, *51*, 3074. (b) Neff, R. K.; Frantz, D. E. Recent Advances in the Catalytic Syntheses of Allenes: A Critical Assessment. *ACS Catal*. **2014**, *4*, 519. (c) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. Phase-Transfer-Catalysed Asymmetric synthesis of Tetrasubstituted Allenes. *Nat. Chem.,* **2013**, *5*, 240. (d) Yu, J.; Chen, W.-J.; Gong, L.-Z. Kinetic Resolution of Racemic 2,3-Allenoates by Organocatalytic Asymmetric 1,3-Dipolar Cycloaddition. *Org. Lett.* **2010**, *12*, 4050. (e) Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. Catalytic Synthesis of Allenes via Isomerization of Alkynes under Phase-Transfer Catalyzed Conditions. *Synlett* **2000**, 493. (f) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. Enantioselective Synthesis of Chiral Allenoates by Guanidine-Catalyzed Isomerization of 3-Alkynoates. *J. Am. Chem. Soc*. **2009**, *131*, 7212. (g) Inokuma, T.; Furukawa, M.; Suzuki, Y.; Kimachi, T.; Kobayashi, Y.; Takemoto, Y. Organocatalyzed Isomerization of α-Substituted Alkynoates into Trisubstituted Allenoates by Dynamic Kinetic Resolution. *ChemCatChem* **2012**, *4*, 983. (h) Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. Bifunctional Hydrogen-Bond Donors That Bear a Quinazoline or Benzothiadiazine Skeleton for Asymmetric Organocatalysis. *Chem. Eur. J*. **2011**, *17*, 10470. (i) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. Enantioselective Bromolactonization of Conjugated (Z)-Enynes. *J. Am. Chem. Soc.* **2010**, *132*, 3664.

(6) (a) Eelkema, R.; Feringa, B. L. Amplification of Chirality in Liquid Crystals. *Org. Biomol. Chem.* **2006**, *4*, 3729. (b) Solladié, G.; Zimmermann G. Liquid Crystals: A Tool for Studies on Chirality. *Angew. Chem. Int. Ed.* **1984**, *23*, 348. (c) H. Brewster, J.; Privett, J. E. The Absolute Configuration of an Axially Dissymmetric Compound. (*S*)-(+)-1 -Benzylidene-4-methylcyclohexane. *J. Am. Chem. Soc.* **1966**, *88*, 1419. (d) Duraisamy, M.; Walborsky, H. M. Syntheses of Chiral Cyclohexylidenepropenes and Cyclohexylideneacetaldehydes. *J. Am. Chem. Soc.* **1983**, *105*, 3252. (e) Zhang, Y.; Schuster, G. B. Photoresolution of an Axially Chiral Bicyclo[3.2.1]octan-3-one: Phototriggers for a Liquid Crystal-Based Optical Switch. *J. Org. Chem*. **1995**, *60*, 7192. (f) Bradford, R. F.; Schuster, G. B. Investigation of Bicyclic Thioketones as Triggers for Liquid Crystal Optical Switches. *J. Org. Chem.* **2003**, *68*, 1075.

(7) (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. Design and Reactivity of Topologically Unique, Chiral Phosphonamides. Remarkable Diastereofacial Selectivity in Asymmetric Olefination and Alkylation. *J. Am. Chem. Soc*. **1984**, *106*, 5754. (b) Denmark, S. E.; Chen, C.-T. Electrophilic Activation of the Horner-Wadsworth-Emmons-Wittig Reaction: Highly Selective Synthesis of Dissymmetric Olefins. *J. Am. Chem. Soc*. **1992**, *114*, 10674. (c) Mizuno, M.; Fujii, K.; Tomioka, K. The Asymmetric Horner-Wadsworth-Emmons Reaction Mediated by An External Chiral Ligand. *Angew. Chem. Int. Ed*. **1998**, *37*, 515. (d) Iguchi, M.; Tomioka, K. External Chiral Ligand-Mediated Enantioselective Peterson Reaction of α-Trimethylsilanylacetate with Substituted Cyclohexanones. *Org. Lett*., **2002**, *4*, 4329. For an interesting review on asymmetric olefination reaction see: (e) Tanaka, K.; Furuta, T.; Fuji, K. in Asymmetric Carbonyl Olefination. In Modern Carbonyl Olefination. (Ed: T. Takeda), Wiley-VCH, Weinheim, **2004**, pp. 286-342. For interesting examples using arsonium yilides: (f) Dai, W.-M.; Wu, J.; Huang, X. Asymmetric Wittig reaction of chiral arsonium ylides I. Asymmetric olefination of 4-substituted cyclohexanones. *Tetrahedron: Asymmetry*, **1997**, *8*, 1979. (g) Wei-Min Dai, W.-M.; Wu, A.; Wu, H. Asymmetric Wittig reactions of chiral arsonium ylides. Part 3: Reversal of stereochemistry caused by metal cation in enantioselective olefination of 4-substituted cyclohexanones using a C_2-symmetric chiral arsine. *Tetrahedron: Asymmetry*, **2002**, *13*, 2187.

(8) Agudo, R.; Roiban, G. D.; Reetz, M. T. Induced Axial Chirality in Biocatalytic Asymmetric Ketone Reduction. *J. Am. Chem. Soc.* **2013**, *135*, 1665.

(9) Gramigna, L.; Duce, S.; Filippini, G.; Fochi, M.; Comes Franchini, M.; Bernardi, L. Organocatalytic Asymmetric Wittig Reactions: Generation of Enantioenriched Axially Chiral Olefins Breaking a Symmetry Plane. *Synlett*, **2011**, *18*, 2745.

(10) (a) Knoevenagel, E. Ueber eine Darstellungsweise der Glutarsaure. *Ber. Dtsch. Chem. Ges*. **1894**, *27*, 2345. (b) List, B. Emil Knoevenagel and the Roots of Aminocatalysis. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730. (c) Tietze, L. F.; Beifuss, U. in Comprehensive Organic Synthesis, Vol. 2 (Ed.: B. M. Trost, I. Fleming), Pergamon Press: Oxford, **1991**, pp 341-392.

(11) (a) Lee, A.; Michrowska, A.; Sulzer-Mosse, S.; List, B. The Catalytic Asymmetric Knoevenagel Condensation. *Angew. Chem. Int. Ed.*, **2011**, *50*, 1707. (b) For a tertiary amine catalyzed Knoevenagel condensation via DKR see: Gu, X.; Tang, Y.; Zhang, X.; Luo, Z.; Lu, H. Organocatalytic Knoevenagel Condensation by Chiral C_2-Symmetric Tertiary Diamines. *New J. Chem.,* **2016**, *40*, 6580.

(12) (a) Nichi, Y.; Wakasugi, K.; Koga, K.; Tana, Y. Chirality Exchange from sp^3 Central Chirality to Axial Chirality: Benzannulation of Optically Active Diaryl-2,2-dichlorocyclopropylmethanols to Axially Chiral α-Arylnaphthalenes. *J. Am. Chem. Soc*. **2004**, *124*, 5358. (b) Zhang, Y.; Wang, Y.; Dai, W.-M. Efficient Remote Axial-to-Central Chirality Transfer in Enantioselective SmI_2-Mediated Reductive Coupling of Aldehydes with Crotonates of Atropisomeric 1-Naphthamides. *J. Org. Chem*. **2006**, *71*, 2445.

(13) 3-Alkylideneoxindoles has been previously synthesized as racemic by Feng and used for a deracemization reaction using a Lewis acid catalysed Michael addition to chalcones: Mei, H.; Lin, L.; Wang, L.; Dai, L.; Liu, X.; Feng, X. Highly regio-, diastereo- and enantioselective deracemization of axially chiral 3-alkylideneoxindoles. *Chem. Commun*. **2017**, *53*, 8763.

(14) (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398. (b) LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. Assessing Atropisomer Axial Chirality in Drug Discovery and Development. *J. Med. Chem.* **2011**, *54*, 7005.

(15) See supporting information for more details.

(16) (a) Melchiorre, P. Cinchona-based Primary Amine Catalysis in the Asymmetric Functionalization of Carbonyl Compounds. *Angew. Chem. Int. Ed*. **2012**, *51*, 9748. (b) Jadhav, M. S.; Righi, P.; Marcantoni, E.; Bencivenni, G. Enantioselective α-Benzoyloxylation of Ketones Promoted by Primary Amine Catalyst. *J. Org. Chem*. **2012**, *77*, 2667. (c) Lifchits, O.; Demou-

lin, N.; List, B. Direct Asymmetric α-Benzoyloxylation of Cyclic Ketones. *Angew. Chem., Int. Ed.* **2011**, *50*, 9680.
(17) A further enantioenrichement of the product is observed if the crude reaction mixture is readily filtered through a PTFE syringe filter. This outcome is caused by a preferential precipitation of a scalemic fraction (e.r. 73.5:26.5) of the product which, thus leaves the enriched major enantiomer in solution with e.r. up to 97:3. This observation was found to be reliable, reproducible and general in regard to both the substrates and the reaction scale. The e.r. values reported in Figure 3 are those obtained after a careful and complete dissolution of the whole crude reaction mixture, without any filtration.
(18) Bruckner, R. Knoevenagel Reaction. In Organic Mechanisms (Ed: M. Harmata), Springer-Verlag: Berlin Heidelberg, **2010**, p. 571.