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

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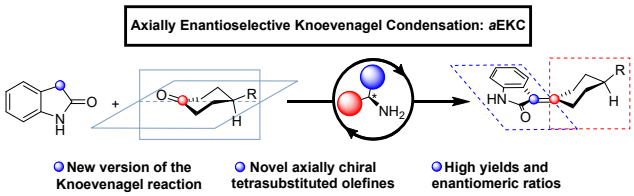
Supporting Information Placeholder



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).

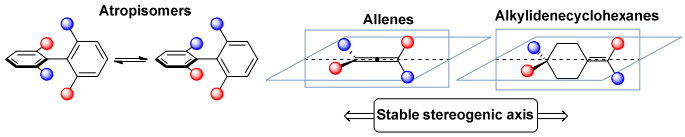


Figure 1. Examples of axially chiral compounds.

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 ole-

fination 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.

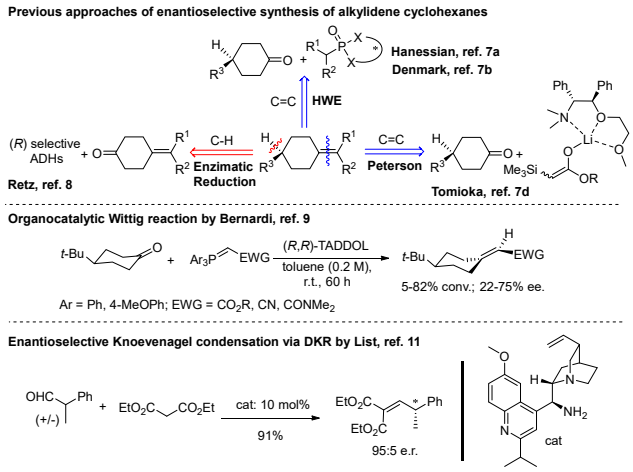
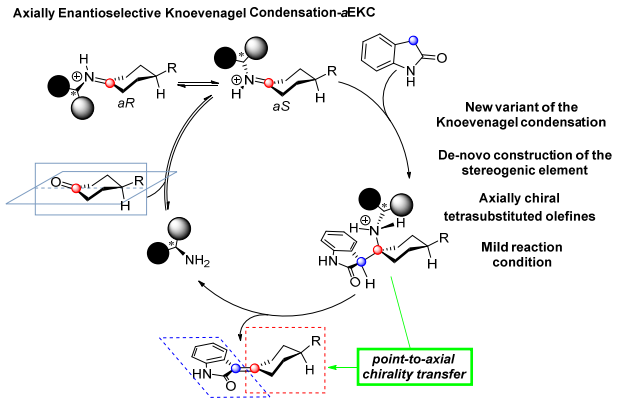


Figure 2. Previous examples of asymmetric olefinations and catalytic enantioselective Knoevenagel condensation.

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).

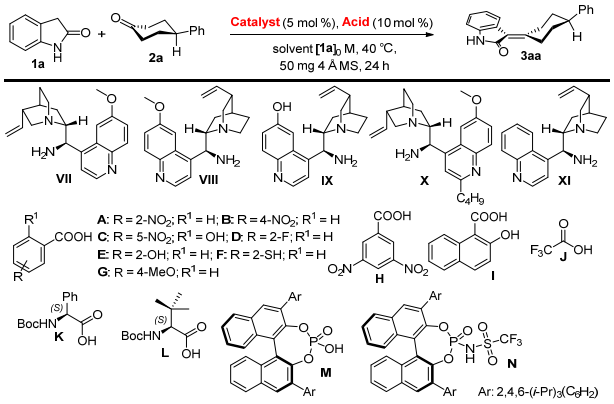
Scheme 1. Strategic plan for the axially enantioselective Knoevenagel condensation (*a*EKC).



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).

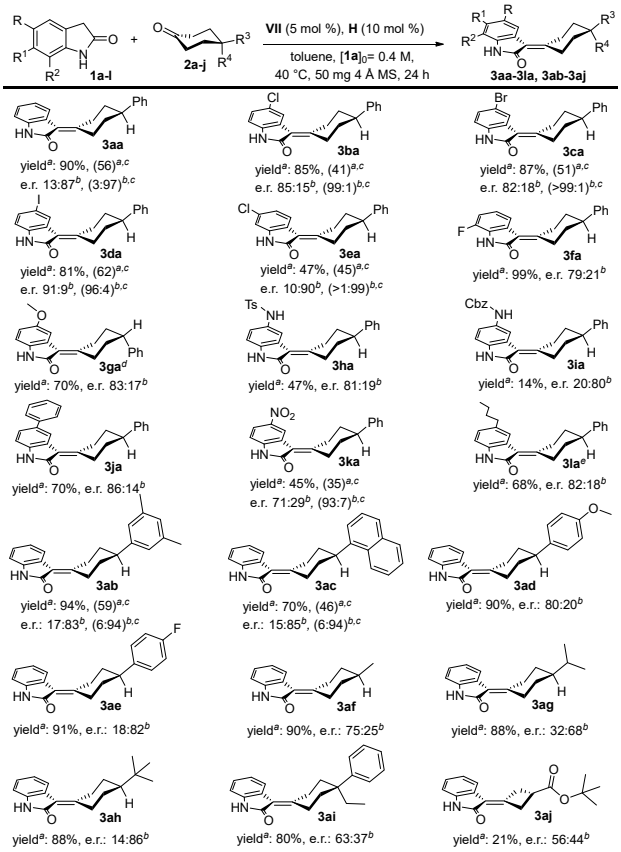
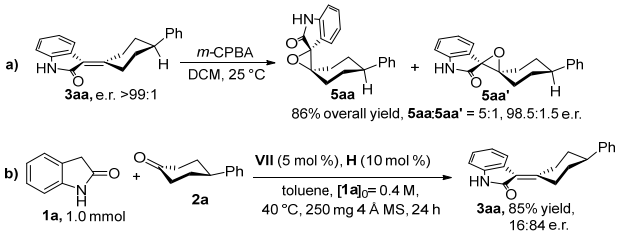


Figure 3. Knoevenagel condensation of oxindoles **1a-l** with prochiral 4-phenylcyclohexanones **2a-j**. The reactions were performed on a 0.2 mmol scale with a 1:1 ratio between **1a-l** and **2a**. [a]Determined via ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. In all cases NMR yields 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]$[\mathbf{1a}]_0$= 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.

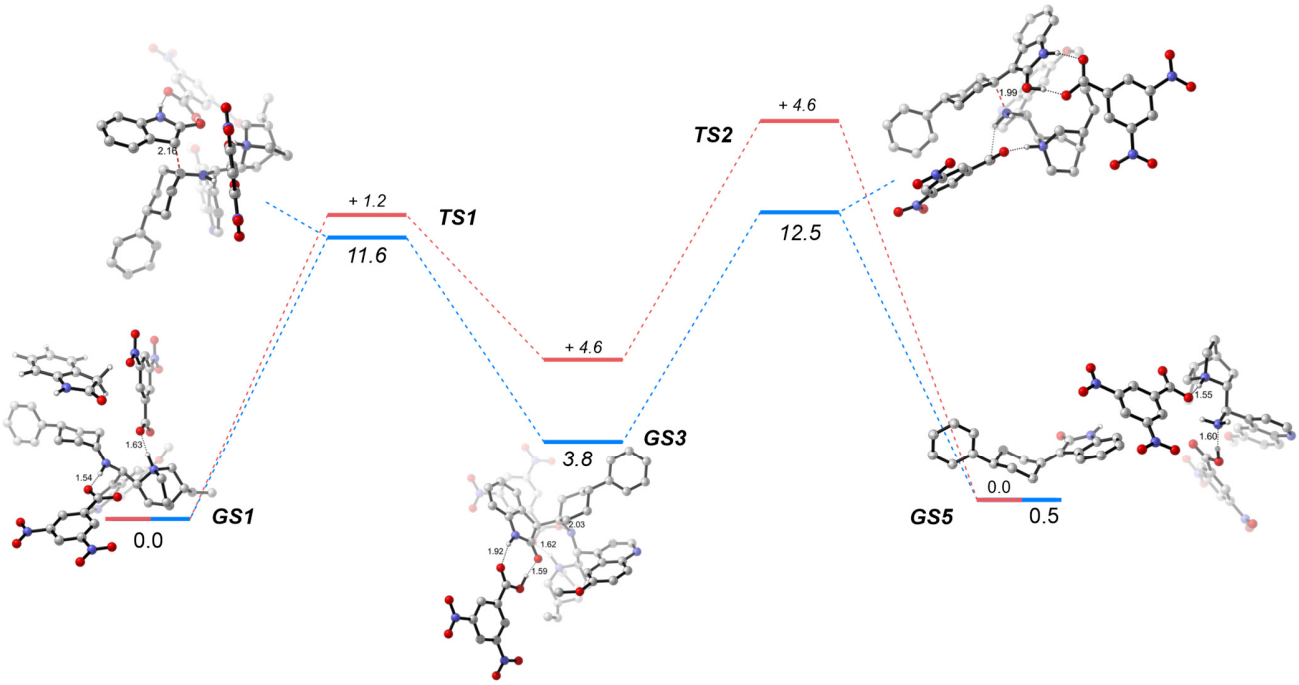


Figure 4. Main steps of the proposed reaction mechanism. Corrected relative free energies ($\Delta\Delta G_{313}$) at the M06-2X/6-311++G(2d,p)/SMD(toluene)//M06-2X/6-31G(d)/SMD(toluene) level of theory. All values are in kcal/mol. Blue: reaction path to the major (*aR*)-product; red: reaction path to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

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Notes

The authors declare no competing financial interests.

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