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Chiral Fidelity in the Diastereoselective and Enantiospecific Synthesis of Indenes from Axially Chiral Benzylidene Cyclanes

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Abstract: Enantioenriched indenenes were reached through a chirality conversion strategy using original axially chiral benzylidene cyclanes. Good to high remote diastereocontrol and excellent enantiocontrol were observed in this cascade involving copper-catalyzed homologation of terminal alkynes, in situ allenolate formation and Alder-ene cyclization.

Asymmetric synthesis occupies a prime space in the development of enantiomerically pure compounds. This goal has stimulated numerous researches for new strategies and original chiral building blocks have been devised. Different routes that afford stereochemistry control are routinely available. Among them, chirality transfer from a non-racemic starting material is now recognized as a potent method to reach chiral building blocks.^[1]

We have recently highlighted the importance of the indanyl core by reviewing the synthesis and the applications of compounds possessing this structural unit.^[2,3] This scaffold has shown recently a tremendous progress as chiral ligands and organocatalysts. Different enantioselective routes have been devised to access to this family of compounds. However, the chirality relay strategy has not much been used to address this issue.^[4] The use of remote stereocontrol was challenging, as examples of remote asymmetric induction are scarce.^[5] We propose hereafter a new pathway to build the indene architecture through dia- and enantioselective cyclizations using benzylidene cycloalkane scaffolds.

Non-planar cyclohexylidenes in which asymmetry results from restricted rotation are axially chiral molecules.^[6] These enantiomerically enriched dissymmetric olefins bearing a chiral axis have been known since the beginning of the 20th century.^[7] In contrast to biaryls and allenes, they have been underexplored as chiral templates. To our knowledge,

the only report of axial-to-central chirality transfer (CT) from these compounds refers to the isomerization of the alkylidene moiety to afford cyclohexene (Scheme 1a).^[8] A few applications in asymmetric synthesis have been reported. Soai has applied the polarized light (CPL) mediated photoequilibrium of chiral alkylidene cycloalkanes in conjunction with asymmetric autocatalysis to the addition of dialkylzinc to pyrimidyl aldehydes.^[9]

Examination of the literature revealed no report relaying a cyclization process involving chirality transfer from axially chiral cycloalkylidenes. The stereocontrolled formation of a C–C bond through an Alder-ene process taking advantage of diastereofacial discrimination in chiral cyclohexylidene derivatives was an attractive potential route to the diastereo- and enantioselective synthesis of chiral indenenes (Scheme 1b).

Cascade reactions have already been applied to the enantioselective construction of indenenes.^[10] The originality of our approach is to combine the homologation of terminal alkynes^[11] with the trapping of the resulting allene in an Alder-ene cyclization.^[12] Because of the distance between the alkynolate and cyclohexyl group, the isomerization of alkynolate **2** to allenolate **3** should lead to a pair of diastereomers in nearly equimolar amount. In all likelihood, provided that the ring conformation is locked by a bulky R group, the axially chiral alkylidene cyclohexane should control the axis-to-center chirality transfer in the cyclization step. The selection between the two diastereotopic axial hydrogens on the cyclohexyl moiety in the transition state should simultaneously control the second created stereocenter, whatever the relative configuration of the allene axis.

We privileged semi-preparative chiral HPLC separations of racemic **1** to isolate both enantiomers in high optical purity.^[13] For this purpose, we have used commercially available chiral stationary phases such as Lux-Cellulose-2, Chiralpak IB and IC, Chiralcel OJ-H and Lux-Amylose-2 delivering both enantiomers with *ee* values > 99%. The availability of (+)-**1** and (–)-**1** with high enantiopurity was critical for the investigation of the chirality conversion and also to evidence the enantiospecificity of the reaction. Once resolved, (+)-**1a** and (–)-**1a** were reacted with 1.4 equivalents of diazoester in the presence of a catalytic amount of copper(I) and Et₃N. Pleasingly, product **4a** was isolated as a 85:15 mixture of diastereomers and the major diastereomer exhibited an *ee* superior to > 90%. The Alder-ene step proved to be enantiospecific since enantiomeric mixtures of the same diastereomers of the product were isolated from both enantiomers of the starting material (Table 1). The whole

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a) Known strategy: axial to central chirality transfer b) Designed cascade: CuI/Et₃N-catalyzed cascade cyclization of terminal alkyne with chirality transfer

Scheme 1. Synthetic route to enantioenriched indenes.

process was thus diastereoselective and enantiospecific. Both NMR and HPLC analyses showed that the same major diastereomer was formed in the two reactions. Due to the anticipated low control of the allene chiral axis in the homologation step, we could affirm that the original axial chiral element, that is the cycloalkylidene moiety, was responsible for the transfer of the chirality in the cyclization step.

Table 1. Diastereoselective and enantioselective cyclization of dienyne **1** leading to indenes **4**.

<p>4a 85:15 d.r.; >99% ee 67% yield</p>	<p>4a' 85:15 d.r.; 98.5% ee 60% yield</p>	<p>4b 85:15 d.r.; 98% ee 59% yield</p>	<p>4c 85:15 d.r.; 89% ee 65% yield</p>
<p>ent-4a 85:15 d.r.; 91% ee</p>		<p>ent-4b 85:15 d.r.; >95% ee</p>	
<p>4d 57:43 d.r. 71% yield</p>	<p>4d' 55:45 d.r. 55% yield</p>	<p>4e 95:5 d.r.; 89% ee 55% yield</p>	<p>4f 75:25 d.r.; 98% ee 74% yield</p>

[a] Diastereomeric ratio (d.r.) determined by ¹H NMR analysis of the crude reaction mixture. [b] ee of the major diastereomer of **4** was determined by chiral HPLC analysis. [c] Isolated yields are reported.

In order to investigate the possible effect of the ester group on the diastereoselectivity, substrate **1a** was reacted with *tert*-butyl diazoester. Under the same experimental conditions, the desired product **4a** was isolated with the same d.r. and high ee. The nature of the ester group has no impact on the diastereoselectivity.

We then extended the reaction to other substrates bearing different R-groups. The methyl-substituted substrate **1b** showed the same behavior: high chirality transfer and an identical d.r. were observed. The diastereoselectivity remained unchanged when the *tert*-butyl group was replaced by a phenyl

group. An X-ray crystal structure was obtained for the major diastereomer formed from *rac*-**4c** which demonstrated the (*S**,*S**)-relative stereochemistry.^[14]

When the substituent at the cycloalkylidene moiety was OH, the reaction afforded the Alder-ene product **4d** with a low diastereoselectivity (57:43). It has been previously demonstrated that, due to the electrostatic forces, the equilibration between equatorial and axial conformers of 4-hydroxycyclohexylidene is facilitated.^[15] These data support the assumption that both OH_{axial} and OH_{equatorial} conformers contribute to the cyclization process. Interestingly, despite the substitution of the cyclane by a polar group, and due to the steric bulk of the NMeBoc substituent, a d.r. of 95:5 was observed for **4e**. Ester **4f** was also found reactive. The d.r. was 75:25, slightly lower than that of the alkyl derivative. Epimerization due to presence of the α -acidic hydrogen might explain this decrease.

Interestingly, chiral substrate **1g**, prepared from the corresponding *meso* ketone, afforded a nearly total diastereocontrol (Scheme 2). Again, the reaction was enantiospecific, as (+)-**1g** and (–)-**1g** led to enantiomeric indenes (+)-**4g** and (–)-**4g**, respectively, with chirality transfer higher than 99%.

The terminal alkyne **1h** (96% ee) afforded the dihydropyranic product **4h** that was also isolated as a single diastereomer in 63% yield without any chirality erosion. A high diastereocon-

Scheme 2. Axial-to-center chirality conversion in the synthesis of indenes possessing three stereocenters.

Scheme 3. Enantioselective synthesis of conjugated dienes.

trol was also registered from the diphenyl thiopyran **4i** with 94% ee.

Analogously, compound (–)-**1j** (98.5% ee) derived from tropanone was subjected to the standard conditions. However, the expected product **4j** was not isolated. It was further isomerized to the conjugated diene (–)-**5j** obtained as a single isomer with very high chirality conversion (95% ee) (Scheme 3).

Again, the enantiomeric substrate (+)-**1j** afforded the optical isomer of (+)-**5j** with the same chirality transfer efficiency. The basicity of this product might be responsible for the observed isomerization.^[16] The chiral product offers several possibilities and could possibly be further exploited as a Brønsted base to catalyze asymmetric isomerization. The diene moiety could also be used in Diels–Alder reaction.^[17]

We also synthesized the axially chiral alkylidene possessing a fused bicyclopentane framework **1k** (Scheme 3).^[18] Under the above used experimental conditions, conjugated diene **5k** was

formed via 1,3-proton shift from the expected product **4k**. The strain of the double bond in the resulting fused-bicycloalkene moiety might facilitate the evolution towards the conjugated diene.

These additional examples further highlighted the scope and limitations of this original cascade with regard to the synthesis of chiral indene units. They open new possibilities for building enantioselective chiral frameworks of increased complexity.

Two mechanisms can be envisaged for the cyclization step, as depicted in Scheme 4. The scenario implying a concerted Alder–ene is consistent with a diastereoselective process since the cyclization involves a strained six-membered ring transition state.^[19] The second scenario in which a zwitterionic intermediate would be formed seems less likely, as low stereo-discrimination would result.

Scheme 4. Mechanistic investigations.

In order to demonstrate that the latter assumption held true, a reaction known to proceed via a carbocation, that is, the halocyclization of *o*-(alkynyl)styrenes reported by Rodriguez and co-workers^[20] was investigated on alkyne **6a**. Under the halocyclization conditions, **6a** led to indene **7a** in high yield, but two diastereomers were isolated in 1:1 ratio (Scheme 4b). In the carbocationic intermediate, there is no discrimination between the diastereotopic protons H_a and H_b.

We have also evidenced the nature of the reaction intermediates by monitoring the reaction by NMR spectroscopy. We first stopped the reaction at its early stage where alkynoate **2a** was the major product. The latter was then submitted to isomerizing conditions, that is, Et₃N in CD₃CN at room temperature, and the cyclization was monitored by ¹H NMR up to its completion 24 h later (Scheme 4a). Interestingly, allenolate **3a**, possessing two chiral axes, was formed as a 50:50 mixture of diastereomers. The d.r. of product **4a** so formed was the same as in the one-pot procedure (85:15), which suggests that the copper salt is not playing the role of a Lewis acid catalyst in the Alder-ene reaction.

From these investigations, we could confidently conclude that the generation of a zwitterionic intermediate was not the most likely route for the cascading reaction mediated with diazoesters.

All these experimental observations pointed out the complete control of the stereochemical feature of the process by the cyclohexylidene chiral axis whatever the relative configuration of the axis of the intermediate allene.

Additional insight and confirmation were provided by the theoretical investigation of the concerted cyclization of diastereomeric intermediates (*aR,aR*)-**3A** and (*aS,aR*)-**3A** (Figure 1), using the IRC approach. For the sake of simplification, the ethyl ester was replaced by a methyl ester in the model diastereomeric compounds.^[21]

All the transition-state geometries were confirmed with the IRC^[22] approach at the M06-2X/6-31G(d) level of theory for the pathway leading from allene **3A** to indene **4A**. The calculated values for the activation enthalpy, the activation free energy and the exothermicity of the reaction are reported in Figure 1.

Theoretical modelling clearly confirmed the enantiospecificity of the concerted Alder-ene step. The diastereomeric inter-

mediates (*aR,aR*)- and (*aS,aR*)-**3A** which differ by the absolute configuration of the chiral allene axis, both lead to the same (*S,S*) enantiomer of indene **4A**. No significant difference was found in the activation parameters. As expected, their images that is, (*aS,aS*)- and (*aR,aS*)-**3A** lead both to (*R,R*)-**4A**.

These calculations are in good agreement with the above experiments which showed that stereochemical fidelity was intimately dependent on the configuration of the cyclohexylidene moiety but not at all on the intermediate allene chirality.^[23]

The transition state structures were scrutinized to look at the synchronicity of C–C bond forming and C–H bond breaking. They are almost identical, except of course the position of the carboxylate, they show that the rearrangement is asynchronous, the formation of the indene C–C bond is more advanced than the C–H bond breaking.

No concerted pathway could be found to the (*S*,R**)-diastereomer of **4A** even when searching for a possible transition state by forcing the cyclohexylidene ring to adopt a boat conformer which is 3 kcal mol^{−1} destabilized with respect to the chair one. Therefore, we searched for an alternative pathway to explain the observation of the minor diastereomer. A two-step asynchronous process was found that led backward from the minor diastereomer (*R,S*)-**4A** (less stable than (*S,S*)-**4A** by 2.4 kcal mol^{−1}) to a tetracyclic intermediate.^[21] According to the calculation, a 26.0 kcal mol^{−1} activation barrier has to be passed to reach the intermediate. It is higher by 2.8 kcal mol^{−1} than the barrier for the concerted pathway leading to (*S,S*)-**4A** from (*aS,aR*)-**3A**. This competing route could account for the formation of the minor diastereomer of **4A**.

In conclusion, dia- and enantioselective syntheses of indenenes were achieved from easily accessible starting materials, originating from cheap commercial chemicals. Upon copper-catalysis, high chiral fidelity was observed in the cascade reaction involving successively alkynoate homologation, base-catalyzed allenolate formation and Alder-ene cyclization. The overall reaction revealed a good efficiency and high ee values were observed in the formation of up to three controlled stereocenters. Mechanistic investigations credited a concerted mechanism as being responsible for the remote diastereocontrol in the Alder-ene reaction.

Figure 1. Calculated reaction profiles for diastereomeric allenenes (*aR,aR*)-**3A** (left) and (*aS,aR*)-**3A** (right). $\Delta H^\ddagger$ (grey) and $\Delta G^\ddagger$ (black) values are given in kcal mol^{−1}, distances are given in Å.

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