Photochemical Deracemization of Allenes and Subsequent Chirality Transfer

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Abstract: Trisubstituted allenes with a 3-(1′-alkenyldiene)-pyrrolidin-2-one motif were successfully deracemized (13 examples, 86–98% ee) employing visible light (λ = 420 nm) and a chiral triplet sensitizer as the catalyst (2.5 mol%). The photocatalyst likely operates by selective recognition of one allene enantiomer via hydrogen bonds and by a triplet-sensitized racemization process. Even a tetrasubstituted allene (45% ee) and a seven-membered 3-(1′-alkenyldiene)-azepon-2-one (62% ee) could be enantioselectively enriched under the chosen conditions. It was shown that the axial chirality of the allenes can be converted into point chirality by a Diels–Alder (94–97% ee) or a bromination reaction (91% ee). Ring opening of the five-membered pyrrolidin-2-one was achieved without significantly compromising the integrity of the chirality axis (92% ee). Open access funding enabled and organized by Projekt DEAL.

Deracemization reactions are defined as processes “in which a racemate is made nonracemic by increasing the quantity of one enantiomer at the expense of the other.”[1] Several methods to achieve a deracemization in solution have been described but all of them eventually rely either on the intermediacy of an achiral intermediate which is enantioselectively re-converted to the substrate or on the use of a stoichiometric chiral reagent.[2,3] If a deracemization is performed catalytically, the entropy loss associated with a deracemization needs to be energetically compensated. Although photochemistry offers in principle a solution to this challenge,[4,5] highly enantioselective catalytic deracemization reactions have remained elusive until very recently. In 2018, it was discovered that a class of allenes, 3-(1′-alkenyldiene)-piperidin-2-ones, can be deracemized in high yields (> 56%) and with high enantioselectivity (80–97% ee) by a chiral triplet sensitizer that operates with visible light.[6] Chiral cyclopropanes and sulfoxides were subsequently shown to be also amenable to a sensitized deracemization (up to 55% ee).[7] A more recently disclosed photochemical deracemization approach is based on the creation of a non-covalent two-point hydrogen bond (Scheme 1). The chiral photocatalyst distinguishes between the two enantiomeric forms of a compound by non-covalent binding. The enantiomer that binds to the catalyst is excited via sensitization and subsequently undergoes a racemization via an achiral intermediate. Since, in an ideal scenario, only one enantiomer is processed by the catalyst, the non-binding enantiomer gets increasingly enriched in solution and is obtained ideally in enantiopure form. In a more realistic scenario, the binding situation is not as perfect as described and other parameters may influence the selectivity.[6] The chiral photocatalysts used in our work (see below) rely on a non-covalent two-point hydrogen bond interaction for enantiomer recognition. They operate by triplet energy transfer from a xanthone or thioxanthone chromophore.[6,7]

In the context of allene deracemization, our previous work had focused on a single class of allenes and consecutive reactions had not been studied. Given the importance of allenes in organic synthesis[10] it seemed desirable to extend the scope of the deracemization to other allenes and to explore their reactivity. Specifically, the lactam recognition motif of the chiral triplet sensitizer raised the question whether other lactams would be equally suited for binding and what degree of enantioselectivity could be achieved. In

Scheme 1. Simplified scheme for a photochemical deracemization achieved by a single chiral photocatalyst. The tetrahedrons represent chiral molecules in both enantiomeric forms.
the work now presented we focused mainly on 3-(1′-alkenylidene)-pyrrolidin-2-ones and their reactivity. A highly enantioselective deracemization was established and three valuable transformations have been found, which gave access to the respective products in high enantioselectivity (>90% ee). Results of our preliminary experiments are summarized in this Communication.

Racemic allenes rac-1 (Scheme 2) were prepared from N-para-methoxybenzyl(PMB)-pyrrolidin-2-one by a four-step sequence, including α-iodination, conversion to the triphenylphosphonium salt, Wittig reaction and final deprotection (see SI for further details). The compounds are stable at room temperature but show some decomposition under acidic conditions. The deracemization was attempted with thioxanthone 2 that exhibits a significant absorption in the visible part of the electromagnetic spectrum. In line with previous data on the triplet energy of thioxanthone 2,

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E_T = \frac{1}{C_0} \cdot \text{bonding} \]  

and the sensitizer by hydrogen bonding[12] is preferred (2-ent-1) which leads to an enrichment of the observed enantiomer 1. A key aspect is the fact that the energy transfer to the allene is highly efficient within complex 2-ent-1 while an intermolecular energy transfer is slower.[5,6] The functional group tolerance of the reaction was demonstrated for alkyl, phenyl, chloro, methoxycarbonyl, alkynyl, and methoxy (1a-1m) although some yields suffered due to the instability of the allenes during purification. No decomposition was observed during the irradiation.

In order to explore the limits of the deracemization, the tetrasubstituted allene rac-3 was submitted to the optimized irradiation conditions (Scheme 3). In this instance the size difference between methyl and ethyl is responsible for the different binding properties and it is remarkable that sensitizer 2 does allow for a significant distinction which in turn results in 45% ee. Likewise, even a seven-membered lactam, azepan-2-one rac-4, with a higher flexibility within the ring could be partially deracemized and delivered a major enantiomer with the putative structure 4.

Subsequent reactions of allenes 1 were mainly performed with the most easily accessible product 1a which was obtained in high enantiopurity (98% ee). A concerted cycloaddition[15] seemed most rewarding regarding the desired transfer of axial point chirality.[16,17] After some optimization we found the Diels–Alder reaction with cyclopentadiene to be feasible if performed under Lewis acid catalysis at low temperature (Scheme 4). Two diastereoisomers 5a and 5a′ were obtained and could be fully separated. The cycloaddition occurred exclusively at the internal α,β-unsaturated but not at the β,γ-unsaturated double bond. After N-substitution of the major

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Scheme 2. Photochemical deracemization of various 3-(1′-alkenylidene)-pyrrolidin-2-ones rac-1 upon visible light irradiation in the presence of chiral sensitizer 2 and binding of allene enantiomer ent-1 to catalyst 2 (inset).

Scheme 3. Photochemical deracemization reaction of tetrasubstituted allene rac-3 and of 3-(3′,3′-dimethyl-1′-butenylidene)-azepan-2-one (rac-4) upon visible light irradiation in the presence of chiral sensitizer 2.
diastereoisomer with para-nitrobenzenesulfonyl chloride a crystalline product was obtained which was suitable for X-ray crystallography. In line with NOESY (nuclear Overhauser enhancement spectroscopy) data, the crystal structure supported the assignment of the relative configuration to theexo product. Anomalous diffraction established the absolute configuration of product 5a which in turn confirmed the assumed absolute configuration of allenes 1. Indeed, diene addition is known to occur from the more accessible face of a trisubstituted allene. In the specific case of allenes 1a and 1b there is anexo preference for the approach of the diene as seen by the observed diastereomeric ratio (d.r.). The chirality transfer in the Diels–Alder reaction is close to perfect both for allenes 1a and 1b. Products 5 invite further functionalization at several positions and represent potentially useful building blocks.

When searching for possible ways which allow for an electrophilic attack on allenes, we discovered a useful bromination protocol. Treatment with bromine in CH2Cl2 resulted in the formation of a dibrominated product to which we assign structure 7 (bottom left); structure of the N-para-nitrobenzenesulfonyl derivative of compound 5a as determined by anomalous X-ray diffraction (bottom right).

Scheme 4. Diels–Alder reaction of allenes 1a and 1b with cyclopentadiene: Transfer of axial chirality to point chirality in products 5 (top); exo approach of the diene to substrates 1 (bottom left); structure of the N-para-nitrobenzenesulfonyl derivative of compound 5a as determined by anomalous X-ray diffraction (bottom right).

In summary, a new, versatile class of allenes has become accessible in enantiomerically enriched form by a visible light-mediated deracemization reaction. Since either enantiomer of the deracemization catalyst is available not only allenes 1 but also their enantiomers ent-1 can be selectively obtained. The success of the reactions underlines the high efficiency of deracemization processes with substrates which display a lactam binding motif. Applications of the allenes have been successfully explored by addition to the internal allene double bond with concomitant axial-to-point chirality transfer. An alicyclic allene could be obtained with high enantioselectivity after lactam ring opening. Applications of chiral allenes in more complex synthetic sequences are currently being pursued.

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Conflict of interest

The authors declare no conflict of interest.

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