Atroposelective arene-forming alkene metathesis

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Alkene metathesis catalysed by enantiopure metal alkylidene complexes enables versatile strategies to products with configurationally-defined stereocentres. Desymmetrisation processes thereby provide particularly reliable stereoselective routes to aliphatic structures, while the differentiation of aromatic stereogenic units remained an outstanding challenge. Herein, we describe the feasibility of alkene metathesis to catalytically control stereogenic axes by traceless arene formation. Stereodynamic trienes are selectively converted into corresponding binaphthalene atropisomers upon exposure to a chiral molybdenum catalyst. Remarkably, stereoselective arene-forming metathesis allows high yields and enantioselectivities of up to 98:2 e.r. As the disconnection of each bond of aromatic products is retrosynthetically conceivable, it is anticipated that forging arenes by means of stereoselective metathesis will enable versatile approaches for the synthesis of a broad range of molecular topologies with precisely defined configuration.

On account of increasingly sophisticated metal-alkylidene complexes as catalysts, alkene metathesis advanced to an exemplary transformation with exquisite characteristics for broad implementations. The availability of alkene feedstocks, the unproblematic byproducts and the catalytic efficiency under mild conditions often render metathesis the method of choice across various reaction scales, from bulk commodities to the exploratory synthesis of molecular systems of striking complexity. Furthermore, catalysts bearing chiral ligands induce high levels of enantioselectivity, typically by employing molybdenum or ruthenium alkylidene complexes. Pioneered by Hoveyda and co-workers, the configuration of stereocentres is thereby usually controlled by converting meso-compounds in highly stereoselective ring-opening or ring-closing metathesis reactions (Fig. 1a & b). Notably, this concept was translated to desymmetrise phosphapherocenes and related metal complexes with excellent selectivity (Fig. 1c). However, in comparison, catalytic strategies for stereoselective arene formation provide a more comprehensive range of topologically-defined scaffolds with different stereogenic units. Nonetheless, current enantiocontrolled arene-forming methods require functionalities that are transferred into the products as remnants of their synthesis, such as oxygenated units from carbonyl groups or appended rings from tethers required for chemoselectivity. In contrast, ring-closing metathesis to create arenes constitutes a traceless process, which considerably improves the versatility of arene formation with feasible retrosynthetic disconnections for every bond of an aromatic target. For instance, by using a chiral catalyst, ring-closing metathesis allows a kinetic resolution to form [7]helicene by partial conversion of a racemic substrate (Fig. 1d). Remarkably, stereoselective metathesis to catalytically control the stereogenic axes of atropisomers nonetheless remained unprecedented, despite the ideal features of arene formation for stereoselective catalysis. We hence anticipated that a triene substrate would undergo atroposelective metathesis controlled by a chiral metal alkylidene catalyst and that a complete conversion into enantioenriched atropisomers is possible based on the dynamic behaviour of open-chained substrates. More specifically, geared bond rotations would lead to equilibrated conformers of the substrate until binding to the metal alkylidene catalyst of a specific configuration (Fig. 1e, left vs right direction), while the rigid structure of ring-closed products results in restrained steric interactions to
ensure configurational stability. Moreover, the stereoselective construction of an aromatic ring constitutes an irreversible process, further underscoring the advantage of arene formation for stereoselective metathesis. Herein, we report that atroposelective arene-forming metathesis to catalytically control stereogenic axes proceeds in high yields and with excellent stereoselectivity by an efficient aromatisation of triene substrates.

**Fig. 1.** Background and concept. **a**, Desymmetrisation of *meso*-compounds by stereoselective ring-opening cross metathesis. **b**, Control over the configuration of a stereocentre by stereoselective ring-closing metathesis. **c**, Ring-closing metathesis to stereoselectively desymmetrise *phosphaferrocenes*. **d**, Kinetic resolution by ring-closing metathesis to enantioenriched helicenes by partial conversion. **e**, Atroposelective arene-forming metathesis converting stereodynamic trienes to catalytically control the configuration of a stereogenic axis.

**Results**

**Evaluation of feasibility.** To assess the viability of atroposelective metathesis, a model substrate (*E/Z*)-**1a** with a disubstituted terminal alkene that favours the initiation of alkene metathesis on the diene moiety was prepared in a short synthetic sequence (Supplementary Methods). The commercially available chiral metathesis catalysts **C1** and **C2** were subsequently evaluated to study the prospects of atroposelective arene-forming metathesis (Fig. 2a). Gratifyingly, the feasibility of the method was confirmed by using the chiral monoalkoxide pyrrolyl molybdenum catalyst **C1** in toluene as reaction medium, which afforded the anticipated product with a selectivity of 83:17 e.r.25. Interestingly, catalyst **C2** with a *C*<sub>r</sub>-symmetric biphenolate ligand that avoids a stereocentre at molybdenum with potentially interconverting configuration12,26 led to product formation with the same level of enantioselectivity. However, extensive efforts to increase selectivity with the commercial catalysts **C1** and **C2** under various conditions remained unfruitful.
Method development. Having observed that catalyst C2 with a bidentate ligand promotes arene formation, we pursued an in situ formation of the catalysts using the Mo-dipyrrolyl precursor27 to assess the effect of ligand variations (Fig. 2b). Gratifyingly, an e.r. of 93:7 was measured when employing binaphthol L1, albeit with a moderate yield of 43% (Fig. 2c). A bulkier binaphthol L2 was detrimental to turnover as well as to selectivity (84:16 e.r.) and the binaphthol L3 bearing an electron-withdrawing group showed an enantioenrichment of 92:8 e.r. with a modest yield of 39%. However, we were pleased to find that a selectivity of 95:5 e.r. and a 72% yield was obtained when using binaphthol L4 with perfluorinated 3,3′-aryl substituents. Notably, the yield of the reaction was further improved to 99% with a selectivity of 96:4 e.r. by increasing the reaction temperature to 40 °C when the (E)-1a isomer was used28. The quantitative conversion to the desired product within 24 hours confirmed that atroposelective arene-forming metathesis is possible with remarkable efficiency and selectivity.

Fig. 2 | Feasibility and optimisation studies: a. Feasibility of catalyst control over a stereogenic axis by metathesis using commercially available chiral Mo catalysts. b. Synthesis of the Mo-dipyrrolyl precatalyst and the in situ formation of molybdenum catalysts with variable ligand structures27. c. Optimisation of the atroposelective arene-forming metathesis with (E/Z)-1a, 5 mol% Mo-dipyrrolyl precatalyst and 15 mol% binaphthol ligand L1-L4 in toluene. Entry 5 with (E)-1a.
Scope of the concept. We next investigated the scope and limitations of our method with differently substituted triene substrates. Interestingly, triene (E)-1a led to a quantitative transformation to the desired product (Ri)-2a with 99 % isolated yield using only 1.0 mol% of the catalyst while maintaining a high level of selectivity (92:8 e.r.), confirming the remarkable reactivity of the triene substrate towards arene-forming ring-closing metathesis. Furthermore, a single crystal of product (Ri)-2a was obtained, enabling the determination of the absolute configuration by X-ray crystallography. Under standard conditions (Fig. 2c, entry 5) with reduced ligand loading and reaction time (12 hours), the substrates (E)-1b and (E)-1c with a methoxy or a fluorine substituent, respectively, displayed selectivities of 92:8 and 90:10 e.r. with (Ri)-2c isolated in an excellent yield of 96%. Substrates (E)-1d and (E)-1e with and without an oxygenated substituent both converted reliably with 88:12 e.r. (94% yield for (Ri)-2d). We next explored the bromine-substituted substrate (E)-1f and observed a selectivity of 91:9 and a yield of 83%. Remarkably, the methylenedioxy functionalised substrate (E)-1g afforded a selectivity of 98:2 e.r., while a somewhat lower selectivity of 89:11 e.r. was observed with the methyl substituted substrate (E)-1h. Moreover, systems (E)-1i and (E)-1j with a fluorine or trifluoromethyl group led to high selectivities (93:7 e.r. and 91:9 e.r.), while product (Ri)-2j was isolated in nearly quantitative yield. These findings underscore the generality of stereoselective arene-forming alkene metathesis.

![Scope of the concept](image)

**Fig. 3. | Atroposelective arene-forming alkene metathesis.** a, Scope evaluation using 1.0 mol% Mo-dipyrrolyl precatalyst and 5.0 mol% binaphthol ligand L4 for (E)-1a or 5.0 mol% precatalyst and 10 mol% ligand L4 for other examples. b, Comparison with a substrate lacking a coordinating methoxy substituent.
To test the influence of a potential coordination with the methoxy substituent, we converted triene \((E/Z)-3\) with a methyl group under otherwise identical conditions. Interestingly, the formation of desired binaphthalene 4 was observed with significantly reduced selectivity (Fig. 5a, 70:30 e.r. vs 95:5 e.r. in Fig. 2c, entry 4). We thus surmise that the coordination of the methoxy group to the molybdenum centre further promotes the formation of the \(anti\)-alkylidene, hampers rotation about the biaryl axis and allows for a precise positioning of the two naphthyl rings during ring-closing metathesis (see SI). The higher reactivity of the \(anti\)-configured Mo-alkylidene as observed in previous studies and the minimisation of interactions with the protruding \(\text{CF}_3\) group thereby act in concert to differentiate the competing pathways in the cyclisation step.

**Conclusions**

Atroposelective arene-forming metathesis allows to control the configuration of stereogenic axes with excellent selectivity and yield by using a chiral molybdenum catalyst. The triene substrates are conformationally dynamic and efficiently convert with catalyst control into valuable binaphthyl atropisomers as a result of ring-closing metathesis. As the formation of each bond of aromatic product offers a possible route to stereochemically-defined scaffolds, we expect that stereoselective arene-forming metathesis will inspire the development of innovative synthetic strategies to access a broad range of molecular architectures with defined configuration. Our attention is currently focused on catalyst-controlled metathesis for the synthesis of stereochemically complex atropisomers and the development of ruthenium-catalysed stereoselective arene-forming metathesis.

**Methods**

**General procedure.** Ligand \(L_4\) (1.55 mg, 2.50 \(\mu\)mol, 5.00 mol%) under inert conditions (glovebox) at ambient temperature was treated with a solution of Mo-dipyrrrol precatalyst (5.00 \(\mu\)L, 0.100 molL\(^{-1}\) in toluene, 1.00 mol%). The mixture was stirred for 15 minutes and a solution of the triene substrate \((E)-1a\) (16.3 mg, 50.0 \(\mu\)mol) in toluene (225 \(\mu\)L) was added. The vial was tightly capped, taken out of the glovebox and heated for 12 h to 40 °C. To the mixture was added EtOAc (1.0 mL), the volatiles were removed under reduced pressure and the residue was purified by chromatography to give \((R)_3-2a\) as a white solid (14.8 mg, 49.6 \(\mu\)mol, 99% yield, e.r. 92:8).

**Data availability**

Experimental details, supplementary methods, NMR spectra and crystallographic data are available in the Supplementary Information. Supplementary crystallographic data can be obtained from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/structures (CCDC 2132439).

**References**


25. The (Z)-isomer remains unreacted and can be converted to the (E)-isomer by LED-light irradiation using methylene blue as photocatalyst, while the combination of isomerization and metathesis was unproductive. See Supplementary Methods for details.
28. Obtained by recrystallization or chromatography.

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Author contributions
C.S. and Z.J. conceived the study, designed the experiments and analysed the data. Z.J. performed the experiments. Z.J. and C.S. wrote the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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