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Asymmetric Catalysis

Atroposelective Arene-Forming Alkene Metathesis**

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Dedicated to Professor Karl Gademann on the occasion of his 50th birthday

Abstract: Alkene metathesis catalyzed by enantiopure metal alkylidene complexes enables exceptionally versatile strategies to products with configurationally-defined stereocenters. Desymmetrization processes thereby provide 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 enantioselectivities of up to 98:2 e.r. and excellent yields. As the disconnection of each bond of an aromatic target 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.

Enabled by increasingly sophisticated metal-alkylidene complexes as catalysts, alkene metathesis advanced to an exemplary transformation with exquisite characteristics for a broad implementation.[1–7] 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.[8,9] Pioneered by Hoveyda, Schrock and coworkers, the configuration of stereocenters is thereby usually controlled by converting *meso*-compounds in highly stereoselective ring-opening or ring-closing metathesis reactions (Figure 1A & B).[10–12] Notably, this concept was translated to desymmetrize phosphaferrocenes and related metal complexes with excellent selectivity (Figure 1C).[13–15] However in comparison, catalytic strategies for stereoselective arene formation provide an even more comprehensive range of topologically-defined scaffolds with different stereogenic units.[16] 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[17–19] or appended rings from tethers required for chemoselectivity.[20–22] In contrast, ring-closing metathesis to create arenes[23] 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 a [7]helicene by partial conversion of a racemic substrate (Figure 1D).[24] Remarkably, stereoselective metathesis to catalytically control the stereogenic axes of atropisomers 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 behavior of an open-chained substrate. More specifically, geared bond rotations would lead to equilibrated conformers until binding to the metal alkylidene catalyst of a specific configuration (Figure 1E, left *vs* right direction), while the rigid structure of ring-closed products results in well-defined steric interactions that ensure high configurational stability. It is worth noting that the stereoselective construction of an aromatic ring represents an irreversible process, further underscoring the advantage of arene formation for stereoselective metathesis. We report herein, that atroposelective arene-forming metathesis to catalytically control stereogenic axes proceeds in high yields and with excellent stereoselectivity by an efficient aromatization of triene substrates.

To assess the viability of atroposelective metathesis, a model substrate (*E*/*Z*)-**1a** with a disubstituted terminal alkene that favors the initiation of the alkene metathesis on the diene moiety was prepared in a short synthetic sequence (Supporting Information). The commercially available chiral

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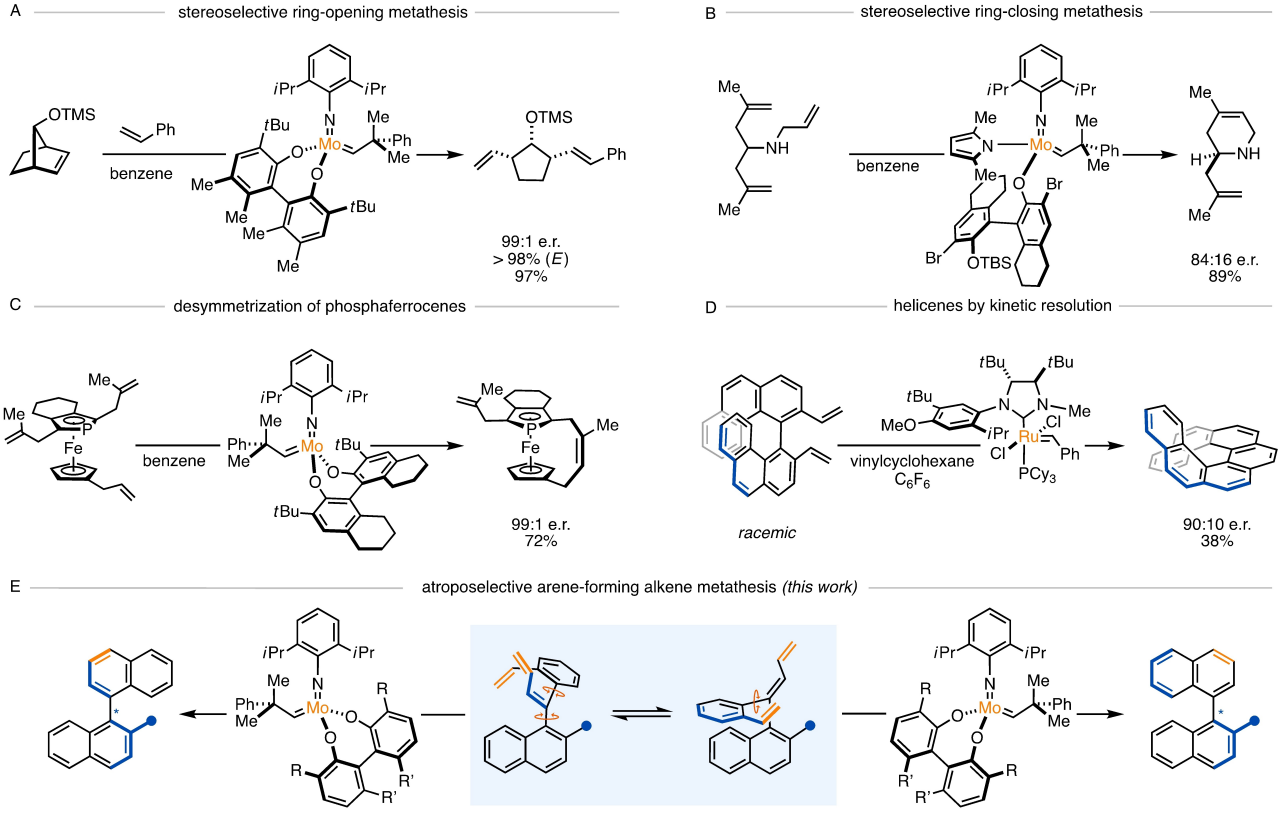

Figure 1. Background and concept. A) Desymmetrization of *meso*-compounds by stereoselective ring-opening cross metathesis. B) Control over the configuration of a stereocenter by stereoselective ring-closing metathesis. C) Ring-closing metathesis to stereoselectively desymmetrize phosphaferrocenes. D) 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.

metathesis catalysts **C1** and **C2** were subsequently evaluated to study the prospects of the atroposelective arene-forming metathesis (Figure 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_2-symmetric biphenolate ligand that avoids a stereocenter at molybdenum with potentially interconverting configuration[12,26] led to product formation with the same level of enantioselectivity. However, extensive efforts to increase the selectivity with the commercial catalysts **C1** and **C2** under various conditions remained unfruitful.

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 precursor (precatalyst)[27] to assess the effect of ligand variations (Figure 2B). Gratifyingly, an e.r. of 93:7 was measured when employing binaphthol **L1**, albeit with a moderate yield of 43 % (Figure 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 utilizing 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 used.[28] The quantitative conversion to the desired product within 24 hours confirmed that atroposelective arene-forming metathesis is possible with remarkable efficiency and selectivity.

We next investigated the scope and limitations of our method with differently substituted triene substrates (Figure 3A). Interestingly, triene (*E*)-**1a** led to a quantitative transformation to the desired product (R_a)-**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 (R_a)-**2a** was obtained, enabling the determination of the absolute configuration by X-ray crystallography.[29] Under standard conditions (Figure 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, displayed selectivities of 92:8 and 90:10 e.r. with (R_a)-**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 (R_a)-**2d**). We next explored the bromine-substituted substrate (*E*)-**1f** and observed a selectivity of

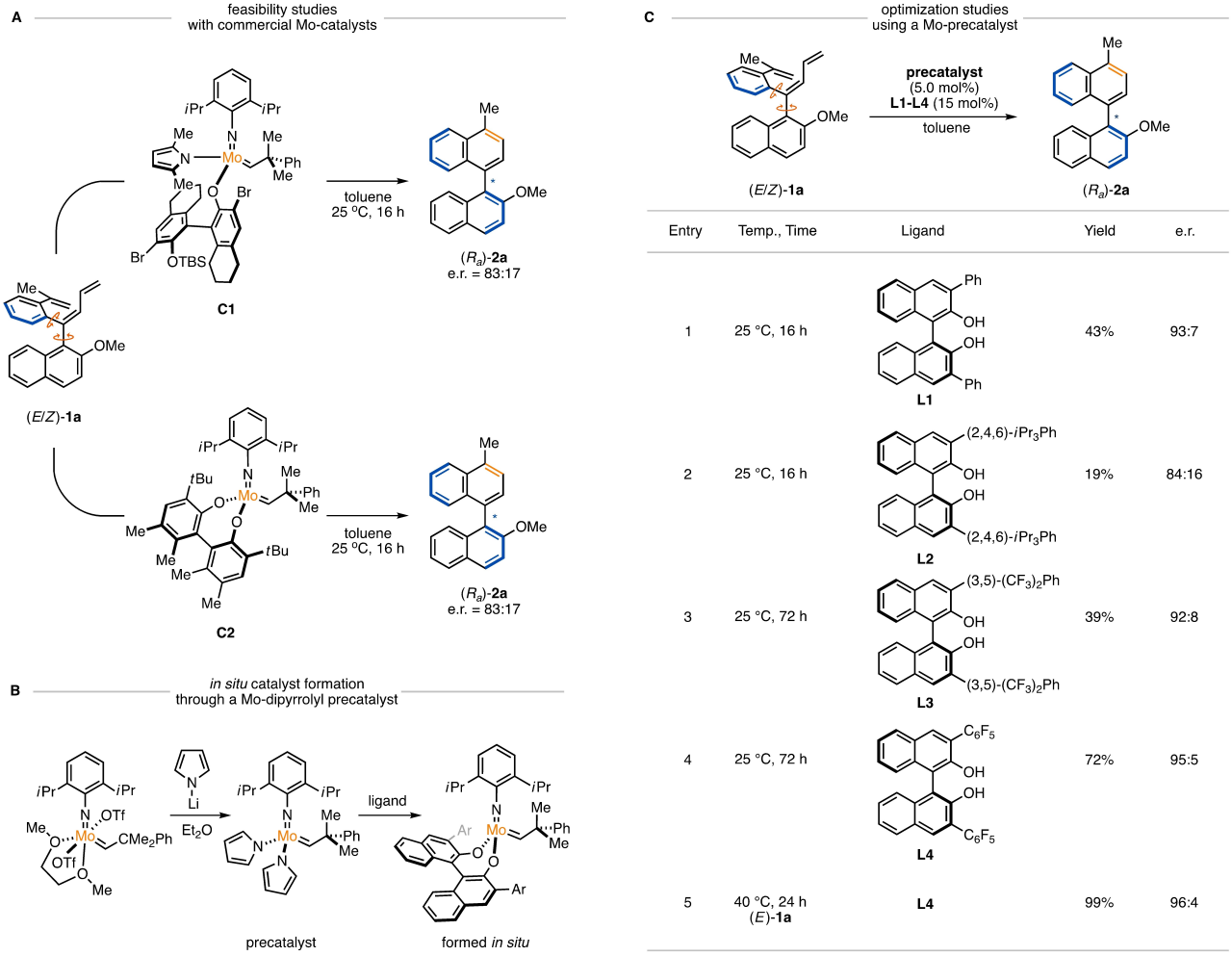

Figure 2. Feasibility and optimization studies. A) Feasibility of catalyst control over a stereogenic axis by metathesis using commercially available chiral Mo catalysts. B) Synthesis of the Mo-dipyrrolyl precatalyst and the in situ formation of molybdenum catalysts with variable ligand structures.[27] C) Optimization 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**.

91:9 and a yield of 83%. Remarkably, the methylenedioxy functionalized 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 (R_a)-**2j** was isolated in nearly quantitative yield (99%). These findings underscore the generality of stereoselective arene-forming alkene metathesis.

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 the desired binaphthalene **4** was observed with significantly reduced selectivity (Figure 3B, 70:30 e.r. *vs* 95:5 e.r. in Figure 2C, entry 4). We thus surmise that the coordination of the methoxy group to the molybdenum 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 (Supporting Information).[30–32] The higher reactivity of the *anti*-configured Mo-alkylidene as observed in previous studies[33,34] and the minimization of interactions with the protruding C_6F_5 group thereby act in concert to differentiate the competing pathways in the cyclisation step.

Atroposelective arene-forming metathesis allows to control the configuration of stereogenic axes with excellent selectivity and yields 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 products 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 using molybdenum complexes and

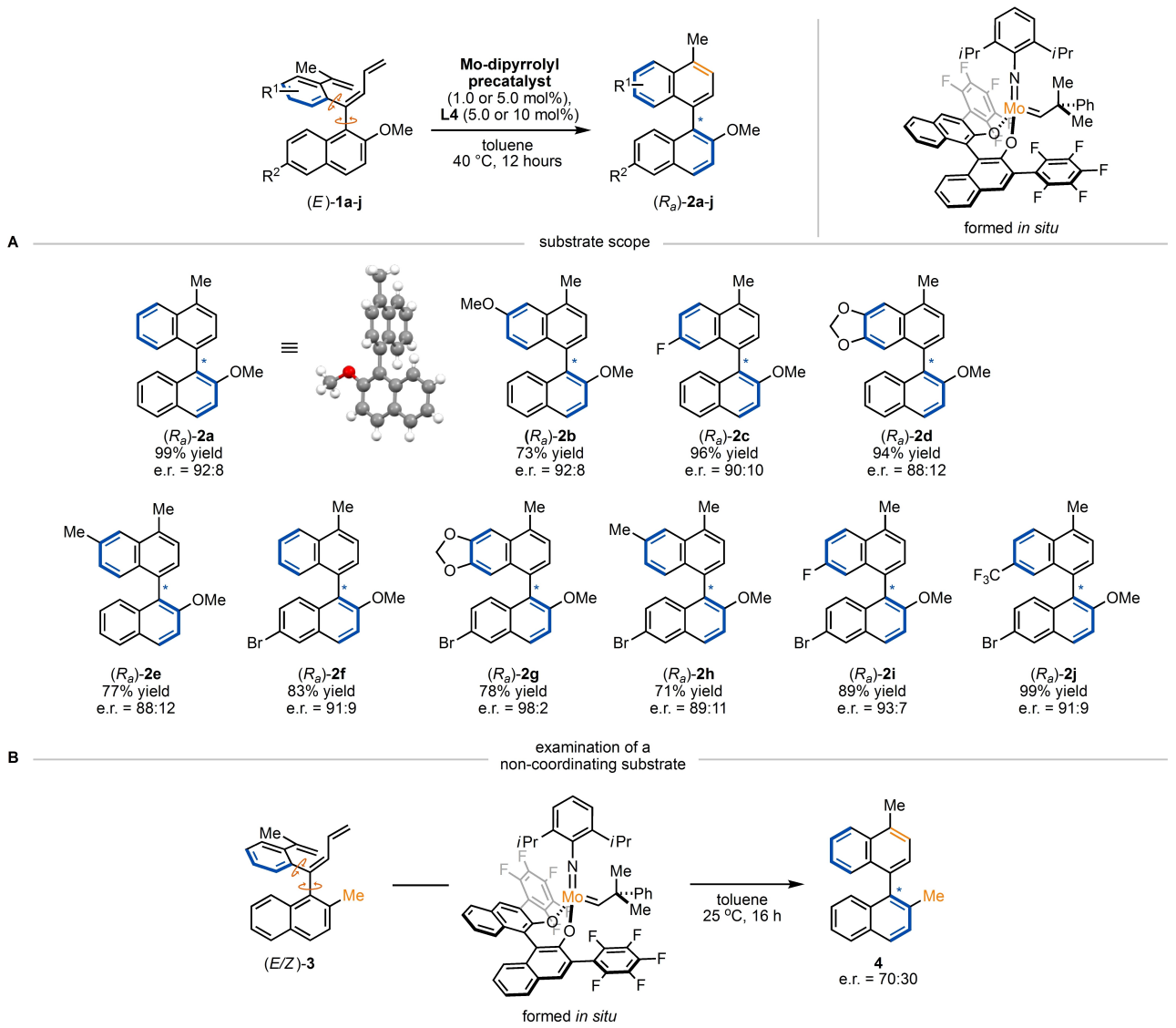

Figure 3. Atroposelective arene-forming alkene metathesis. A) Scope evaluation using 1.0 mol% Mo-dipyrrolyl precatalyst and 5.0 mol% binaphthol ligand **L4** for (*E*)-**1a** or 5.0 mol% precatalyst and 10 mol% ligand **L4** for other examples. B) Comparison with a substrate lacking a coordinating methoxy substituent.

the development of ruthenium-catalyzed stereoselective arene-forming metathesis.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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