Asymmetric Catalysis

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Asymmetric Ring-Closing Metathesis with a Twist**

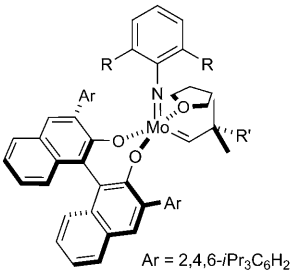
*Hendrik F. T. Klare and Martin Oestreich**

alkenes · asymmetric catalysis · fluxionality · metathesis · molybdenum

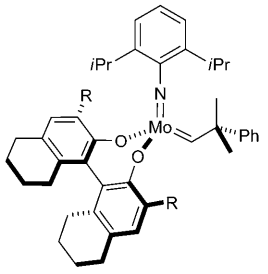
Chiral, metal-based catalysts are an integral part of modern asymmetric synthesis.[1] Normally, enantioselective transition-metal catalysis hinges upon the deliberate combination of optically active ligands and metal cations. Conversely, stereodefined transition-metal complexes that contain only achiral ligands and thus display chirality exclusively at the metal center are relatively scarce,[2] and their infrequent use in asymmetric catalysis is still perceived as a curiosity.[3] Any stereoinduction arising from a conventional chiral complex is intuitively ascribed to the chiral ligands, and latent stereochemical information at the metal atom is often ignored. This situation is not as uncommon as one might think, in particular with non-C_2-symmetric bidentate ligands. In fact, this additional stereogenic element might be formed during or even exist throughout a catalytic cycle; the catalytically active intermediate might then be one of several diastereomers. Therefore, the true origin of stereoinduction, that is, the contribution of the chirality at the central metal atom, in these catalytic systems is vague, and this ambiguity might have deterred researchers from a closer investigation into this stereochemical challenge. A detailed understanding of the interplay of chirality in the ligand backbone and at the metal center might, however, prepare the ground for conceptually novel strategies for targeted catalyst design. The continuing collaboration of the Hoveyda and Schrock laboratories in the area of asymmetric ring-closing metathesis (ARCM) has now produced a particularly intriguing example, in which an asymmetrically substituted molybdenum atom is directly involved in several stereospecific bond-forming steps.[4]

Despite considerable advances in enantioselective alkene metathesis,[5] more reactive and more selective catalysts with improved functional-group compatibility are still needed; sterically congested alkenes are still poor substrates for metathesis processes. These shortcomings have been overcome for isolated cases by extensive catalyst screening; however, there is no single catalyst available that promotes ARCM of a broad range of precursors with equal efficacy. This weakness[6] was clearly exposed in an ARCM-based total synthesis of the *Aspidosperma* alkaloid (+)-quebrachamine, a challenge which was the nucleus for the development of a general catalyst.

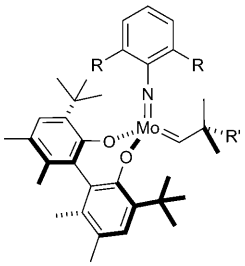
Several privileged chiral molybdenum–alkylidene complexes for ARCM,[7,8] **1**–**4**,[9] were among those tested in the aforementioned synthetic endeavor. These high-oxidation-state catalysts are assembled in a modular fashion from imido and alkoxide ligands, which, once coordinated to molybdenum, do not dissociate during catalysis. Axially chiral diolates were used to install chirality and afford the binaphthol-derived complexes **1a**–**c**,[9a,b] the octahydrobinaphthol-derived complexes **2a**–**c**,[9b,c] and the biphenol-derived complexes **3a**–**c**,[9d–f] as well as **4**.[9g]



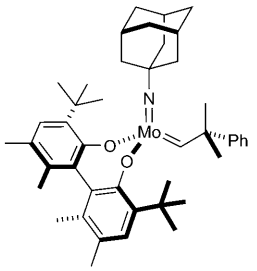
1a[9a] R = *i*Pr R' = Ph
1b[9a] R = Me R' = Ph
1c[9b] R = Cl R' = Me



2a[9c] R = *t*Bu
2b[9b] R = 2,4,6-Me3C6H2
2c[9b] R = CHPh2



3a[9d] R = *i*Pr R' = Ph
3b[9e] R = Me R' = Ph
3c[9f] R = Cl R' = Me



4[9g]

However, the structural rigidity of the bidentate ligands—which had been deemed necessary—was identified as a reason for the poor activities in the ambitious ARCM

[*] H. F. T. Klare, Prof. Dr. M. Oestreich
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-36501
E-mail: martin.oestreich@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/research/oestreich/oe_welcome.html

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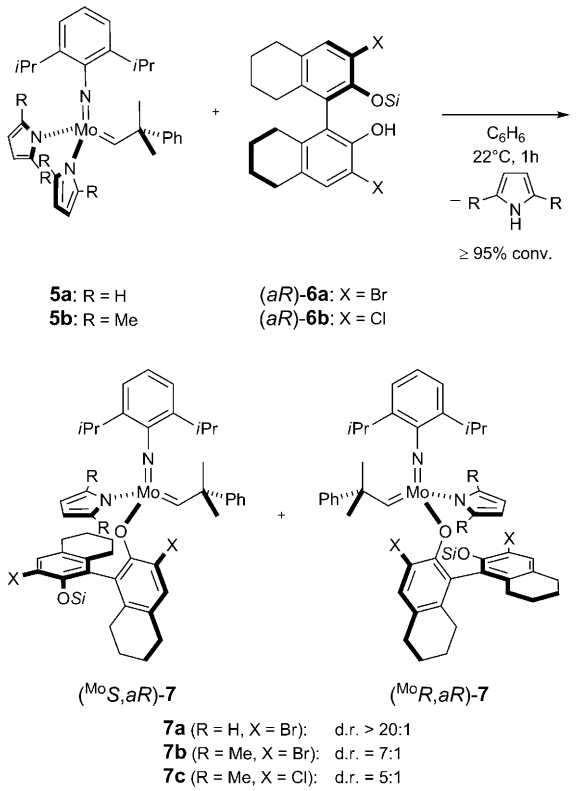
towards (+)-quebrachamine.[4] On the assumption that structural fluxionality of the ligand backbone could facilitate its adaptation to the variable steric requirements in the catalytic cycle, monodentate alkoxides were selected as ligands. Enantiomerically pure, monoprotected binaphthols were (in hindsight) the obvious choice. The coordination of just one of these ligands to molybdenum inevitably produces a diastereomeric mixture of complexes with a stereogenic molybdenum center; the stereoselective preparation of these complexes is noteworthy, as stereocontrol stems from discrimination between enantiotopic ligands in an intermolecular reaction.[10] The treatment of prochiral dipyrrolide precursors **5** with equimolar amounts of a monoprotected diol (*aR*)-**6** resulted in facile ligand exchange to yield diastereomerically enriched aryl oxide–pyrrolide complexes (^{Mo}S,*aR*)-**7** (Scheme 1).[4,11]



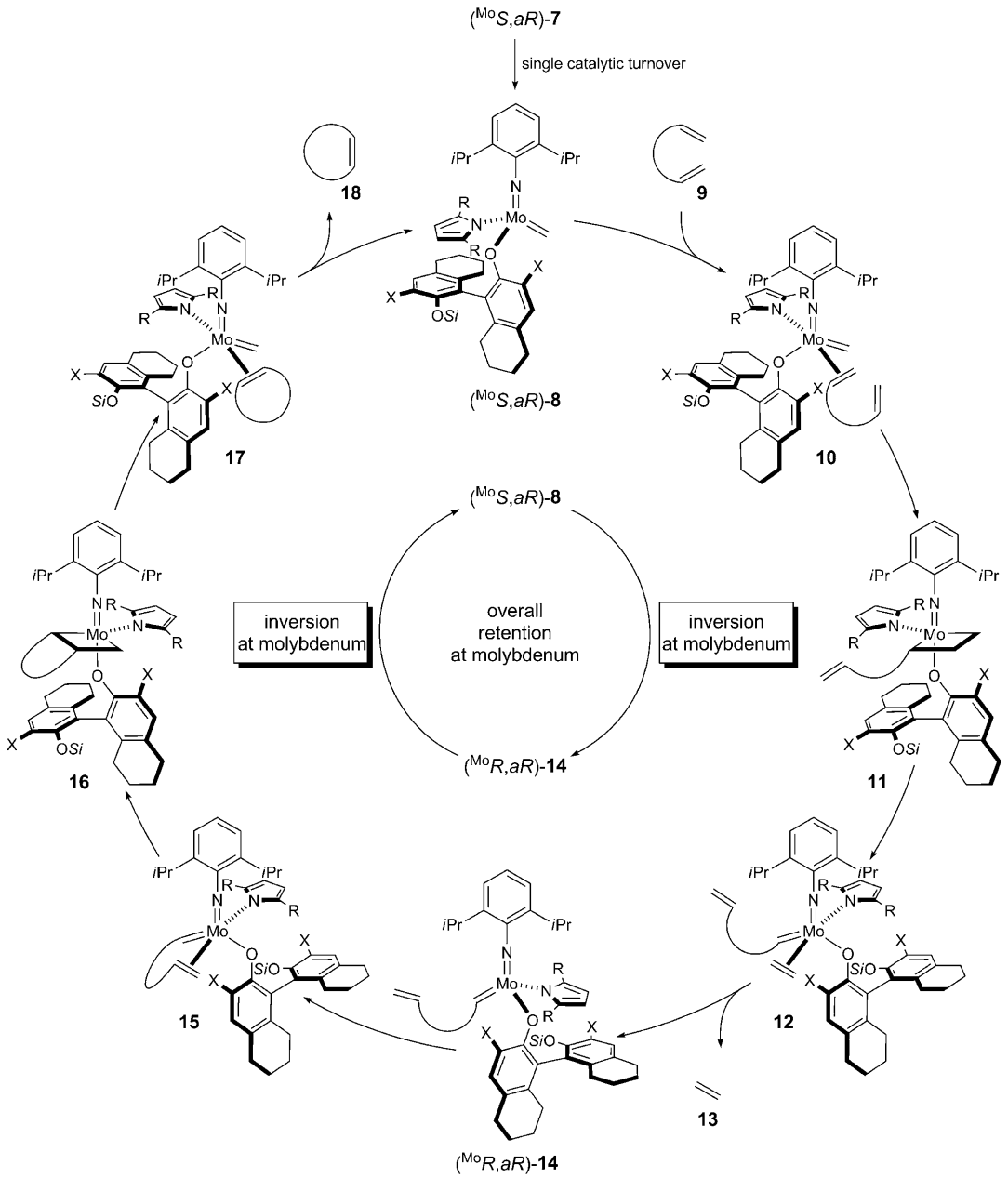
Scheme 1. Differentiation of enantiotopic ligands in the stereoselective preparation of complexes **7** with a stereogenic molybdenum center (*Si* = Si*t*BuMe$_2$).

The relative configuration of (^{Mo}S,*aR*)-**7b** and the distorted tetrahedral geometry at the molybdenum atom were identified by X-ray crystallography. Although complexes **7** were shown to be configurationally stable in solution,[4,12] the ligands are of course mobile. As well as stereochemical and conformational aspects, the stereoelectronic environment of the molybdenum center in these complexes must be considered: A donor ligand (pyrrolide) and an acceptor ligand (aryl oxide) determine the site of alkene coordination.[13] The "constitutional fluxionality"[4] and the stereoelectronic nature of the novel complexes are the pivotal features of the unique catalytic cycle depicted in Scheme 2. The stereoelectronic situation in (^{Mo}S,*aR*)-**8** creates an accessible coordination site *trans* to the pyrrolide ligand; this site is then occupied by alkene **9** to give the square-pyramidal complex **10**.[12] The trigonal-bipyramidal intermediate **11** with axial imido and aryl oxide ligands is then formed rapidly. Cycloreversion of metallacyclobutane **11** yields **12** with ethylene (**13**) coordinated *trans* to the pyrrolide; **13** immediately dissociates and is released from the catalytic cycle. This first metathesis step proceeds with inversion of configuration at molybdenum. The resulting tetrahedral complex (^{Mo}R,*aR*)-**14** has to participate in a second (intramolecular) metathesis step to complete the cycle ((^{Mo}R,*aR*)-**14**→(^{Mo}S,*aR*)-**8**); however, in contrast to the initial metathesis sequence ((^{Mo}S,*aR*)-**8**→(^{Mo}R,*aR*)-**14**), the subsequent steps proceed with (^{Mo}R,*aR*)-**14**, a pseudodiastereomer of (^{Mo}S,*aR*)-**8**. This four-step sequence ((^{Mo}R,*aR*)-**14**→**15**→**16**→**17**→(^{Mo}S,*aR*)-**8**) again occurs with inversion at molybdenum. Within one catalytic cycle, catalytically active (^{Mo}S,*aR*)-**8** experiences double inversion, that is, overall retention of configuration!

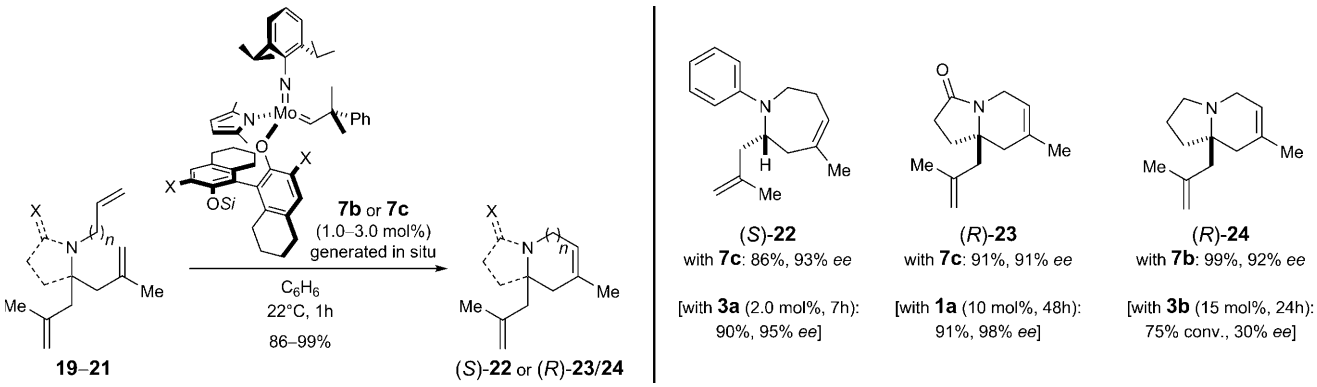
The unprecedented reactivity and versatility of the new ARCM catalysts are illustrated in the synthesis of nitrogen-containing heterocycles. Representative of the types of structures accepted by the chiral molybdenum complexes (^{Mo}S,*aR*)-**7b** and (^{Mo}S,*aR*)-**7c** are trienes **19**–**21** (Scheme 3). Formerly, three different diolate-derived catalysts were required for the enantioselective ring closure to give the monocyclic amine (*S*)-**22** (catalyst **3a**),[14a] the bicyclic amide (*R*)-**23** (catalyst **1a**),[14b] and the bicyclic amine (*R*)-**24** (catalyst **3b**).[14b] All three transformations proceed with (^{Mo}S,*aR*)-**7** with a markedly increased reaction rate (86–99% yield after 1 h at 22°C) and high levels of enantioselectivity (91–93% *ee*). Furthermore, (^{Mo}S,*aR*)-**7c** catalyzed the elusive desymmetrization en route to (+)-quebrachamine (**25**→(*S*)-**26**, Scheme 4), in which all known chiral catalysts had previously failed.[4] A platinum-catalyzed hydrogenation of the advanced intermediate (*S*)-**26** then afforded the target compound.

The rational and elegant development of this new enviably effective class of catalysts leaves the reader with some thought-provoking questions:

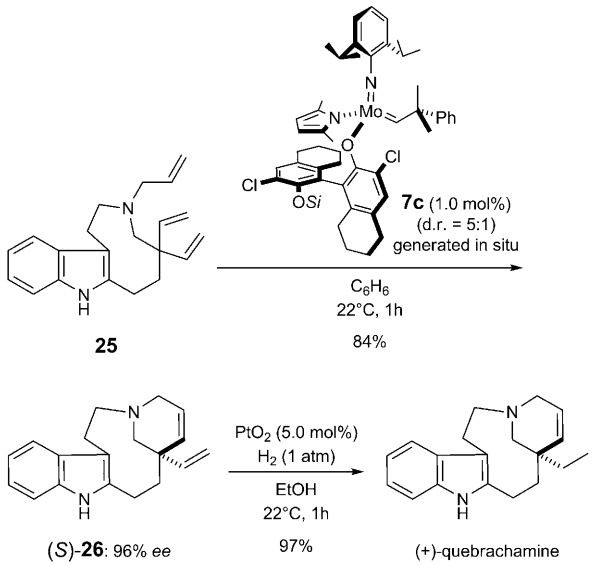
- The catalytic reactions were performed with the diastereomers (^{Mo}S,*aR*)-**7** (major and substantially more reactive) and (^{Mo}R,*aR*)-**7** (minor and less reactive),[4] but the catalytic cycle involves a molybdenum complex (see (^{Mo}R,*aR*)-**14**, Scheme 2) with the undesired relative configuration. Is it merely a difference in reactivity that determines which catalyst enters metathesis (either a *syn* alkylidene complex in the intermolecular scenario or a destabilized and more Lewis acidic *anti* alkylidene complex in the intramolecular scenario)?
- Another interesting observation is that substituents on the pyrrolide ligand are crucial for overall catalyst performance (Scheme 5):[4] The pyrrole nitrogen atom must be flanked by methyl groups **7**. In their absence (with (^{Mo}S,*aR*)-**7b**), turnover and enantioselectivity are poor—but why is the sense of stereoinduction inverted? Does the



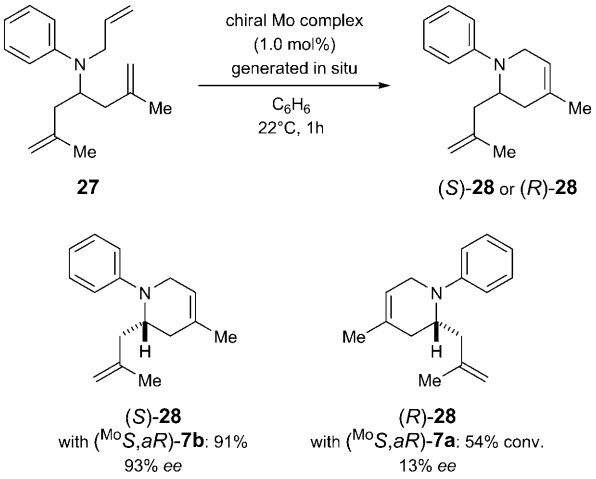
Scheme 2. Catalytic cycle for ring-closing metathesis with complexes **7** (R = H or Me, *Si* = Si*t*BuMe$_2$, X = Cl or Br). Although not explicitly shown, all individual steps are fundamentally reversible; there is free rotation about the Mo–O–C(sp^2) bonds.



Scheme 3. Comparison of new and reported catalysts in the enantioselective synthesis of cyclic amides and amines through ARCM.



Scheme 4. Final steps in the enantioselective synthesis of (+)-quebrachamine.



Scheme 5. Influence of the "innocent" pyrrolide ligand on catalyst performance and the sense of stereoinduction.

pyrrolide ligand affect the conformation around the chirality axis of the monodentate chiral ligand?

- The previous finding poses the question of the contribution of the central chirality at the molybdenum center towards the overall stereoinduction. A purist might call for an enantiomerically pure alkylidene complex that is only chiral at the molybdenum center. What would then be the level of stereoinduction? The present investigation shed light on how to control the stereochemical course of a metathesis sequence at a molybdenum center. The next tremendous challenge will be to satisfy the purist!

The contribution by Hoveyda, Schrock, and co-workers pushed ARCM to the next level. It is also a wonderful example of the advantageous interplay of total synthesis and methodology development. ARCM is now forging ahead into new "stereochemical territories", and more important advances can be expected.

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