LETTERS

Highly efficient molybdenum-based catalysts for enantioselective alkene metathesis

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Discovery of efficient catalysts is one of the most compelling objectives of modern chemistry. Chiral catalysts are in particularly high demand, as they facilitate synthesis of enantiomerically enriched small molecules that are critical to developments in medicine, biology and materials science[1]. Especially noteworthy are catalysts that promote—with otherwise inaccessible efficiency and selectivity levels—reactions demonstrated to be of great utility in chemical synthesis. Here we report a class of chiral catalysts that initiate alkene metathesis[1] with very high efficiency and enantioselectivity. Such attributes arise from structural fluxionality of the chiral catalysts and the central role that enhanced electronic factors have in the catalytic cycle. The new catalysts have a stereogenic metal centre and carry only monodentate ligands; the molybdenum-based complexes are prepared stereoselectively by a ligand exchange process involving an enantiomerically pure aryloxide, a class of ligands scarcely used in enantioselective catalysis[2,3]. We demonstrate the application of the new catalysts in an enantioselective synthesis of the *Aspidosperma* alkaloid, quebrachamine, through an alkene metathesis reaction that cannot be promoted by any of the previously reported chiral catalysts.

A chiral catalyst may promote a transformation with exceptionally high degrees of efficiency and enantioselectivity if the modes with which it associates with substrate molecules are sterically—as well as electronically—distinct[4,5]. Design of a chiral metal-based catalyst, where stereoelectronic interactions affect the energetics of the catalytic cycle, can lead to consideration of complexes that bear a stereogenic metal centre; stereoselective preparation and preservation of the stereochemical identity of the catalyst then become crucial issues. In the limited number of chiral stereogenic-at-metal catalysts prepared, stereoselective synthesis is addressed through multidentate ligands[6–8]. As stereogenic-at-metal complexes can undergo stereomutation[9], polydentate ligation ensures minimal erosion of stereochemical integrity. The rigidity of bi- or polydentate ligation may be detrimental, however, if catalyst structural fluxionality gives rise to enhanced activity and/or enantioselectivity. Chiral complexes that bear a stereogenic metal centre and only monodentate ligands, therefore, offer attractive opportunities in enantioselective catalysis[10,11]. Such options are, nonetheless, almost entirely unexplored; it is particularly challenging to design and synthesize enantiomerically pure stereogenic-at-metal catalysts that are devoid of polydentate ligands, do not readily stereomutate and can thus serve as effective chiral catalysts.

The growing list of alkene metathesis transformations that cannot be promoted by the existing metal complexes has underlined the need for more effective classes of catalysts[1,12,13]. One instance that points to such limitations is a key step in an enantioselective synthesis[14] of the adrenergic blocker quebrachamine[15] (Fig. 1): the conversion of achiral **1** to the strained chiral tetracycle **2** by reaction of sterically hindered alkenes. The results illustrated in Fig. 1, regarding molybdenum alkylidene **3** (refs 12, 16) and ruthenium carbene **4a** (ref. 17), although being somewhat inefficient, represent the optimal among available achiral catalysts. The faster initiating **4b** (ref. 18) proceeds only to 48% conversion, most likely as a result of lower stability of the carbene intermediates. In relation to an enantioselective quebrachamine synthesis, the existing chiral catalysts, represented by **5**–**7** (ref. 12), are entirely ineffective in promoting the formation of **2** (≤5% conversion with up to 50 mol% loading after up to 48 h at 22–80 °C). With 16 mol% **8** (ref. 19) at 80 °C, there is approximately 50% conversion, but only *rac*-**2** is generated; related monodentate *N*-heterocyclic chiral ruthenium carbenes[20] are equally ineffective.

As the first step towards identifying a new set of chiral catalysts, we considered reasons for the higher activity of alkylidene **3** in comparison with **5**–**7**, a variance that exists despite the similar electron-withdrawing ability of the oxygen-based ligands. We surmised that such differences may originate from the structural rigidity of the diolates and the resulting higher energy transition states and intermediates in the catalytic cycle. The O–Mo–O angle in tetrahedral **5a** (∠(O–Mo–O), ~127° (ref. 21)), compared to that in a related square pyramidal tungstacyclobutane (∠(O–W–O), ~99° (ref. 22)), supports the hypothesis that structural adjustments within the catalytic cycle may be better accommodated in a less rigid metal complex.

The above considerations imply that a chiral molybdenum catalyst, bearing monodentate ligands—either two that are chiral (identical enantiomers, non-stereogenic-at-Mo; see Fig. 2) or one achiral and one chiral ligand (stereogenic-at-Mo)—would be more active. Recent theoretical studies suggest that high-oxidation-state complexes containing two electronically distinct ligands should be particularly effective promoters of alkene metathesis[4,5] (Fig. 2). According to theoretical explorations, an acceptor ligand (**A** in **I**, Fig. 2) ensures sufficient metal Lewis acidity, necessary for effective binding of the Lewis basic alkene. Efficient alkene coordination, however, requires the presence of a sterically accessible ligation site, made available through alteration of the structure of the initial tetrahedral complex **I** (Fig. 2). It has been proposed that the donor group (**D**) causes **I** to distort dissymmetrically; ligand **D** preferentially interacts with the most available metal orbital such that a trigonal prismatic complex bearing an open ligation site is rendered energetically more accessible. The donor ligand thus occupies an apical site in **II** (the alkylidene, acceptor and imido ligands constitute the basal plane of the trigonal prism), coordinated opposite only to a weakly bound alkene (*trans* effect). The resulting complex, **III**, leads to trigonal bipyramidal **IV**, which undergoes facile cycloreversion (Fig. 2) in which the metallacyclobutane carbons, constituting the alkene being released, are positioned *trans* to **D**, affording **V**. The aforementioned electronic effects thus facilitate formation of complex **V** as well. Such a scenario suggests acceleration at two critical

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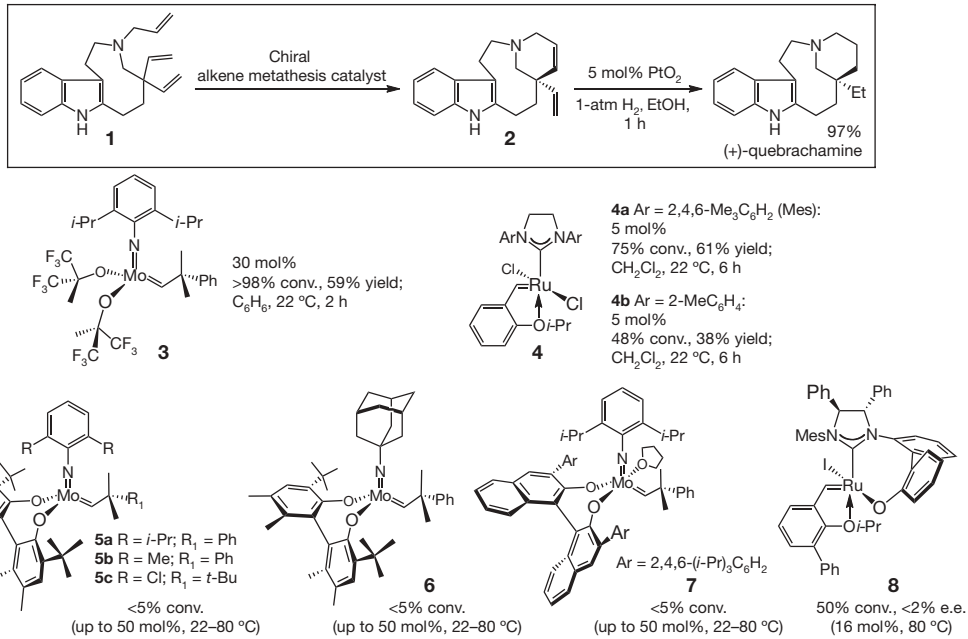


Figure 1 | Catalytic ring-closing metathesis of triene 1. This alkene metathesis reaction, required for total synthesis of alkaloid natural product quebrachamine, is not efficiently promoted by the available achiral or chiral molybdenum or ruthenium catalysts, indicating that significantly more effective catalysts are needed. Me, CH_3; Et, C_2H_5; Ph, C_6H_5; *i*-Pr, $(CH_3)_2CH$; and *t*-Bu, $(CH_3)_3C$. e.e., enantiomeric excess.

stages of the catalytic cycle: substrate–catalyst association and metallacyclobutane decomposition. The above hypothesis finds support in the efficient reaction shown in Fig. 2: 1 mol% *rac*-**9** (ref. 23) promotes formation of *rac*-**2** within 1 h. Such a level of activity is in stark contrast to **3** (Fig. 1), a complex with two hexafluoro-*t*-butoxides.

Stereoselective synthesis of stereogenic-at-Mo complexes became our next objective. One approach would involve diastereoselective mono-protonation of bis-pyrrolides **10a** and **10b** (Fig. 3)[24] with 1 equiv. of a chiral enantiomerically pure alcohol. Preliminary experiments (T. Pilyugina, A.H.H. and R.R.S., unpublished work), involving chiral diols (for example **5**–**7**, Fig. 1), indicated that pyrrole molecules, released upon alcohol exchange, are not deleterious to catalyst activity. These observations suggested that mono-aryloxides might be prepared and used *in situ*. To this end, we favoured binaphthol-derived alcohols, because this class of ligand possesses several important attributes: (1) ease and low cost of synthesis, (2)

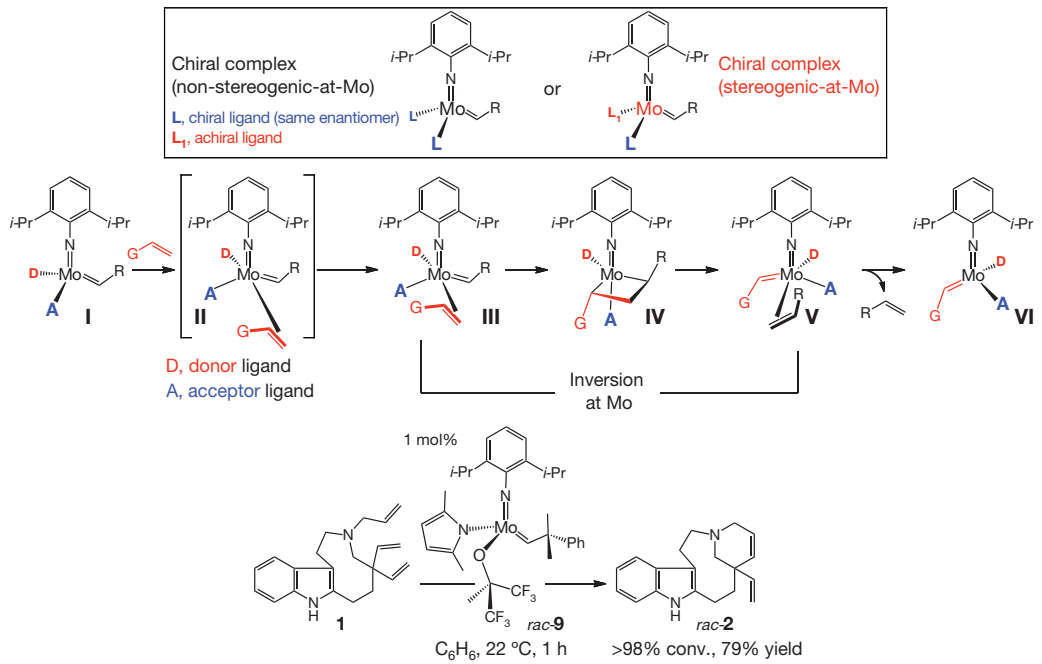


Figure 2 | Stereoelectronic effects have a critical role in alkene metathesis reactions promoted by a molybdenum complex that bears a donor and an acceptor ligand. Such a chiral complex distorts dissymmetrically, leading to an open ligation site *trans* to **D** (see **II**), thus facilitating catalyst–substrate association; the donor ligand also causes a more facile decomposition of the metallacyclobutane intermediate (**IV**). These attributes are expected to lead to a catalyst that is substantially more effective than one that bears two electronically identical acceptor ligands (see the molybdenum complexes illustrated in Fig. 1). The high activity of a complex bearing a donor (pyrrolide) and an acceptor (aryloxide) ligand is illustrated by the efficient conversion of triene **1** to diene **2** (compare with the reaction of molybdenum-based bis-alkoxide **3** shown in Fig. 1). G, functional group.

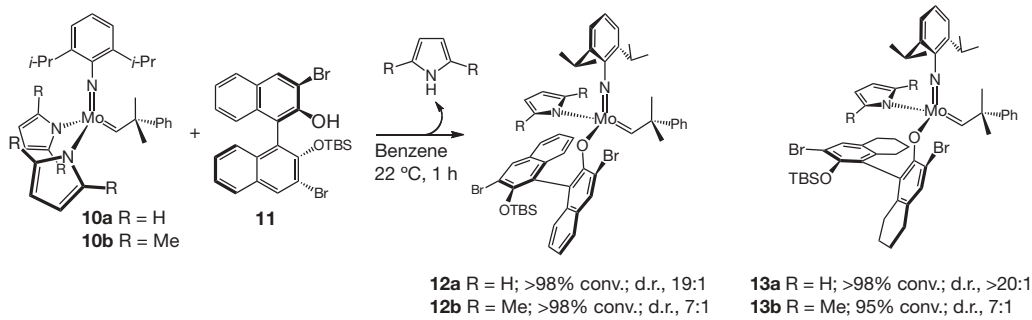


Figure 3 | Diastereoselective synthesis of stereogenic-at-Mo complexes. Such processes are achieved by efficient and stereoselective ligand exchange reactions involving enantiomerically pure aryl alcohols, derived from commercially available binaphthol, and achiral molybdenum-based bis-pyrrolides. TBS, *t*-butyldimethylsilyl; d.r., diastereomeric ratio.

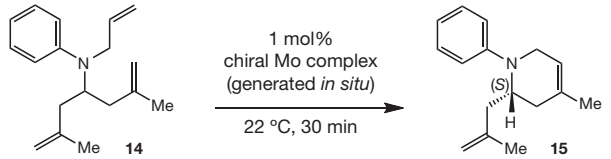
facility of modification and (3) appropriate electron-withdrawing ability.

We subjected bis-pyrrolides **10a** and **10b** to mono-protected diols derived from binaphthol. Treatment of **10a** with 1 equiv. of enantiomerically pure **11** affords **12a** in 19:1 d.r.; with **10b**, **12b** is generated as a 7:1 mixture. Under identical conditions, **13a** and **13b** are obtained with similar selectivity. The identity of the major diastereomer of **13b** was established by X-ray crystallography (Supplementary Information page SI18); assignment of other isomers in Fig. 3 is by inference. The configurational stability of the above complexes is indicated by the absence of detectable variations in the diastereomeric ratios; for example, even after one month, a toluene solution of **13b** remains a 7:1 mixture of the same diastereomers.

Attempts to prepare the mono-aryloxides with the parent ligand lacking the bromides led to a mixture containing bis-aryloxides as well as the unreacted bis-pyrrolides. Synthesis of such complexes can be accomplished with 1 equiv. of the related octahydrobinaphthol, but the process is less stereoselective (d.r., 1–2.5:1) and, unlike the bromides, excess alcohol causes bis-aryloxide formation. In reactions to form **13a** and **13b**, bis-aryloxides are not detected even under relatively forcing conditions (60 °C, 2 h). The bromine atoms are therefore required for efficient and stereoselective formation of **12** and **13** (minimal non-stereogenic-at-Mo bis-aryloxide). Delineation of principles that govern stereoselective ligand exchange reactions is a topic of ongoing investigations.

We then turned our attention to probing the ability of mono-aryloxides to perform as catalysts for enantioselective ring-closing metathesis (RCM). The transformation in Table 1 (**14** → **15**) served as the model process; reactions were performed with complexes prepared and used *in situ*. With 1 mol% **12a** (d.r., 19:1; entry 1, Table 1), RCM proceeds to 50% conversion, affording (*R*)-**15** in 18% e.e. With **12b** (d.r., 7:1; entry 2, Table 1), complete conversion is achieved and (*S*)-**15** is obtained in 50% e.e. The above trend is again observed in reactions involving **13a** and **13b** (entries 3 and 4, Table 1), but with a wider selectivity gap: with 1 mol% **13a**, RCM proceeds to 54% conversion to afford (*R*)-**15** in 13% e.e., whereas in the presence of **13b** there is >98% conversion and (*S*)-**15** is isolated in 93% e.e. With **13b**, the RCM can be performed in a fume hood at 22 °C with 1 mol% loading (30 min, 96% conversion, 86% yield, 92% e.e.). These results illustrate the significant potential of the new catalysts in practical procedures for enantioselective synthesis. Despite providing slightly lower selectivity, **13b** is more effective than the corresponding optimal molybdenum diolate (5 mol% **5a**: 20 min, 95% conversion, 98% e.e. (ref. 25)).

Table 1 | Initial examination of the chiral complexes as catalysts for enantioselective RCM



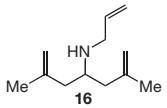
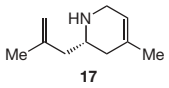
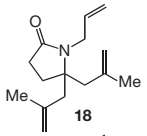
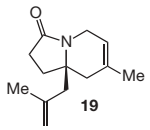
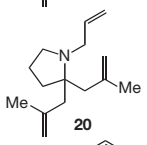
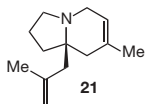
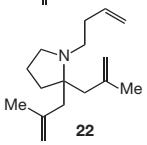
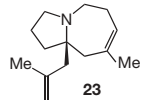
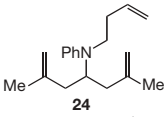
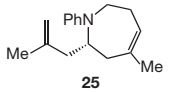
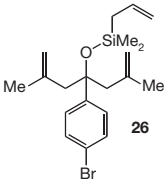
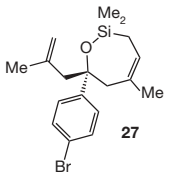
Entry no.	Chiral complex	Conv. (%)*; Yield (%)†	e.r.‡	e.e. (%)§; Config.‖
1	**12a**	50; ND	41:59	18; (*R*)
2	**12b**	>98; 91	75:25	50; (*S*)
3	**13a**	54; ND	43.5:56.5	13; (*R*)
4	**13b**	>98; 91	96.5:3.5	93; (*S*)

The reactions were carried out in purified benzene or toluene under an atmosphere of nitrogen gas (see the Supplementary Information for details). ND, not determined.
* Conversion measured by analysis of 400-MHz ^{1}H NMR spectra of unpurified mixtures.
† Yield of isolated product after purification (see the Supplementary Information for details).
‡ The enantiomeric ratio (e.r.) was determined by gas liquid chromatography analysis. See the Supplementary Information for details as well as for proof of product absolute configuration.
§ The e.e. was calculated from the e.r.; the variances of e.e. values are estimated to be between −2% and +2%.
‖ Configuration of the major enantiomer.

The reduced reactivity and selectivity in reactions of complexes that are more stereochemically pure (that is, **12a** and **13a**) raises the question of whether the minor diastereomers are more active. To investigate this, a stereochemically pure sample of **13b** (d.r., >25:1) was used to initiate enantioselective RCM of **14** (1 mol%, 22 °C, 30 min): (*S*)-**15** was isolated in 93% e.e. and 94% yield, results identical to those obtained with the 7:1 mixture (entry 4, Table 1). Moreover, by monitoring the reaction progress spectroscopically (400-MHz ^{1}H NMR) in the presence of **13b,** generated *in situ*, we established that >98% of the major isomer is consumed, presumably through initiation with the alkene substrate, whereas the minor diastereomer remains largely intact (>95%). Related experiments indicate that in the case of binaphtholate **12b**, both isomers are initiated with nearly equal facility, a finding that might explain why the product is obtained with lower selectivity with this complex.

A variety of enantioselective RCM reactions illustrate the special utility of the new catalysts (Table 2). None of the previously reported diolates promotes RCM of secondary allylamine **16** (entry 1, Table 2)[26]; by sharp contrast, with 2.5 mol% **13b**, there is 94% conversion to piperidine **17** within 1 h, furnishing the desired product in 89% yield and 67% e.e. Diolate **7** (see Fig. 1) and **13c** (see Fig. 4 for structure; d.r., 5:1) promote formation of **19** (entry 2, Table 2) with high enantioselectivity (98% and 91% e.e., respectively), but RCM with the mono-aryloxide is significantly more efficient: 3 mol% dichloro-substituted **13c** furnishes 95% conversion to **19** within 1 h, whereas 48 h are required with 10 mol% diolate **7**. Reaction of amine **20** (entry 3, Table 2), which requires 15 mol% **5b**, proceeds to only 75% conversion after 24 h, yielding **21** with low selectivity (e.r., 65:35). By contrast, 1 mol% **13b** is sufficient for >98% conversion within 1 h, affording **21** in >98% yield and 92% e.e. Similarly, enantioselective synthesis of azepine **23** (entry 4, Table 2) is more efficient (1 h versus 20 h) and substantially more selective (81% e.e. versus 40% e.e.) when **13c** is used (versus diolate **5b**). RCM of arylamine **24** (entry 5, Table 2) proceeds with high enantioselectivity when diolate **5a** (ref. 25) or mono-aryloxide **13c** is used; with 1 mol% **13c**, however, there is >98% conversion in 1 h (versus 7 h with 2 mol% **5a**). With enantioselective RCM of silyl ether **26** (entry 6, Table 2), diolate

Table 2 | Comparison of catalytic enantioselective RCM promoted by chiral molybdenum diolates and chiral aryloxide–pyrrolide complexes

Entry no.	Substrate	Product	Mo diolate; mol%*	Time (h); Temp. (°C)	Conv. (%)†; Yield (%)‡	e.r. (%); e.e. (%)§	Mo aryloxide; mol%*	Time (h); Temp. (°C)	Conv. (%)†; Yield (%)‡	e.r. (%); e.e. (%)§
1	 **16**	 **17**	All available	>36; >40	<5; —	—	**13b**; 2.5	1; 22	94; 89	83.5:16.5; 67
2	 **18**	 **19**	**7**; 10	48; 22	>95; 91	99:1; 98	**13c**; 3	1; 22	95; 88	95.5:4.5; 91
3	 **20**	 **21**	**5b**; 15	24; 22	75; ND	65:35; 30	**13b**; 1	1; 22	>98; >98	96:4; 92
4	 **22**	 **23**	**5b**; 5	20; 22	>98; ND	70:30; 40	**13c**; 3	1; 22	95; 86	90.5:9.5; 81
5	 **24**	 **25**	**5a**; 2	7; 22	>98; 90	97.5:2.5; 95	**13c**; 1	1; 22	>98; 86	96.5:3.5; 93
6	 **26**	 **27**	**5c**; 5	12; 22	>98; 98	97:3; 94	**13c**; 1	1; 22	>98; 84	94:6; 88

* The reactions in entries 1–2 and 4–6 were carried out in purified benzene or toluene under an atmosphere of nitrogen gas (see the Supplementary Information for details); the reaction in entry 3 was performed in pentane.
† Conversion measured by analysis of 400-MHz ^{1}H NMR spectra of unpurified mixtures.
‡ Yield of isolated product after purification (see the Supplementary Information for details).
§ The e.r. was determined by high-performance liquid or gas liquid chromatography analysis. See the Supplementary Information for details as well as for proof of product absolute configuration. The e.e. was calculated from the e.r.; the variances of e.e. values are estimated to be between −2% and +2%.

5c initiates a slightly more selective ring closure (97:3 e.r. versus 94:6 e.r. with **13c**); with 1 mol% **13c**, conversion of **26** to **27** is complete in 1 h (versus 5 mol% and 12 h with **5c**)[27]. Three points regarding the transformations in Table 2 merit mention. First, in certain cases, dichloro complex **13c** affords similar, but higher, selectivity in comparison with dibromo complex **13b**. Second, the molybdenum centre undergoes two inversions in the course of each catalytic cycle (Fig. 2). The high enantioselectivities observed might suggest that adventitious isomerization occurs at a minimum or not at all, as such isomerizations would furnish the alternative product enantiomers. Third, chiral ruthenium-based alkene metathesis catalysts developed so far only promote enantioselective RCM of trisubstituted alkenes with high selectivity (≥80% e.e. or ≥ 90:10 e.r.)[20,28,29].

The most notable demonstration of the attributes of molybdenum mono-aryloxides is in the context of enantioselective synthesis of quebrachamine (Fig. 1). In the presence of 1 mol% **13c,** generated *in situ*, triene **1** is transformed entirely in 1 h to **2** in 84% yield and 96% e.e. (Fig. 4). The target alkaloid is subsequently obtained in high enantiomeric purity and yield (97%). The molybdenum-catalysed process in Fig. 4 thus constitutes the application of a highly effective

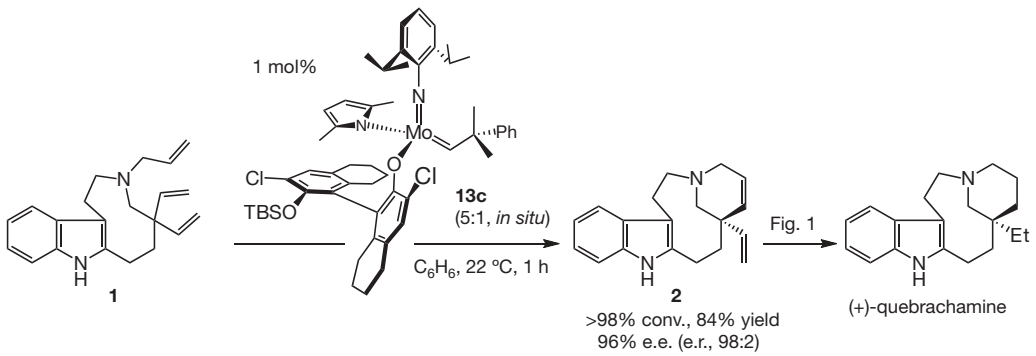


Figure 4 | Efficient and highly enantioselective synthesis of (+)-quebrachamine. The new chiral molybdenum aryloxides, represented by **13c**, promote the ring-closing metathesis of **1** to afford **2** with unprecedented efficiency (see Fig. 1 for comparison with previously known catalysts). Moreover, the molybdenum-catalysed ring-closing metathesis of **1**, a process that cannot be promoted by any of the available chiral molybdenum or ruthenium catalysts, proceeds with exceptionally high enantioselectivity (e.r., 98:2) in the presence of **13c**. Palladium-catalysed hydrogenation of **2** affords the alkaloid natural product quebrachamine in high enantiomeric purity.

catalytic enantioselective RCM (e.r., ≥95:5) to the total synthesis of a relatively complex natural product[1,12].

The chiral complexes discovered in this study are examples of configurationally stable, enantiomerically pure, diastereomerically enriched, stereogenic-at-metal catalysts that bear only monodentate ligands. We have demonstrated that constitutionally fluxional stereogenic-at-metal complexes that effectively exploit stereoelectronic factors should be considered as viable and attractive options in future catalyst design.

METHODS SUMMARY

The general procedure for *in situ* catalyst preparation and catalytic enantioselective alkene metathesis is as follows. An oven-dried (135 °C) 25-mL round-bottom flask, equipped with a magnetic stir bar, is charged with Mo bis-pyrrolide (0.01 equiv.) under N_2 atmosphere (dry box). The flask is sealed with a septum, taped, and brought to a fume hood, in which all manipulations are performed. An 8-mL vial is charged with the alcohol (0.01 equiv.), which is subsequently dried by azeotropic distillation with C_6H_6. Toluene (0.02 M) is added to the alcohol and the resulting solution immediately transferred by syringe to the Mo bis-pyrrolide (flask pressurized on addition; that is, no outlet needle). The mixture is allowed to stir for the appropriate period of time at 22 °C. A 20-mL vial is charged with substrate (1 equiv.), which is dried by azeotropic distillation with C_6H_6. Toluene (final substrate concentration, 0.2 M) is added and the solution immediately transferred by syringe to the 25-mL flask (flask pressurized on addition); the mixture is allowed to stir for the required period of time. The reaction is quenched by addition of wet diethyl ether and concentrated *in vacuo* (percent conversion determined by 400-MHz ^{1}H NMR analysis). Purification is performed by silica gel chromatography and enantiomeric purity of the product determined by gas or high-performance liquid chromatography analysis in comparison with authentic racemic material.

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Author Information X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, UK; CCDC 703841 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request/cif). Reprints and permissions information is available at www.nature.com/reprints. Correspondence and requests for materials should be addressed to A.H.H. (amir.hoveyda@bc.edu).