Kinetically \(E\)-selective macrocyclic ring-closing metathesis

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Macroyclic compounds are central to the development of new drugs, but preparing them can be challenging because of the energy barrier that must be surmounted in order to bring together and fuse the two ends of an acyclic precursor such as an alkene (also known as an olefin)\(^1\). To this end, the catalytic process known as ring-closing metathesis (RCM)\(^2\)–\(^4\) has allowed access to countless biologically active macrocyclic organic molecules, even for large-scale production\(^5\). Stereoselectivity is often critical in such cases: the potency of a macrocyclic compound can depend on the stereochemistry of its alkene; alternatively, one isomer of the compound can be subjected to stereoselective modification (such as dihydroxylation)\(^6\). Kinetically controlled \(Z\)-selective RCM reactions have been reported\(^7\)–\(^10\), but the only available metathesis approach for accessing macrocyclic \(E\)-olefins entails selective removal of the \(Z\)-component of a stereoisomeric mixture by ethenolysis\(^10\), sacrificing substantial quantities of material if \(E/Z\) ratios are near unity. Use of ethylene can also cause adventitious olefin isomerization—a particularly serious problem when the \(E\)-alkene is energetically less favoured. Here, we show that dienes containing an \(E\)-alkenyl–B(pinacolato) group, widely used in catalytic cross-coupling\(^6\), possess the requisite electronic and steric attributes to allow them to be converted stereoselectively to \(E\)-macrocyclic alkenes. The reaction is promoted by a molybdenum monooaryl oxide pyrrolide complex and affords products at a yield of up to 73 per cent and an \(E/Z\) ratio greater than 98/2. We highlight the utility of the approach by preparing recifeiolide (a 12-membered-ring antibiotic)\(^12,13\) and pacritinib (an 18-membered-ring enzyme inhibitor)\(^14,15\), the \(Z\)-isomer of which is less potent than the \(E\)-isomer\(^16\). Notably, the 18-membered-ring moiety of pacritinib—a potent anti-cancer agent that is in advanced clinical trials for treating lymphoma and myelofibrosis—was prepared by RCM carried out at a substrate concentration 20 times greater than when a ruthenium carbene was used.

We recently showed that kinetically \(E\)-selective cross-metathesis may be effected between \(\alpha\)-olefins and \(E\)-dihaloethene catalysts when molybdenum monooaryl oxide pyrrolide (MAP) complexes are used as catalysts\(^17\). However, kinetically \(E\)-selective ring-closing metathesis (RCM) poses several distinct challenges. Larger amounts of an alkene reactant cannot be used to maximize efficiency. Moreover, linear products generated by cross-metathesis or RCM are more hindered than the cyclic alkenes generated by RCM and cannot as easily reassociate with an active complex to cause loss of kinetic selectivity. In an RCM reaction in which one of the substrate olefins is 1,2-disubstituted, this distinction no longer applies. Thus, in considering a strategy for preparing biologically active molecules such as recifeiolide\(^13\) and pacritinib\(^14\), we envisioned that a diene precursor could contain an \(E\)-1,2-disubstituted olefin and a suitable substituent (\(R\); Fig. 1a) that can induce facile and selective generation of metallacyclobutane (intermediate II, via intermediate I), leading to an \(E\)-macrocyclic alkene. As with the \(E\)-selective cross-metathesis of alkyl halides, intermediate II should be preferred (over intermediate III): the steric pressure induced by the \(\beta\)-substituent of the metallacycle and by the larger aryloxide group (as opposed to an imido group) in II should be less costly than that involving the group at the more proximal Co in III.

A suitable starting \(E\)-alkene must satisfy the following six requirements. First, it must be accessible in a stereoisomerically pure form (that is, \(\geq 98\% \ E\)) through reliable, efficient and inexpensive transformations. Second, it must possess the appropriate steric and/or electronic attributes so that it is immune to stereoisomerization. Third, the substituent (\(R\)) must not be so large such that the 1,2-disubstituted olefin is reluctant to undergo RCM (that is, \(I \rightarrow II\); Fig. 1a) at a reasonable rate. Fourth, the substituent must be able to stabilize the accumulated electron density at the adjacent molybdenum–carbon bond (see intermediate I, Fig. 1a). Fifth, the corresponding molybdenum alkylidene generated after metallacyclobutane cycloreversion (\(syn\)-i; Fig. 1a) must be long-living and robust enough to promote catalyst turnover, but not so reactive that it engenders post-metathesis isomerization and/or facile decomposition. Finally, the aforementioned stabilization of alkylidene complex \(syn\)-i caused by the substituent (\(R\)) must be balanced in order for the RCM to occur at a reasonable rate.

We first investigated several model substrates as precursors to the 16-membered unsaturated ring lactone (2); representative data obtained by using MAP complex Mo-1 in reactions carried out at ambient temperature and under 28 torr of pressure are shown in Fig. 1b. Bis(\(\alpha\)-olefin) (1a) was consumed completely after two hours, and 80% of the product mixture was macrocycle 2, which was generated with inferior selectivity (70/30 \(E/Z\)). We next investigated RCM of the chloro-substituted alkene 1b, in part because we had previously found chloro-olefins to be resistant to isomerization\(^17\); the issue was whether the electronegative halogen atom would provide the necessary charge stabilization (see intermediate I; Fig. 1a). Attempts at cyclization of 1b resulted in only 5% of macrocycle 2 (77/23 \(E/Z\)). This might be because of the low stability of the chloro-substituted molybdenum alkylidene; such low stability can be more detrimental in a macrocyclic RCM reaction than in the concentrated solution of a cross-metathesis reaction, because in the RCM reaction the alkylidene is less likely to encounter an \(\alpha\)-olefin before it decomposes. We then explored the possibility of using an \(E\)-\(\beta\)-substituted styrene—another structural motif that has been successfully adopted in cross-metathesis, leading to \(E\)-chloro-substituted olefins\(^17\). Here too the results were disappointing: attempted RCM with alkene 1c gave a mixture of compounds (90% conversion), within which we could detect around 15% of macrocyclic product 2. The excessive generation of side products (see Extended Data Fig. 1 for details) pre-empted accurate determination of stereoselectivity; among several possibilities, the derived molybdenum benzylidene might react with the substrate to generate stilbene (detected in the unpurified mixture) along with bis(\(\alpha\)-olefin), 1a. Again, in cross-metathesis, excess dichloroethene may react with a benzylidene to yield \(\beta\)-chlorostyrene.

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Figure 1 | The strategy and the optimal substituent. a, One way to achieve high kinetic E selectivity in macrocyclic RCM would be to use a substrate in which one of the reacting alkenes is E-1,2-disubstituted (‘R’ represents the substituent), such that preferential transformation through mode of association (I) and via metallocyclotetane II (not III) affords the desired stereochemical preference. In other words, the concept is that the substituent can induce facile and selective generation of II (via intermediate I, catalysed by a molybdenum MAP), leading to the production of an E-macroyclic alkene (E). Intermediate II should be preferred over intermediate III because the steric pressure induced by the metallocycle's C3-substituent is less costly than that induced by the more proximal Cα-group in III. The starting acyclic E-alkene must meet several key criteria. It must be readily accessible as the pure E-isomer, sufficiently electron-withdrawing to facilitate metallocyclotetane formation (I→II), resistant to post-metathesis isomerization, and not so large that it diminishes reaction rates; it must also generate an alkylidene intermediate (syn-I) that is not detrimental to the reaction outcome. Here, ‘large’ and ‘small’ refer to the relative sizes of the respective ligands; δ signifies a change in charge density. b, A model RCM process performed with 5.0 mol% Mo-1 and affording the 16-membered ring lactone (2) indicated that the (pin)B-substituted E-alkene represents the most effective option. In most cases, the major side product is derived from homocoupling of the two terminal alkenes. Abbreviations: R, functional group; Ln, ligands; ND, not determined. Reactions were performed under atmospheric nitrogen. Conversion values and E/Z ratios were determined by analysis of 1H NMR spectra of unpurified product mixtures (± 2%); stereoselectivity for the reaction with 1c could not be determined because a comparatively complex mixture formed. See Supplementary Information for all experimental and analytical details.
systems. Accordingly, we chose to explore further RCM with substrates that contain an \( \alpha \)-olefin and an \( \alpha \)-alkenyl–B(pin).

The \( E \)-alkenyl–B(pin) moiety is stable to air and moisture and can be accessed by several exceptionally \( E \)-selective and broadly applicable protocols, catalysed by readily available and inexpensive complexes and/or reagents (see the references in the Methods section). For example, subjecting alkene 3 to Fig. 2a), which has an unprotected hydroxy group, to 20 mol% Schwartz’s reagent (Cp₂ZrHCl), 4.0 equivalents of pinacolborane and 10 mol% triethylamine (60°C for 17 hours; all are commercially available) followed by routine ester formation furnished diene 1e with an overall yield of 70% as a single isomer (>98% \( E \)). Treatment of 1e with 5.0 mol% Mo-1 for 6 hours (versus 2 hours in Fig. 1b) at ambient temperature and 28 torr furnished lactone 2 at a yield of 60% and an \( E/Z \) ratio of 96/4. By comparison (Fig. 1b), the \( E \)-selective RCM reported for bis(\( \alpha \)-olefin) (1a) was performed with 4.0 mol% Ru-4 and generated product 2 in a \( 77/23 \) \( E/Z \) ratio.

Twelve- to nineteen-membered unsaturated macrocyclic lactones 4, 5, 7 and 8 are additional examples of the sequence that begins with \( E \)-selective zirconocene-catalysed hydroboration of a hydroxyl-containing terminal alkene (Fig. 2a; for synthesis of the precursor to 6 by catalytic protoboryl addition, see below). These macrocyclic...
paraffin tablet that contains Mo-1 complex, to obtain the desired macrocycle with similar efficiency and stereoselectivity. **b.** The efficiency of macrocyclic RCM is lower without a methyl substituent, underlining the importance of structural pre-organization to the ease of ring formation. Reactions were performed under atmospheric nitrogen. Conversion values (disappearance of the starting diene) and E/Z ratios were determined by analysis of $^1$H-NMR spectra of unpurified product mixtures (± 2%). Yields are for isolated and purified products (± 2%). See Supplementary Information. All experiments were performed in duplicate or (often) more.

$\alpha$-alkenyl–B(pin) fragments may alternatively be synthesized by $E$-selective protoboryl additions to terminal alkynes, catalysed by NHC–copper catalysts$^{28}$. Reaction of enyne (9) with B$_2$(pin)$_2$ (Fig. 3b), methanol and the NHC–copper complex derived from imidazolium salt (10) and copper chloride (all are commercially available) afforded product 11 in 77% yield, with >98% E/Z selectivity and with >98% chemoselectivity (that is, less than 2% reaction at $\alpha$-olefin). The ensuing RCM gave Boc-protected (Boc, tert-butoxycarbonyl) macrolactam (12) in 44% yield as the pure E-isomer (<2% Z). Likewise, the catalytic protoboryl addition/RCM route led to the formation of 14-membered-ring macrolactam (13) and 21-membered-ring lactone (14) in 38% and 51% yield and >98/2 and 93/7 E/Z isomeric mixture, respectively (Fig. 2b). Lactam 12 was obtained with a comparable yield (47% versus 44% yield) by RCM of the bis($\alpha$-olefin) with Ru-2, but as a near-equil $E$ and $Z$ isomeric mixture. Again, the E/Z ratio was substantially higher with an $E$-alkenyl–B(pin) substrate (in the range of 93/7 to >98/2 E/Z, versus 20/80 to 76/24). The reaction that affords the 14-membered-ring lactam (13) (Fig. 2b) is particularly interesting because, with the more commonly used RCM strategy, slow addition of the ruthenium complex is needed and the Z isomer forms preferentially owing to substrate control (20/80 E/Z); with the present approach, only the $E$-macrocyclic alkene was formed (>98% $E$). Cyclization of the unmasked secondary amide compounds (12 and 13) was inefficient (<5%); these transformations are reported to take place more readily with ruthenium-based carbenes, but again with minimal stereocontrol$^{10,26}$.

There are methods for synthesizing macrocyclic $E$-alkenes that involve catalytic alkyne metathesis. A two-step procedure entails the
stereoselective addition of silyl hydride ((EtO)₂SH) to a macrocyclic alkene, promoted by a cationic ruthenium complex (1.0 mol% (Cp*Ru(MeCN)₃)PF₆, where Cp* is pentamethylcyclopentadienyI), followed by stereoretentive protodesilylation with excess (2.0 equivalents of) silver fluoride and methanol. A more direct approach is by E-selective hydrogenation with the aforementioned ruthenium-based species (5.0 mol%). The RCM of dienes introduced here has value because it is strategically distinct. Furthermore, other than the much higher cost of (Cp*Ru(MeCN)₃)PF₆ (as compared with Cp₂ZrHCl, or salt and copper chloride), alkene hydrogenations are at times accompanied by over-reduction and/or olefin isomerization, affording difficult-to-remove by-products.

We then probed the possibility of the stereoselective synthesis of recifeiolide and pacritinib. A key point was whether increased conformational rigidity of a substrate—however slight it might be—translates into higher yields. Synthesis of recifeiolide’s 12-membered lactone through RCM has been reported previously (Fig. 3a): simultaneous slow addition of a solution of substrate 15 and another of 3.0 mol% of Ru-1 to a third (refluxing) solution of dichloromethane over a 20-hour period, followed by a further 12 hours of reaction time (at 22 °C), afforded the natural product at a yield of 80% and in an 82/18 mixture of difficult-to-separate E and Z isomers. By contrast, subjection of commercially available homopropargyl alcohol (16) to the aforementioned zirconocene-catalysed hydroboronation conditions, followed by its union with 7-octenoic acid (commercially available), gave diene 17 at an overall yield of 73% and with >98% E selectivity (Fig. 3a). Macrocyclic RCM with Mo-1 after 6 hours (versus the 32 hours needed previously) at ambient temperature and 28 torr of pressure (0.00125 M; ~50-mg scale) delivered recifeiolide at a yield of 65% and as a single stereoisomer (versus the 82/18 E/Z ratio reported above), without the need for manipulating several syringe pumps. What is more, with a paraffin pellet containing about 5.0 mol% of Mo-1 (Fig. 3a), diene 17 was transformed to the natural product in 55% yield and >98% E selectivity (0.001 M in toluene, 22 °C, 28 torr, 6 hours). The absence of a methyl group results in a lowering of RCM efficiency, as nor-recifeiolide (19) was isolated at a yield of 48% and a 98/2 E/Z ratio when Mo-1 was used (Fig. 3b); a more notable diminution in yield was observed when the transformation was performed with Ru-2 (29% yield, 79/21 E/Z).

Figure 4 | Application to synthesis of pacritinib. Top, treating bis(allyl ether) (20) with 10 mol% Ru-3 under acidic conditions (to counter catalyst deactivation) affords 21 (an intermediate en route to pacritinib) with 85/15 E/Z selectivity. Bottom (this study), RCM with the E-alkenyloxyborane (B(pin)) to avoid catalyst deactivation, 23 is isolated at 60% yield and 95/5 E/Z selectivity. The same procedure with triether (24) is highly stereoselective, but the yield is lower (34%). Installation of a Boc unit (25) to diminish the Lewis basicity of the pyrimidine and the ether moieties furnishes the macrocycle with similar E/Z selectivity and in 73% yield (after deprotection).

The case of pacritinib (SB1518) is of special interest, owing to its exceptional therapeutic activity and because the Lewis basic nitrogen atoms and the involvement of two relatively electron-deficient allylic ethers render an RCM approach particularly challenging (Fig. 4). One reported case entails reaction of bis(α-olefin) (20) with 10 mol% Ru-3 at 40–45 °C for 4 hours, affording 21 in 74% yield and 85/15 E/Z selectivity (inseparable isomers). An acidic solution (pH 2.0–2.2; added HCl) can generate the ammonium derivative of the pyrimidine moiety, presumably to counter catalyst inhibition, was needed for high efficiency.

We initially examined the RCM of boryl-diene (22; Fig. 4), prepared by zirconocene-catalysed hydroboration of the appropriate propargyl ether. Subjection of 22 to 10 mol% Mo-1 at ambient temperature for 12 hours led to an inefficient reaction (25% conversion; 17% product 23), but E selectivity was high (93/7 E/Z). When the RCM was performed with an equivalent of B(C₆F₅)₃, product 23 could be isolated in 60% yield and 95/5 E/Z selectivity. A notable feature of the transformation with Mo-1 is that it could be carried out at much higher substrate concentration than in the previous reactions or when a ruthenium complex is used (that is, 0.02 M versus 0.001 M in the transformation involving Ru-3 and the MAP-catalysed reactions in Figs 1–3). Thus, 20 times less solvent was needed when a Mo complex was used, rendering our approach more practical and cost effective. The reason for this distinction is that homocoupling of an allylic ether by a molybdenum alkylidene is slower than with a ruthenium...
carbene; we found that with 2.0 mol% Mo-1 there was 83% homocoupling of 4-phenyl-1-butene within 10 minutes (0.1 M in benzene, 22 °C), whereas less than 5% of the same by-product was detected with allyl benzyl ether. By contrast, there was 47% homocoupling with allyl benzyl ether when 2.0 mol% Ru-3 was used. Such advantageous (and largely unappreciated) chemoselectivity probably occurs because the reactivity of a high-oxidation-state molybdienum alkylidene derived from an allylic ether is diminished by the oxygen substituent (owing to the inductive stabilization of electron density at the alkylidene carbon). As a result, the intermolecular reaction of such a species with another electron-deficient allylic ether (that is, homocoupling) is less facile and lower amounts of molybdienum methyldiene are generated. A differently polarized ruthenium carbene does not offer the same advantage. These considerations imply that RCM involving the molybdienum alkylidene derived from an α-olefin of an allylic ether and a 1,2-disubstituted alkyl–B(pin), which is even more electron deficient, is favoured because of the intramolecular nature of the transformation.

There are two reasons why RCM of the more functionalized triether substrate 24 to afford 21 is compelling (Fig. 4; see Supplementary Information for the synthesis route). First, macroyclic olefin 21 has been previously converted to pacritinib. Second, this particular cyclization would allow for further examination of the effect of Lewis basic catalyzing groups on catalyst activity. Compound 24 contains an additional di-ally ether fragment that might coordinate to the Lewis acidic molybdenum centre to cause reduced catalyst activity; this was a concern because the basicity of the new ether oxygen might be enhanced by the para amino group. Indeed, although E selectivity remained high (93/7 E/Z), conversion of 24 to 21 under the conditions used to prepare 23 was lower (34% versus 60% yield). We therefore investigated the Boc-protected variant (25), theorizing that this modification would more firmly diminish the Lewis basicity of the pyrimidine and the bis(ether) moiety. Subjecting the reaction conditions (0.02 M for example, around 25 mg of 24 in about 1.8 ml of toluene), at ambient temperature (but without B(C6F5)3) and then removing the protecting unit, furnished product 21 at an overall yield of 73% and 92/8 E/Z selectivity.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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METHODS

General procedure for E-selective macrocyclic RCM. In an N₂-filled glove box, an oven-dried round-bottom flask equipped with a magnetic stir bar is charged with an alkene substrate (1.0 equiv.) and anhydrous toluene. This mixture is then charged with a solution of complex Mo-1 in benzene (5.0 mol%) and the vessel is then connected to a 28 torr vacuum generated from a diaphragm pump. The mixture is allowed to stir for 4 h at 22 °C under vacuum, after which the reaction is quenched by the addition of wet ether (percentage conversion was determined by ¹H-NMR analysis of the unpurified mixture). Purification may be performed by silica gel chromatography.

Procedure with air- and moisture-resistant paraffin tablets. Under N₂, an oven-dried round-bottom flask equipped with a magnetic stir bar is charged with an alkene substrate and anhydrous toluene. A paraffin tablet containing Mo-1 is added and the vessel is connected to a 28 torr vacuum generated from a diaphragm pump. The mixture is allowed to stir for 6 h at 22 °C under vacuum. At this time the reaction is quenched by addition of wet ether, and the mixture is concentrated under vacuum. Acetonitrile is added and the mixture is allowed to stir at 22 °C for 10 min. The slurry is filtered through a short plug of silica gel and eluted with acetonitrile (5.0 ml). The filtrate is concentrated in vacuo. Silica gel chromatography may be used to obtain pure product.

The E-alkenyl–B(pin) compounds can be accessed through a variety of methods. Some products can be accessed with low E-selectivities through RCM reactions with bis(α-olefin) compounds catalysed by ruthenium complexes. Data availability. The authors declare that all of the data supporting these findings are available within the paper, the Extended Data and the Supplementary Information.

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Extended Data Figure 1 | By-products from RCM with an E-β-substituted styrene. Although pathway i represents the desired route, pathways ii and iii are competitive and can lead to the formation of a variety of undesired byproducts. Mass-spectrometry analysis of the unpurified mixture resulting from the reaction of compound 1c confirmed the existence of by-products A, E, H and I and the desired RCM product. 1H-NMR analysis of the mixture confirmed the existence of stilbene (F).

A. High-resolution mass spectrometry (HRMS) mass of [M+H]⁺, calculated for C_{23}H_{35}O_{2}: 343.26370; found: 343.26277; E, HRMS[M+H]⁺, calculated for C_{44}H_{65}O_{4}: 657.48828; found: 657.48808; H, HRMS[M+H]⁺, calculated for C_{38}H_{61}O_{4}: 581.45730; found: 581.45698; I, HRMS[M+H]⁺, calculated for C_{29}H_{39}O_{2}: 419.29500; found: 419.29383; RCM product, HRMS[M+H]⁺, calculated for C_{15}H_{27}O_{2}: 239.20110; found: 239.20019.
Extended Data Figure 2 | Performance of other catalyst types.

Examination of alternative Mo MAP complexes shows that the precise identity of the aryloxide ligand is crucial for achieving optimal efficiency and E selectivity. Furthermore, with two widely used achiral complexes (Mo-4 and Ru-4), efficiency and E/Z selectivity are low. Two of the more recently introduced Z-selective Ru complexes (Ru-5 and Ru-6) afford only homocoupling products. Mes, 2,4,6-(Me)₃C₆H₂; ND, not determined; R, functional group. Reactions were performed under atmospheric nitrogen. Conversion values and E/Z ratios were determined by analysis of ¹H-NMR spectra of unpurified product mixtures (± 2%). See Supplementary Information for all experimental and analytical details.
| Macrocyclic Alkene | Ru Complex | Reaction Conditions; Outcome | Citation |
|-------------------|------------|-----------------------------|---------|
| ![Structure](image1) | Ru-4       | 4.0 mol %, slow addn, CH₂Cl₂, 22 °C, 32 h: 62% yield, 77:23 E:Z | 25 |
| ![Structure](image2) | Ru-5       | 2.0 mol %, 0.002 M, CH₂Cl₂, 22 °C, 20 h: 72% conv., 31% yield, 59:41 E:Z | 26 |
| ![Structure](image3) | Ru-4       | 4.0 mol %, 0.01 M, CH₂Cl₂, 22 °C, 30 h: 78% yield, 46:54 E:Z | 25 |
| ![Structure](image4) | Ru-1       | 5.0 mol %, 0.005 M, CH₂Cl₂, 50 °C, 5 h: 53% yield, 78:22 E:Z | 43 |
| ![Structure](image5) | Ru-7       | 5.0 mol %, 0.005 M, CH₂Cl₂, 40 °C, 10 h: 90% yield, 73:27 E:Z | 44 |
| ![Structure](image6) | Ru-8       | 5.0 mol %, 0.005 M, CH₂Cl₂, 50 °C, 5 h: 53% yield, 78:22 E:Z | 45 |
| ![Structure](image7) | Ru-7       | 2.0 mol %, 0.002 M, CH₂Cl₂, 22 °C, 32 h: slow addn in 3 h, then another 10 h: 92% conv., 71% yield, 20:80 E:Z | 26 |
| ![Structure](image8) | Ru-5       | 2.5 mol %, <0.005 M, CH₂Cl₂, 22 °C, 32 h: 71% yield, 58:42 E:Z | 13 |

Extended Data Figure 3 | Reported RCM reactions with bis(α-olefin) compounds and promoted by ruthenium complexes. See refs 13, 25, 26, 43–45.