The Pursuit of Atom Economy in Synthesis

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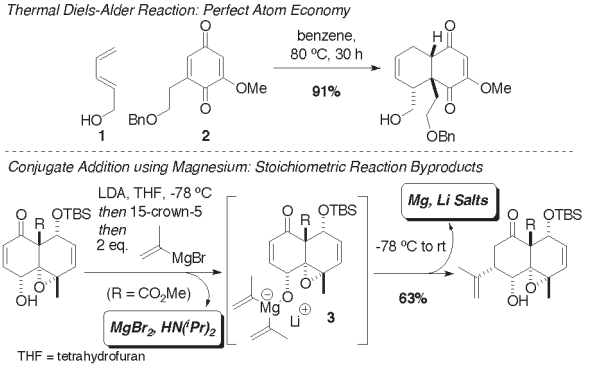
Dedicated to Professor Barry Trost, an inspiring chemist and mentor.

Introduction

Improving the efficiency of chemical synthesis has long been a fundamental goal for the chemical sciences. This goal has been pursued primarily through the development of new chemical transformations that generate molecular complexity in a facile and selective manner.[1] The efficiency of a chemical reaction has been measured using a variety of metrics, one of the most prominent being atom economy.[2] The Trost group has made a number of exemplary contributions to this area, developing powerful transition metal-catalyzed reactions with a wide range of synthetic applications. This article highlights recent applications of atom-economic reactions developed by the Trost group within the context of total synthesis. An emphasis has been placed on natural products connected to New Zealand through their isolation or research into their biological activity.

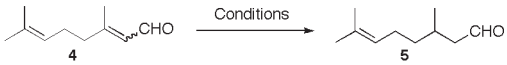
The goal of atom economy is to maximize the mass efficiency of a reaction – ideally, all the atoms of the starting materials are incorporated into the final product using only catalytic quantities of all other reagents. On a fundamental level, atom economy is enabled by the efficient activation of reagents, where control over the selectivity of bond-forming processes is paramount. In some cases the adjacent functional groups make bond forming inherently efficient, as is the case for the Diels-Alder reaction. This reaction can often occur in a stereoselective manner by simply heating the appropriate diene and dienophile, such as **1** and **2** respectively (Scheme 1).[3] The majority of cases are not as simple, and additional atoms are required to activate the reacting centres and direct reactivity. The conjugate addition shown in Scheme 1 highlights the necessity of additional atoms to activate the starting materials and direct the reaction to occur in a stereoselective manner.[4] In this case a nucleophilic carbon atom is created by the presence of an adjacent magnesium atom. Nucleophilic addition is then directed by the formation of the magnesium alkoxide ate complex **3**, which is formed by prior deprotonation of the hydroxyl group using lithium diisopropyl amide (LDA) and manipulation of the Schlenk equilibrium using a crown ether. Intramolecular delivery of the nucleophile ultimately provides a stereoselective conjugate addition, albeit with lithium and magnesium byproducts.



Scheme 1. Considering Atom Economy in Bond Construction.

Maximizing atom economy while maintaining high levels of selectivity remains challenging. The conjugate reduction of the α,β-unsaturated aldehyde, citral (**4**) serves to highlight the extensive efforts that are required to evolve an atom-economic solution (Table 1). This transformation posseses three major challenges: avoidance of 1,2-reduction of the aldehyde, the selectivity for the enone double bond in the presence of an electron-rich trisubstituted alkene and avoiding the generation of a reactive enolate capable of undergoing an aldol condensation. Table 1 shows a variety of conditions used to successfully perform this transformation while also considering the molecular weight of the reaction byproducts.

Table 1. Atom Economy in the Conjugate Reduction of Citral.



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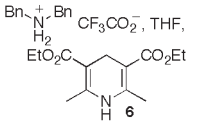
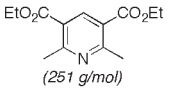
Conditions	Yield	Major Byproducts[a]
0.32 eq. $[(Ph_3P)CuH]_6$, 2.5 eq. TBSCl, benzene then TBAF, *p*H 7 buffer/ THF	**83%**	$[(Ph_3P)CuCl]_4$, TBS-OH[b] *(1445, 132 g/mol)*
3 mol% $Pd(PPh_3)_4$, Bu_3SnH, THF, then H_2O/ CH_2Cl_2	**98%**	Bu_3SnOH *(307 g/mol)*
5 mol%  $CF_3CO_2^-$, THF,	**92%**	 *(251 g/mol)*
10% Pd-C, NEt_3, HCO_2H, neat, 100 °C	**91%**	CO_2 *(44 g/mol)*
0.1 mol% $Rh(CO)_2acac$, (*R,R*)-chiraphos, H_2 (80 bar), toluene	**99.8%** (90% ee from *Z*-**4**)	none[c]

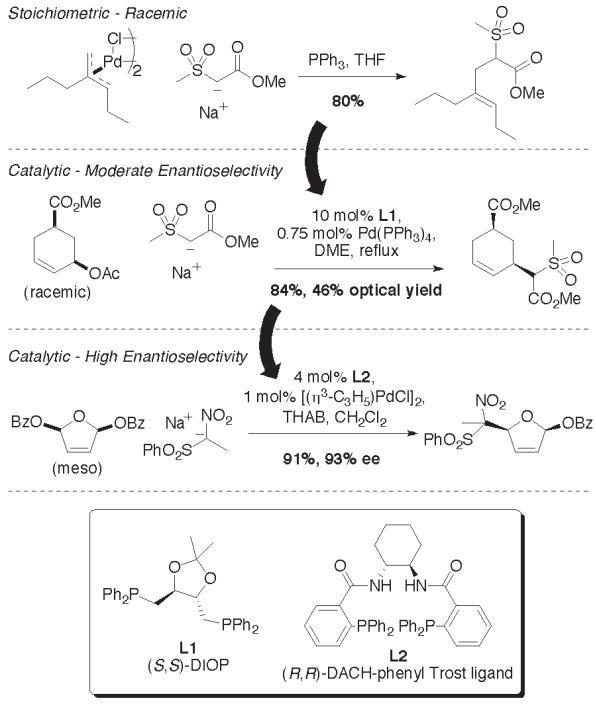
[a]Starting materials used in excess and solvents were not taken into account when considering atom economy as these can, in theory, be recycled. [b]While TBS-F is initially formed, under these conditions it is converted to TBS-OH and TBAF is regenerated. [c]While no byproducts are produced, a large excess of hydrogen gas is needed to facilitate this reaction. TBSCl = *tert*-butyldimethylsilyl chloride, TBAF = tetrabutylammonium fluoride, (*R,R*)-chiraphos = (*2R,3R*)-2,3-bis(diphenylphosphino)butane, ee = enantiomeric excess.

The use of Stryker's reagent, $[(Ph_3P)CuH]_6$, provides a very mild and selective hydride source for 1,4-reduction.[5] The resulting copper enolate is trapped as a silyl enol ether, which is subsequently hydrolyzed to produce the desired aldehyde **5**. This method does not use mass economically, producing the stoichiometric reaction byproducts $[(Ph_3P)CuCl]_4$ and TBS-OH with a combined molecular weight of 1577 g/mol. The remaining methods in Table 1 contain increasing levels of atom economy,

which include: Pd-catalyzed conjugate reduction using Bu_3SnH and hydrolysis of the resulting tin enolate,[6] organocatalytic transfer hydrogenation using the Hantzsch ester (**6**),[7] Pd-catalyzed transfer hydrogenation using formic acid and triethylamine,[8] and lastly, an enantioselective rhodium-catalyzed hydrogenation.[9] While excellent yield of the desired aldehyde **5** is obtained in all cases, the mass efficiency of most of these reactions is poor and therefore limits the broader application of this chemistry. The highly atom-economic rhodium-catalyzed hydrogenation is part of a patented process used by BASF for the industrial preparation of (-)-menthol. The rhodium catalyst used to facilitate this asymmetric transformation can be recovered after the reaction and reused multiple times.

Pd-Catalysed Asymmetric Allylic Alkylation: Total Synthesis of Hamigeran B

Palladium-catalyzed allylic alkylation, often referred to as the Tsuji-Trost reaction, has become a powerful synthetic tool and is capable of high levels of chemo-, regio-, and stereoselectivity.[10] The first report of this reaction was limited to the addition of enamine or malonate-based nucleophiles to stoichiometric π-allyl palladium chloride dimer.[11] Soon after this initial report, Trost and coworkers discovered that the addition of phosphine ligands dramatically enhanced the electrophilicity of π-allyl palladium complexes (Scheme 2).[12] This discovery greatly improved the reactivity of π-allyl palladium complexes, which significantly expanded the substrate scope of these reactions, and ultimately led to the development of chiral phosphine ligands for Pd-catalyzed asymmetric allylic alkylation (Pd-AAA).[13] Scheme 2 highlights the development of this methodology from the original stoichiometric racemic reaction to the modern catalytic enantioselective variant.

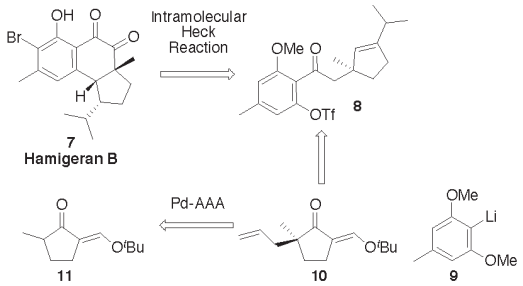


DME = dimethoxyethane, THAB = tetrahexylammonium benzoate.

Scheme 2. The Evolution of Pd-Catalyzed Allylic Alkylation.

Some of the earliest research in the Trost group on the alkylation of stoichiometric π-allyl palladium complexes was performed by Terry Fullerton, a New Zealand Fulbright Scholar conducting post-doctoral research at the University of Wisconsin - Madison.[14] Some of the most elegant applications of Pd-AAA reactions have been in the generation of chiral quaternary centres, a formidable task that often warrants special consideration in the planning of a synthesis.[15] The synthetic strategy for the total synthesis of Hamigeran B (**7**) was based on the use of a Pd-AAA reaction to form a challenging chiral quaternary center.

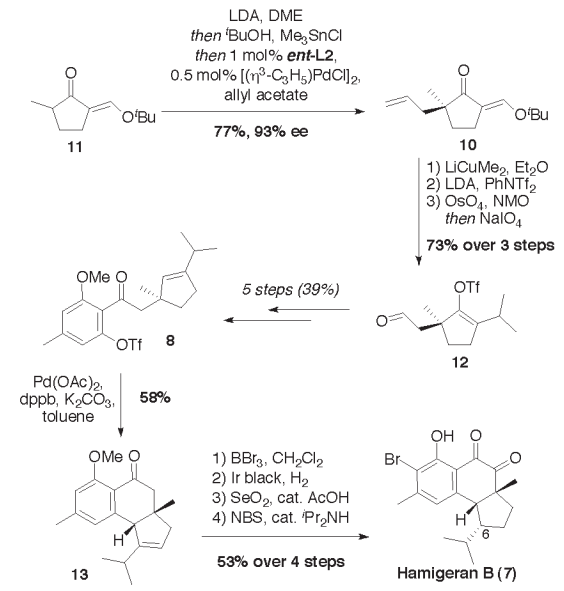
Hamigeran B is a secondary metabolite originally isolated from the poecilosclerid sponge *Hamigera tarangaensis* which Berquist and Fromont collected from the Hen and Chicken Islands in New Zealand.[16] This compound displays potent anti-viral activity against both polio and herpes viruses, with only slight cytotoxicity to host cells. Moderate anti-cancer activity against P-388 leukemia cells was also observed (IC_{50} = 13.5 μM). The principal disconnections in the retrosynthesis of hamigeran B are shown in Scheme 3. The carbocyclic core of **7** was envisioned to arise from the intramolecular Heck reaction of aryl triflate **8**. This intermediate can be traced back to the aryl lithium reagent **9** and the aldehyde produced from ozonolysis of the terminal alkene **10**. Alkene **10** could be generated using a Pd-AAA with a ketone enolate derived from **11**. This class of nucleophiles has proven to be much more challenging to employ in AAA reactions then stabilized enolates derived from β-dicarbonyl compounds.[17]



Scheme 3. Retrosynthetic Analysis of Hamigeran B.

The synthesis begins with the formation of racemic ketone **11** from 2-methylcyclopentanone using a tandem formylation/vinylogous etherification sequence (Scheme 4). The prochiral tin enolate derived from **11** provides excellent yield and enantiomeric excess in the Pd-AAA reaction with only 1 mol% of the active palladium catalyst. It was discovered that when fresh *n*BuLi was used to generate LDA for this reaction the ee of the product, **10**, dropped dramatically. It was hypothesized that the presence of lithium alkoxides in older *n*BuLi sources aids the stereoselectivity of this process. It was ultimately discovered that the addition of 7 equivalents of *t*BuOH provides a reliable and scalable transformation. Lithium dimethylcuprate was then used to convert the *tert*-butyl enol ether into an isopropyl group. This was followed by formation of an enol triflate and a one-pot dihydroxylation–periodate cleavage to produce aldehyde **12**. In five steps this was converted to the aryl ketone **8** required for the intramolecular Heck reaction. The intramolecular Heck

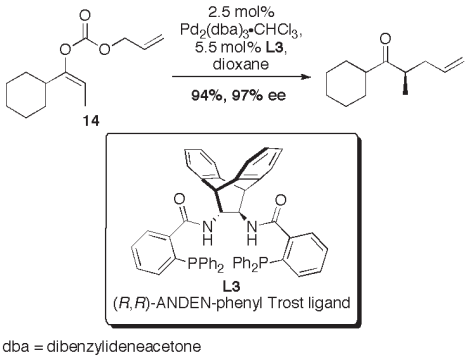
reaction provided the desired product **13** in an optimized yield of 58%, along with two isomeric alkene side products in a combined yield of 29%. The use of a carbonate base rather than a tertiary amine base proved essential to avoid hydrogenolysis of the aryl triflate. Compound **13** was then deprotected using BBr_3, and the trisubstituted double bond reduced using an iridium-catalyzed hydrogenation to give the kinetically favoured product with the isopropyl group on the concave face of the molecule. The corresponding palladium-catalyzed hydrogenation gives the thermodynamically favoured *C6*-epimer, which is presumably a consequence of equilibration of a semi-hydrogenated intermediate. Lastly, oxidation using selenium dioxide and careful monobromination provides the natural product **7**. In total, hamigeran B (**7**) was prepared using a longest linear sequence of 16 steps.



dppb = 1,4-bis(diphenylphosphino)butane,
NMO = 4-methylmorpholine *N*-oxide, NBS = *N*-bromosuccinimide.

Scheme 4. Total Synthesis of Hamigeran B.

The decarboxylative Pd-AAA reaction has recently emerged as an attractive alternative to the traditional Pd-AAA with preformed metal enolates.[18] Allyl enol carbonates, such as **14**, can be used to prepare α-chiral ketones in excellent yield and enantiomeric excess, while also avoiding the use of stoichiometric tin additives (Scheme 5).[19] Ionization of the allyl carbonate and extrusion of carbon dioxide forms a cationic π-allyl palladium complex and an enolate anion. The formation of this tight ion pair is crucial in obtaining high enantioselectivity. This variant of the Pd-AAA reaction enables the use of milder reaction conditions and a wider variety of substrates.

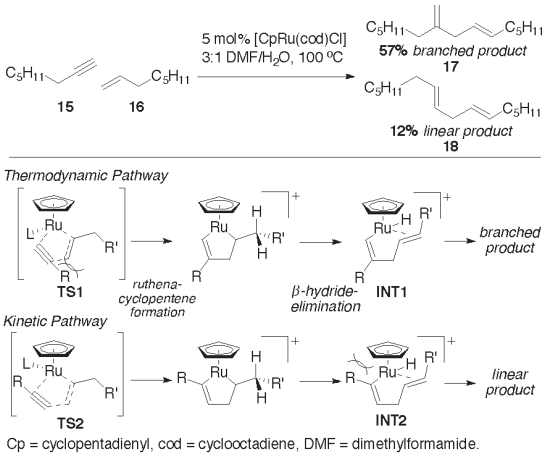


dba = dibenzylideneacetone

Scheme 5. The Decarboxylative Pd-AAA Reaction.

Ruthenium-Catalyzed Alkene-Alkyne Coupling: Formal Synthesis of Mycalamide A

The formation of carbon-carbon bonds is fundamental to chemical synthesis, and yet many syntheses still depend on the use of activating groups or the presence of adjacent polarizing functionality to selectively construct these bonds. The ruthenium-catalyzed alkene-alkyne coupling provides a tool by which simple unsaturated carbons can be coupled in a highly atom-economic fashion (Scheme 6).[20] The coupling of 1-octyne (**15**) and 1-octene (**16**) produces a *ca.* 5:1 mixture of branched (**17**) and linear (**18**) products.[21] No homocoupling products of either alkyne or alkene are observed.



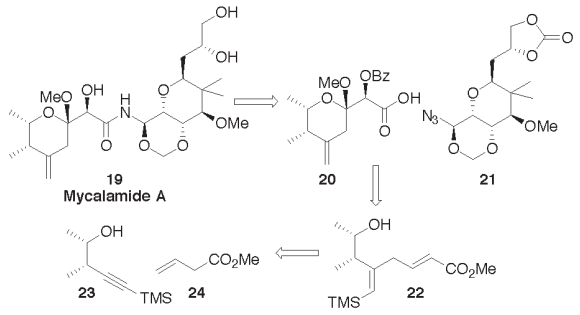
Cp = cyclopentadienyl, cod = cyclooctadiene, DMF = dimethylformamide.

Scheme 6. Ruthenium-Catalyzed Alkene-Alkyne Coupling.

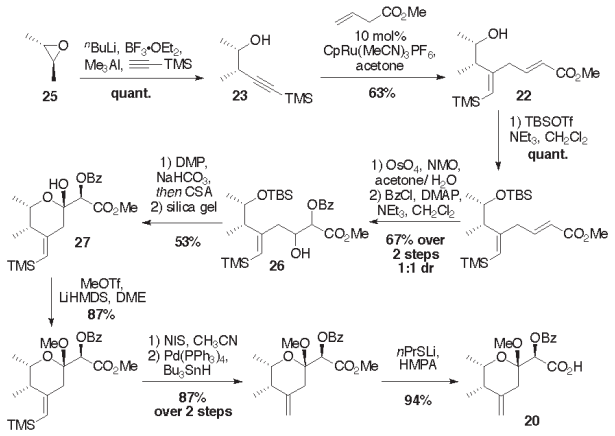
Two major mechanistic pathways have been proposed: one under kinetic control that leads to the linear product, the other under thermodynamic control that produces the branched product. The formation of the kinetic product is governed by the minimization of steric interactions in the transition state, and therefore **TS2**, where the alkynyl substituent points away from the alkene terminus, is favoured over **TS1**. In reactions where β-hydride elimination is slower than ruthenacyclopentane formation, the steric interaction between the alkynyl substituent and the $[CpRu]^+$ moiety becomes differential. Therefore, formation of the thermodynamic product is based on **INT1** being favoured over **INT2**. Utilizing certain alkyne substitution patterns and reaction conditions can lead to regioselective alkene-alkyne coupling, providing a powerful tool for chemical synthesis.

The Ru-catalyzed alkene-alkyne coupling was used to great effect in the synthesis of Mycalamide A (**19**),[22] a highly potent antitumor agent originally isolated from the New Zealand marine sponge *Mycale* sp.[23] Mycalamide A has been shown to inhibit protein synthesis and induce apoptosis in cancerous cells.[24] Retrosynthetic disconnection of the central amide bond provides (-)-7-benzoylpederic acid **20** and azide **21**, two fragments that have been utilized in a previous synthesis reported by Nakata and co-workers (Scheme 7).[25] Compound **20** was envisioned to arise from the 1,4-diene **22**, which in turn comes from the ruthenium-catalyzed alkene-alkyne coupling of **23** and the commercially available alkene **24**.

The homopropargylic alcohol **23** was prepared in a single step by the addition of TMS-acetylene to (*2S*,*3S*)-2,3-epoxybutane (**25**, Scheme 8). The steric bulk of the trimethylsilyl group serves to direct the subsequent Ru-catalyzed alkene-alkyne coupling, producing the branched product **22** regioselectively.



Scheme 7. Retrosynthetic Analysis of Mycalamide A.



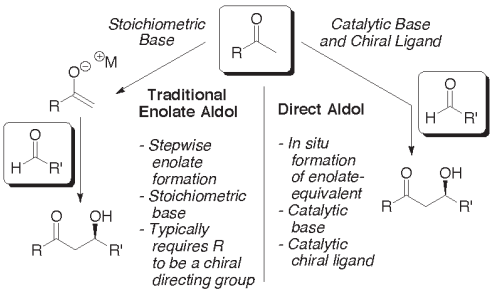
DMAP = 4-dimethylaminopyridine, DMP = Dess-Martin periodinane, CSA = camphor-10-sulfonic acid, NIS = *N*-iodosuccinimide, HMPA = hexamethylphosphoramide.

Scheme 8. Synthesis of (-)-7-Benzoylpederic Acid.

TBS-protection, dihydroxylation and selective monoesterification provided **26** as a 1:1 mixture of *syn* diasteromers. The absence of diastereoselectivity in this transformation proves to be inconsequential, as the oxidative cyclization of alcohol **26** produces a mixture of diastereomeric hemiketals that ultimately equilibrate to the desired compound **27** on silica gel. Methylation of **27** is followed by a two-step removal of the silyl group. Finally, palladium-catalyzed hydrogenolysis, followed by a dealkylative saponification provides (-)-7-benzoylpederic acid **20**. Azide **21** was prepared in 18 steps and together the two fragments constitute a formal total synthesis of mycalamide A.

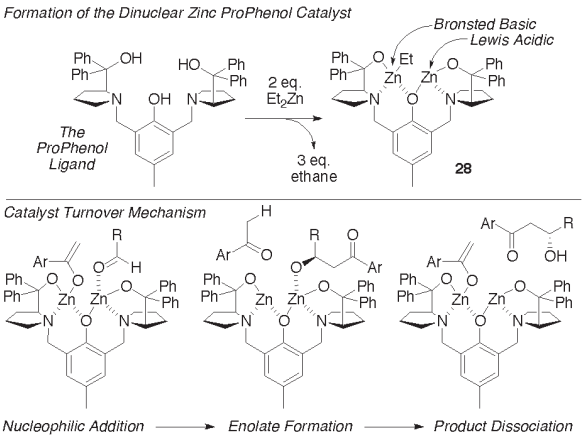
Dinuclear Zinc-Catalyzed Direct Asymmetric Aldol Reaction: Total Synthesis of Laulimalide

The aldol reaction has proven to be an incredibly powerful synthetic tool in the preparation of complex molecular targets.[26] The development of this reaction has enabled highly efficient transformations that produce β-hydroxy carbonyl compounds with excellent control of chemo-, regio- and stereoselectivity. The traditional aldol reaction involves the step-wise formation of an enolate by addition of a stoichiometric amount of base to a carbonyl donor, followed by addition of an aldehyde (Scheme 9). Control of enantioselectivity in this process has typically been achieved through the use of a chiral auxiliary on the donor, such as Evans' chiral oxazolidinone.[27] The direct aldol reaction provides an atom-economic variant of the traditional aldol reaction, avoiding the production of stoichiometric byproducts and the use of chiral auxiliaries.[28]



Scheme 9. Differentiating Traditional Enolate Aldol and Direct Aldol Reactions.

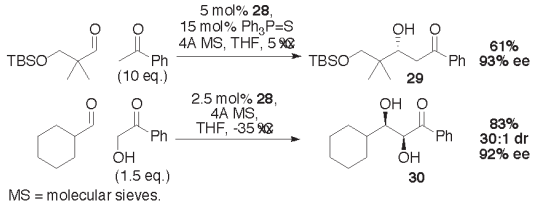
The major challenge of the catalytic direct aldol reaction with transition metal complexes is creating reaction conditions that enable catalyst turnover. The metal alkoxide that results from addition of an enolate to an aldehyde is often less basic then the starting enolate, which prevents catalyst dissociation and turnover. Chemoselectivity can also be a significant problem as the acceptor, an aldehyde, is often more acidic than the ketone or an ester equivalent used as the donor. Failure to address these issues results in low reactivity and the generation of a number of different aldehyde self-aldol side products. The dinuclear zinc ProPhenol catalyst **28** provides an elegant solution to these problems (Scheme 10).[29] This bifunctional Lewis acid/Brønsted base system serves to activate both reactants, create a chiral pocket for enantioselective addition, and acts as a proton shuttle to release the product from the catalyst.



Scheme 10. Zinc ProPhenol Catalyst and Proton Shuttle Turnover Mechanism.

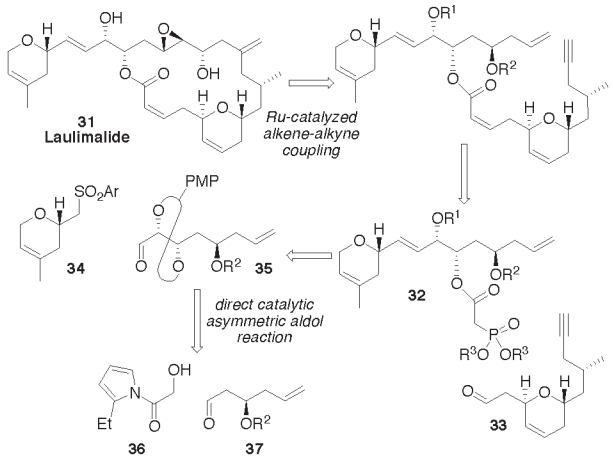
The acetophenone-based donors shown in Scheme 11 afford β-hydroxy ketone products **29** and **30** with excellent levels of enantioselectivity and good yields. Triphenylphosphine thiooxide was used as an additive to improve catalyst turnover; however, it was later discovered that the beneficial effects of this additive were limited to certain substrates.[30] A variety of α-hyxdroxy ketones have been shown to provide excellent yield, diastereoselectivity and enantiomeric excess with this methodology, creating two stereocentres in a single reaction. Interestingly, the aldehyde-derived stereocentre of **30** has the opposite

absolute configuration to the product obtained when acetophenone is used as the donor (**29**). This phenomenon is rationalized by a proposed bidentate co-ordination of the α-hyxdroxy ketone donor, bridging the two zinc atoms and altering the approach of the aldehyde to favour the opposite facial selectivity.



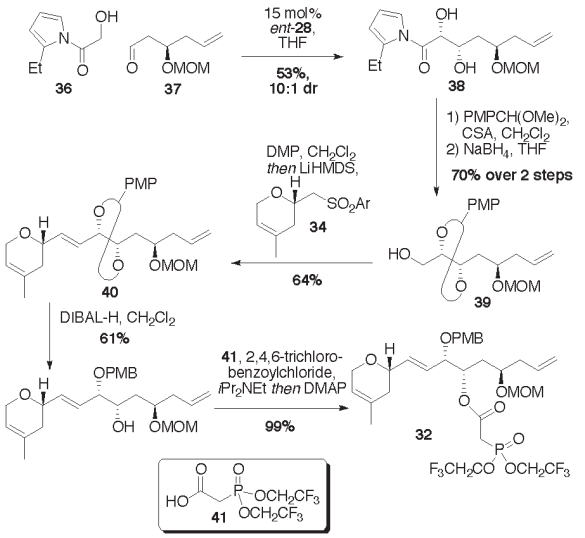
Scheme 11. Direct Asymmetric Aldol Reaction with the Zinc ProPhenol Catalyst.

The excellent atom economy and stereoselectivity of the Zn-ProPhenol aldol reaction was used to great effect in the total synthesis of the complex macrocyclic natural product, laulimalide (**31**).[31] Laulimalide displays microtubule stabilizing activity similar to that of Peloruside A, and, as a result, is highly cytotoxic towards a number of cancer cell lines.[32] The major retrosynthetic disconnections of this synthesis include macrocyclization via a ruthenium-catalyzed alkene-alkyne coupling and a *Z*-selective Still-Gennari olefination to tether the two major fragments **32** and **33** (Scheme 12). The Northern fragment **32** was envisioned to arise from Julia olefination to connect dihydropyran **34** and the protected polyol **35**, which in turn arises from the direct asymmetric aldol reaction of hydroxy 2-ethylacylpyrrole (**36**) and aldehyde **37**.



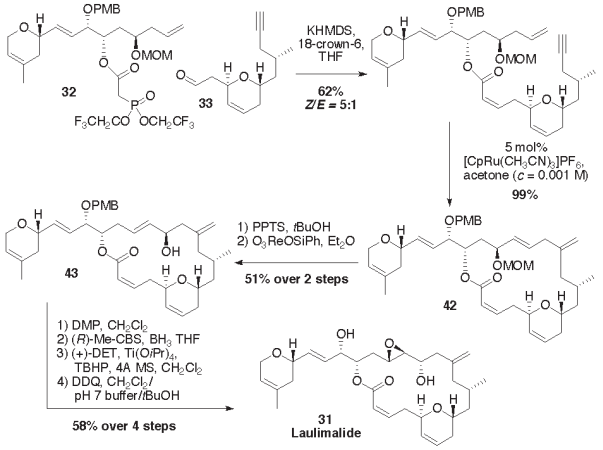
Scheme 12. Retrosynthetic Analysis of Laulimalide.

The forward synthesis commences with the preparation of the donor and acceptor for the direct asymmetric aldol reaction. Aldehyde **37** was prepared in four steps from (*S*)-glycidyl tosylate, via functional group interconversion and epoxide opening with a vinyl cuprate. The zinc ProPhenol catalyst *ent*-**28** facilitates the direct asymmetric aldol reaction of **36** and **37**, providing the desired product **38** in 53% yield and 10:1 diastereomeric ratio (dr) (Scheme 13). Formation of a *p*-methoxyphenyl (PMP) acetal followed by reduction of the *N*-acylpyrrole with $NaBH_4$ leads to alcohol **39**. Oxidation with Dess-Martin periodinane (DMP) and Julia-Kocienski olefination with phenyltetrazole sulfone **34** provided the desired *E*-alkene **40** selectively. The cyclic PMP-acetal is then selectively opened with DIBAL-H and the resulting alcohol is esterified with phosphonoacetic acid **41** under Yamaguchi conditions to complete the Northern fragment **32**.



Scheme 13. Synthesis of the Northern Fragment 32.

The Southern fragment **33** was prepared in 15 steps from *D*-aspartic acid and coupled to **32** using a Still-Genari olefination to produce a 62% yield of the desired product as a 5:1 mixture of *Z*/*E* geometric isomers (Scheme 14). Macrocylization was then achieved using an intramolecular ruthenium-catalyzed alkene-alkyne coupling. Under highly dilute reaction conditions this reaction provides near quantitative yield of the desired macrocycle **42**. MOM-deprotection under acidic conditions was then followed by allylic transposition, using a highly active perrhenate catalyst, $O_3ReOSiPh$. The desired rearranged product **43** was formed in 78% yield with complete retention of stereochemistry. The stereochemistry of the allylic alcohol was then inverted by oxidation with Dess-Martin periodinane (DMP) followed by Corey-Bakshi-Shibata (CBS) reduction. Subsequent Sharpless asymmetric epoxidation and PMB-deprotection furnished the natural product, laulimalide (**31**). The final step was performed in the presence of a pH 7 buffer to prevent the known acid-catalyzed rearrangement of laulimalide to isolaulimalide.[33]



Scheme 14. Total Synthesis of Laulimalide.

Concluding Remarks

The palladium-catalyzed asymmetric allylic alkylation, Ru-catalyzed alkene-alkyne coupling and the Zn-ProPhenol-catalyzed asymmetric aldol reaction all form carbon-carbon bonds in a highly atom-economic manner. The total synthesis of hamigeran B, mycalamide A and laulimalide clearly highlight the power and utility of these transition metal-catalyzed reactions. Although all of these syntheses rely on transformations with poor atom economy at some stage, the merit of each approach lies in the pursuit of atom-economic synthesis and the development of tools and synthetic strategies for this goal. Striving to adhere to the principles of atom economy necessitates an innovative and invention-based approach to synthesis and aids in expanding the frontiers of chemical synthesis.

Acknowledgements

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