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Intramolecular Morita Baylis Hillman and Rauhut Currier reactions. A catalytic and atom economy route for carbocycles and heterocycles

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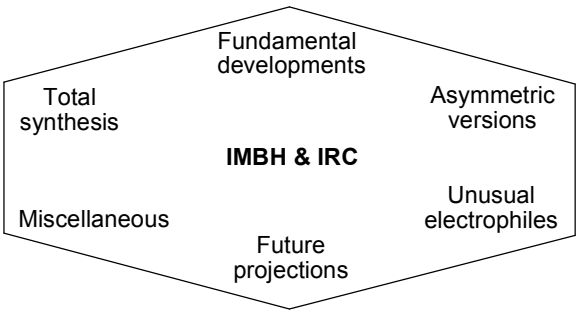
Intramolecular MBH and RC reactions: Glorious past and future opportunities



Biography

Dr. Kishor Chandra Bharadwaj was born in Varanasi (India). He obtained his PhD under the supervision of Dr. Ganesh Pandey at National Chemical Laboratory, Pune. Subsequently he moved to University of Hyderabad for his post doctoral studies with Prof. D. Basavaiah. Presently he is working as a DST scientist at Banaras Hindu University. His research interest includes development of organocatalytic reactions.

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REVIEW

Intramolecular Morita Baylis Hillman and Rauhut Currier reactions. A catalytic and atom economy route for carbocycles and heterocycles.

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Kishor Chandra Bharadwaj

Intramolecular Morita Baylis Hillman and Rauhut Currier reactions are important tools which have constantly grown over several years. This review summarises and highlights their various aspects such as development of activated alkene, electrophile and catalyst both in achiral and chiral fashion, use of non conventional electrophiles, applications in total synthesis. Selected miscellaneous reports of internal promoter, cycloadditions, non conventional routes for IMBH adduct have also been pressented, along with future projections.

Introduction

C-C bond formation happens to be one of the everlasting challenges, which organic chemists have faced. The fundamental and ever growing need to carry out reactions in a better and efficient manner than the existing methods keeps setting new challenges for researchers. Towards this end, natural products and bio active molecules have been a source of inspiration for synthetic and medicinal chemists. The ultimate aim of achieving complex molecular synthesis in the simplest of possible ways has been driving the developments in the area of synthesis. Notably one of the most common features of these molecules has been presence of carbocycle/heterocycle framework. In fact it's hard to find a medicinal target which doesn't have this architecture, while many of them have complex polycyclic core. This has led to a revolution to define and refine methods to obtain such structure (Figure 1). Many approaches like Diels-Alder, RCM, cycloaddition, Nazarov cyclization, Robinson annulation, Yamaguchi lactonization, etc. have been specifically aimed at achieving this synthetic goal. Additionally intramolecular versions of many popular reactions like Diels-Alder, Aldol condensation, Michael addition, Friedel Crafts, cross coupling, allylic substitution and many more contribute towards this objective. Intramolecular versions of any reaction have always been a fascinating endeavour for synthetic chemist, as they offer advantages in terms of better chemo and stereo selectivity and high complexity within a confined cyclic framework. With a gold rush towards these cyclic frameworks intramolecular versions have seen enormous growth and hold key to future.

Morita Baylis Hillman (MBH)[1] and it vinylogus version Rauhut Currier (RC)[2] reaction happens to be a protocol which has

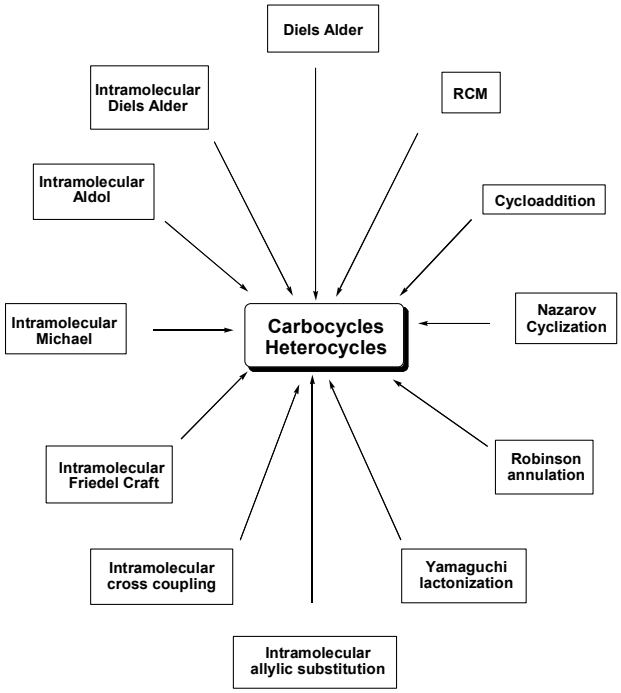

Figure 1. Some approaches for cyclic framework

emerged as a powerful methodology in organic synthesis.[3-5] Reaction involves coupling of an activated alkene (from its alpha position) with an electrophile (generally aldehyde or an imine) in presence of a catalyst (Figure 2). The reaction involves a sequence of Michael addition of nucleophile over activated

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Dedicated to Prof. D. Basavaiah, for thirty years of his seminal contributions to Morita Baylis Hillman reaction

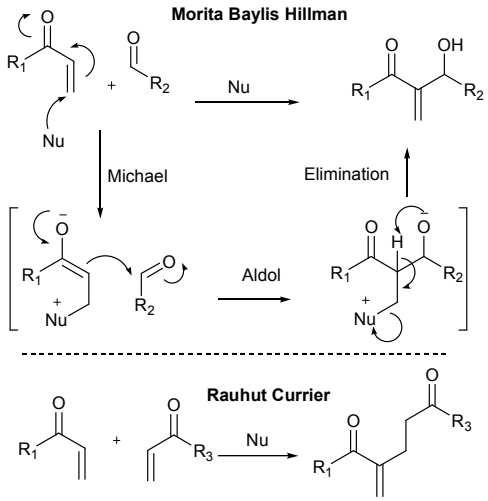


Figure 2. Mechanism of MBH and RC reaction

alkene to generate enolate which is trapped by the elctrophile in aldol fashion. Finally proton transfer and elimination of catalyst leads to delivery of MBH adduct. MBH reaction offers many advantages including its atom economical nature, mild reaction conditions, generation of a chiral center from prochiral molecules and most importantly it delivers densely substituted valuable adducts, which have served as a platform for various other transformations. Several segments of the reaction (Figure 3) such as reaction development,[6] asymmetric version,[7] application of MBH adduct,[8] total synthesis,[9] mechanism investigation[10] and many others have emerged, offering numerous opportunities. An important section of the MBH reaction happens to be intramolecular Morita Baylis Hillman (IMBH) and intramolecular Rauhut Currier (IRC) reactions (Figure 4). When both the reacting partners i.e. activated alkene and electrophile are part of the same molecular skeleton, then there is an opportunity for the synthesis of cyclic framework.

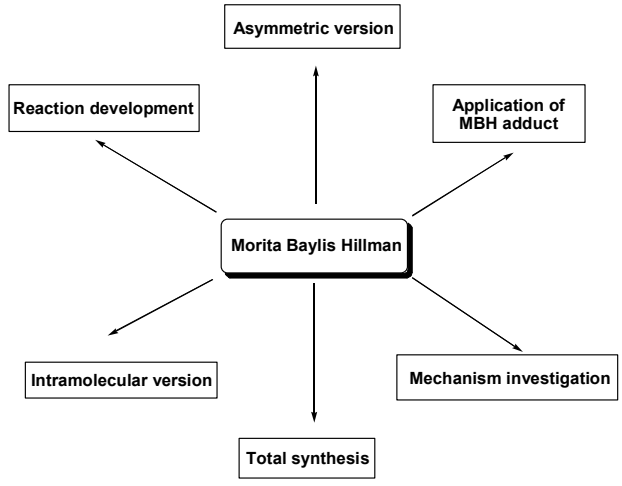


Figure 3. MBH reaction at a glance

These intramolecular versions (IMBH and IRC) have seen huge growth in the last two decades along with the synthesis of various carbocylces and hetrocycles in achiral and chiral fashion. Various activated alkenes along with different electrophiles primarily under the influence of nitrogen/phosphine catalysis, have been used. Incorporation of exceptional sp^3 electrophilic centres and applications in total synthesis have been the prominent developments in gamut of this reaction.

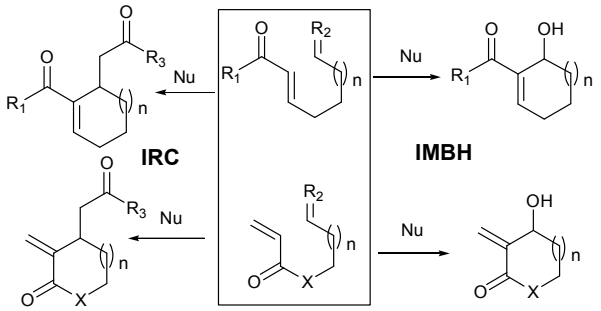


Figure 4. IMBH and IRC reactions at a glance

Quick accessibility to the precursor for cyclization has been important for the growth of IMBH and IRC reactions. Conceptual presentation of frequently used methods has been made in figure 5. Wittig reaction has been the preferred choice to install Michael acceptor. Besides this, acrylation of hetroatom such as Oxygen, Nitrogen has been used for smooth appending of acryl functionality. Corss metathesis has been yet another important tool for quick assembly of required two functionalities.

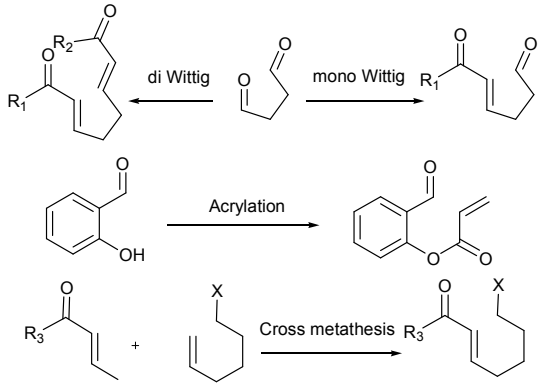


Figure 5. Common methods for synthesis of precursors.

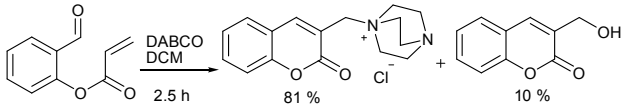
With quick access to these starting materials IMBH and IRC reactions have been vastly explored which would be discussed under following segments.

1. IMBH-Fundamental developments
2. Asymmetric IMBH
3. IRC-Fundamental developments
4. Asymmetric IRC
5. Non conventional electrophiles
6. Application in total synthesis
7. Miscellaneous reports

1. IMBH-Fundamental developments

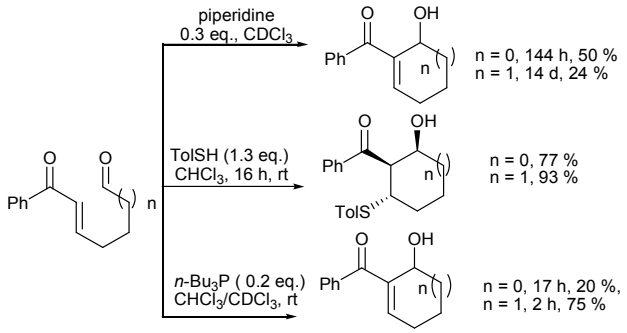
Several developments in the area of activated alkenes, electrophiles and catalyst for IMBH reaction have taken place. Various activated alkenes have been used as a source of enolate, though enones have dominated the arena with their superior reactivity. Similarly aldehyde as electrophilic partner has been most commonly used, along with reports of ketone and imines. Organocatalysis has greatly contributed to IMBH while use of Lewis acids has been confined.

In the preliminary studies in this area (Scheme 1), Drewes et al. attempted to carry out IMBH reaction of salicylaldehyde derived substrate. However they obtained DABCO salt as a major product, along with 3-hydroxymethylcoumarin.[11]



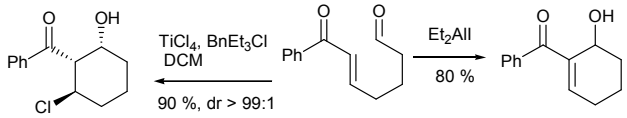
Scheme 1.

Murphy and co-workers[12] (Scheme 2) carried out initial investigations on role of different classes of catalysts. Amongst all the secondary amines screened they found piperidine as best catalyst for IMBH reaction. Latter they also investigated role of Thiol and Phosphine and found that use of TolSH led to Michael addition followed by aldol adduct, but the catalyst failed to eliminate from adduct. However Bu_3P was successful in giving IMBH product.

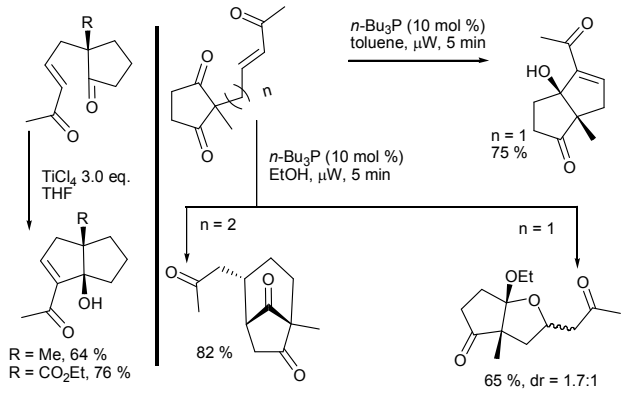


Scheme 2.

In their attempt to explore Lewis acid catalyzed cyclization, Oshima and co-workers[13] (Scheme 3) carried out Et_2AlI mediated ring closure reaction and obtained IMBH product in 80 % yield. However same substrate on treatment with $TiCl_4$ and $BnEt_3Cl$ gave Michael, Aldol product.



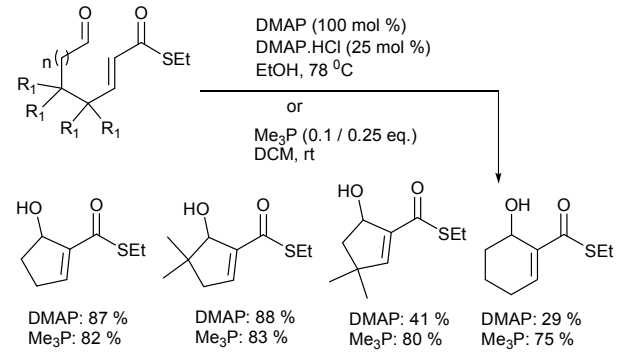
Scheme 3.



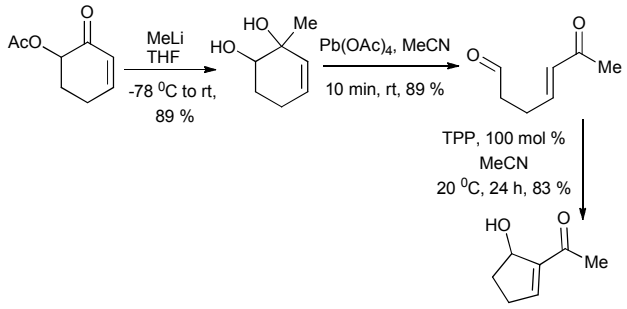
Scheme 4.

Using ketone as electrophile (Scheme 4), which are known to be less reactive for MBH reaction, Miesch and co-workers carried out $TiCl_4$ promoted IMBH reaction giving rise to fused bicarbocylic systems with quaternary centers.[14a] Latter, using phosphine catalysis under microwave conditions they screened out different conditions for the synthesis of IMBH adducts, Bicyclo[3.2.1]octanones and mixed acetals.[14b] An example of each is presented.

Unsaturated thiol ester as a substrate for IMBH was investigated by Keck and Welch.[15] Both DMAP (along with DMAP.HCl) and Me_3P gave comparable results for synthesis of cyclopentenols and cyclohexenol. Thioester showed higher reactivity profile compared to oxo ester (Scheme 5).

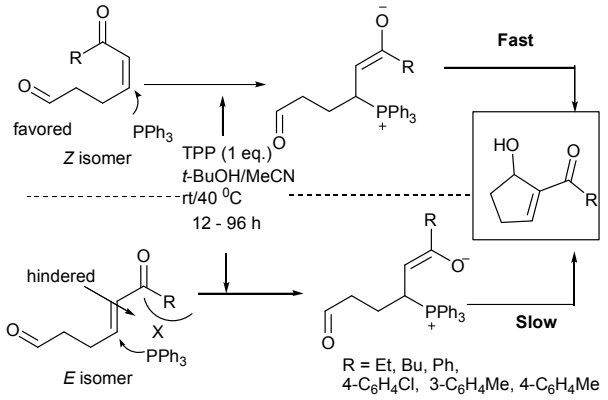


Scheme 5.



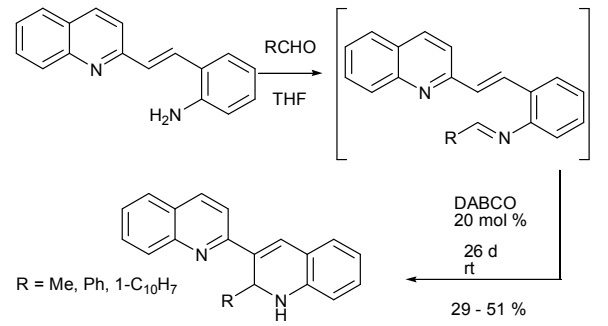
Scheme 6.

Koo and co-workers[16] (Scheme 6) described a convenient approach for the synthesis of ω-formyl-α,β-unsaturated carbonyl compounds and then transformed them to useful IMBH adduct using PPh_3 as catalyst. With the same starting material and choice of different organometallics, different precursors were obtained. Starting from cyclohexenone, cyoheptenone and cyclohexanone they were able to synthesize 5, 6 and 7 membered carbocycles respectively with varrying enone moieties. An example is represented.



Scheme 7.

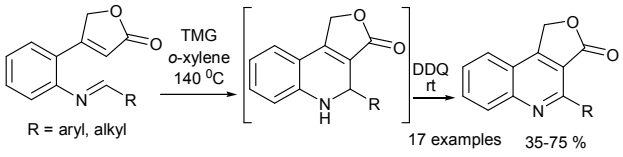
Toy, and co-workers (Scheme 7) studied systematically IMBH reaction of *E* and *Z* alkenes under the influence of TPP, and found that under identical conditions *Z* isomer reacted faster (2.5-8.5 times) than the *E* isomer thus giving higher yield of IMBH adduct under similar time.[17] They attributed this either to the steric reason, which in *E* isomer reduces the attack of Phosphine on alkene or due to formation of different enolates which may have different reactivity.



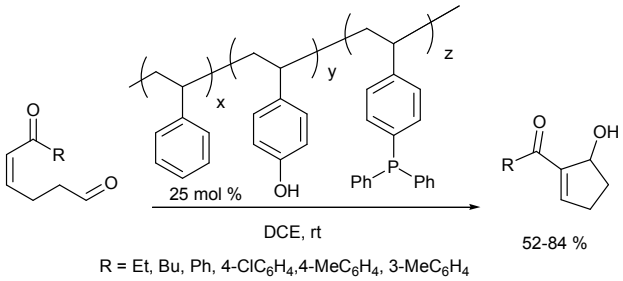
Scheme 8.

Trifonov et al. carried out aza IMBH of insitu generated imines for synthesis of 1',2'-dihydro-2,3'-bisquinolines (Scheme 8).[18] Latter Li, and co-workers developed aza IMBH reaction using furanone as an activated alkene. The cyclized IMBH product was insitu oxidized by DDQ to obtain annulated quionline skeletons (Scheme 9).[19]

In any field of catalysis, development of heterogeneous catalysis/recyclability of catalyst/polymer supported catalyst etc. has seen parallel growth along with development of homogeneous catalysis. Similar has been the case in IMBH. Polymeric organo catalyst for IMBH of enone was developed by Toy and co-workers (Scheme 10).[20] They found that catalyst with a phenolic moiety provided better yields of reaction, probably by hydrogen bond activation or stabilization of enolate intermediate.

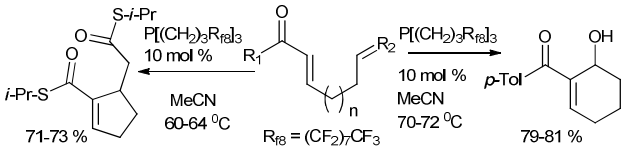


Scheme 9.



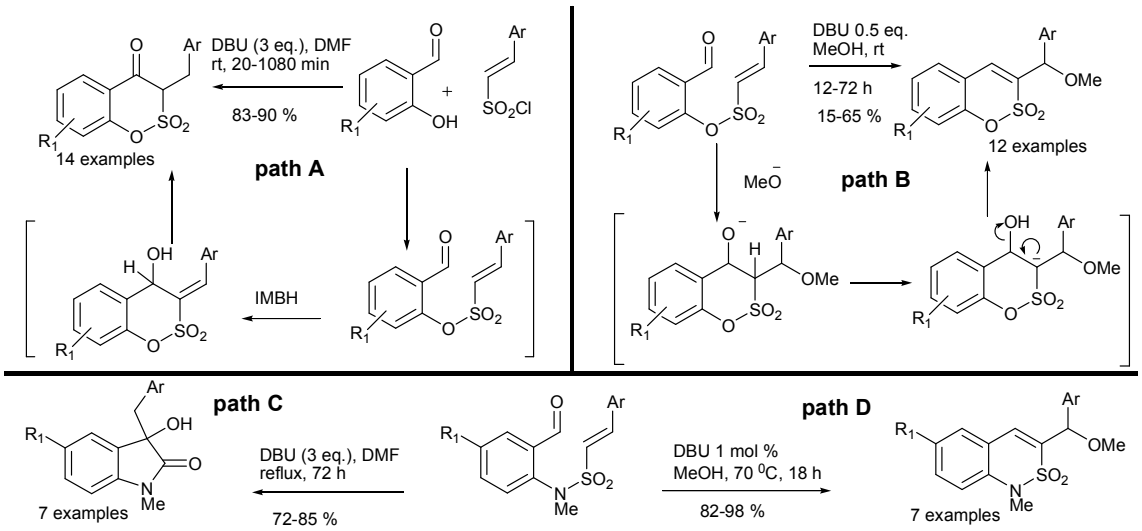
Scheme 10.

Working towards the recyclability of catalyst (Scheme 11) Seidel and Gladysz developed Fluorous phosphine $P[(CH_2)_3R_{f8}]_3$ for both IMBH and IRC reaction.[21] The catalyst could be recovered by cooling it to -30 ^{0}C and could be used for 3-5 cycles.



Scheme 11.

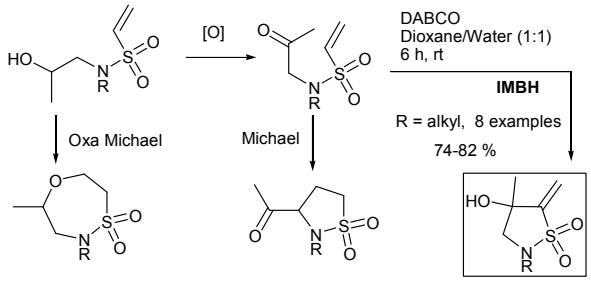
In an interesting study (Scheme 12) Ghandi et al. discovered different course of reaction while studying IMBH reaction of vinyl sulfonate and sulfonamide. Outcome of reaction was substrate and solvent dependent. Initially[22a] carrying out reaction of insitu generated sulfonate in DMF (path A) led to isolation of ketone which was proposed to be formed via 1,3 H shift after IMBH reaction. However conducting IMBH reaction in MeOH on pre synthesized sulfonate (path B), lead to SN_2' substituted adduct. It was reasoned that during the course of reaction after proton transfer, elimination of water takes place, instead of elimination of MeOH. Although reactions led to formation of unusual products, still they had wide reproducibility on different substrates. Switching over to vinyl sulfonamide[22b] as a precursor for IMBH in refluxing DMF led to



Scheme 12.

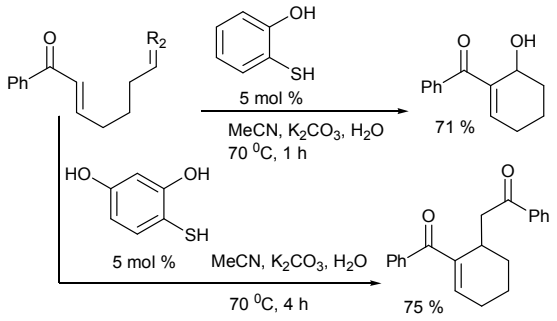
a very different product of substituted indolin-2-ones which was formed after expulsion of SO_2 and subsequently ring contraction (path C). Change of reaction medium to MeOH (path D) and using 1 mol % of DBU led to expected product as obtained in case of sulfonate. Interestingly sulfonate, where reactions were carried out at rt seemed to have higher reactivity over sulfonamide which required higher temperature for IMBH.

Zhou and co-workers[23] (Scheme 13) reported ketone as electrophile in DABCO promoted IMBH reaction, using vinyl sulfonamide as activated alkene. The IMBH reaction led to the synthesis of several sultums. The precursors were also used for intramolecular Michael and oxa Michael additions. For other examples of sulphonamide see scheme 23 (vide infra).



Scheme 13.

Nitrogen and phosphorus catalysis have been the preferred choice for IMBH and IRC reaction. Their corresponding sulfur analogue has not been so popular as it leads to domino addition of Michael and Aldol adduct but fails to eliminate (see scheme 2). However Selig and Miller[24] successfully used sulfur catalysis in form of ortho-acidic aromatic thiols for IMBH reaction (Scheme 14). Reactions

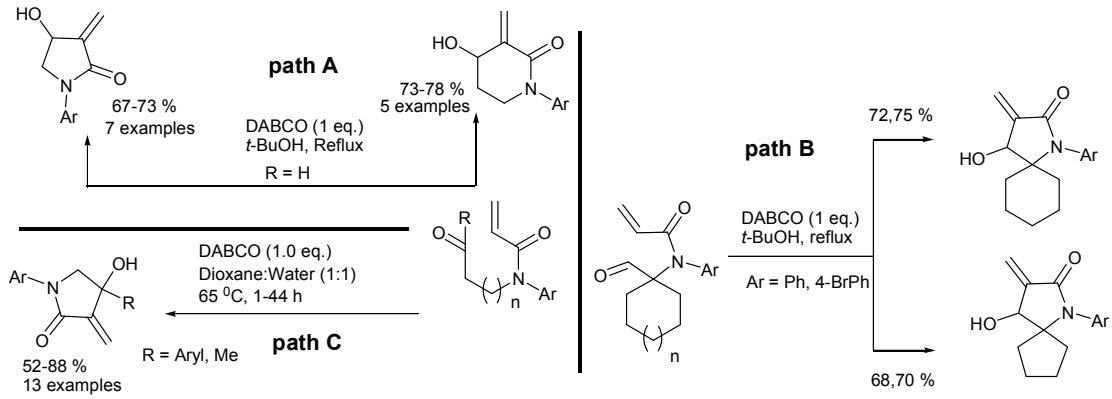


Scheme 14.

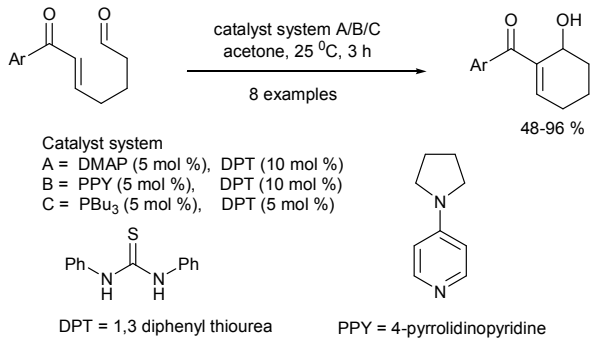
were carried out in basic (K_2CO_3) biphasic system of MeCN and water, which helped in suppressing the side reactions. Rate of reaction was high, delivering good yields. Further extension to IRC reaction was also fruitful giving moderate to good yields. An example of each is presented. However asymmetric version using chiral Binol derivatives under similar conditions gave low to moderate enantioslectivites.

Addressing to the sluggishness of acrylamide in MBH chemistry, Basavaiah et al. have presented a detailed account of its application in IMBH reaction (Scheme 15).[25] Initially they explored the reaction using aldehdye[25a] as an electrophile. Several α methylene lactum (both 5 and 6 membered) were synthesized using DABCO as a promoter in refluxing *t*-BuOH (path A). They also effectively applied the protocol for synthesis of spiro lactum framework (path B). Reaction utility was further extendable by the inclusion of ketone[25b] as electrophile, which are much less reactive as compared to aldehyde in MBH chemistry (path C).

Suga, and co-workers[26] (Scheme 16) carried out rate acceleration of IMBH reaction using different catalytic system. Extensive optimization including screening of



Scheme 15.

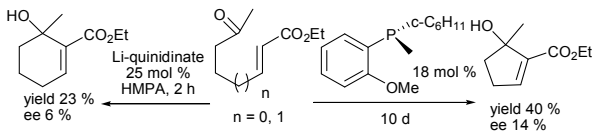


Scheme 16.

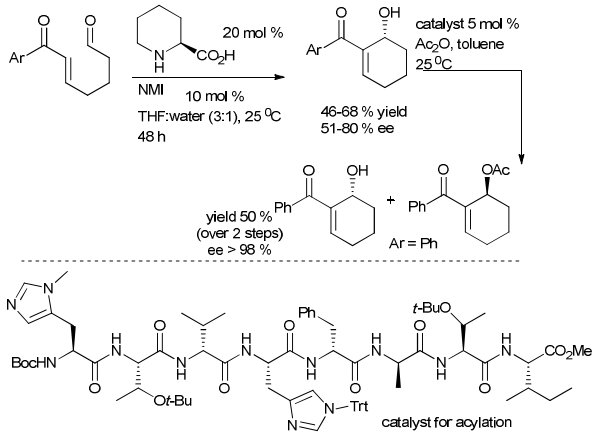
cocatalyst, solvent, catalyst loading and concentration, led to the combination of three different catalytic system in which 1,3 diphenyl thiourea along with different catalysts (DMAP/Bu_3P/PPY) was found to accelerate the reaction.

2. Asymmetric IMBH

Successful asymmetric IMBH reaction has been carried out both on chiral substrates (distereoselctively) and achiral substrate (by using chiral catalyst). First IMBH reaction[27] was reported by Fráter and co-workers which also happened to be the first asymmetric IMBH (Scheme 17). They used chiral phosphine and Li-quinidinate for synthesis of 5 and 6 membered rings respectively. Although the yields were on the lower side and little selectivity was observed, the reaction was significant in giving a new area to the field of MBH reactions. It is worth mentioning that authors succeeded in IMBH reaction using less reactive partners in the form of substituted acrylate and ketone.



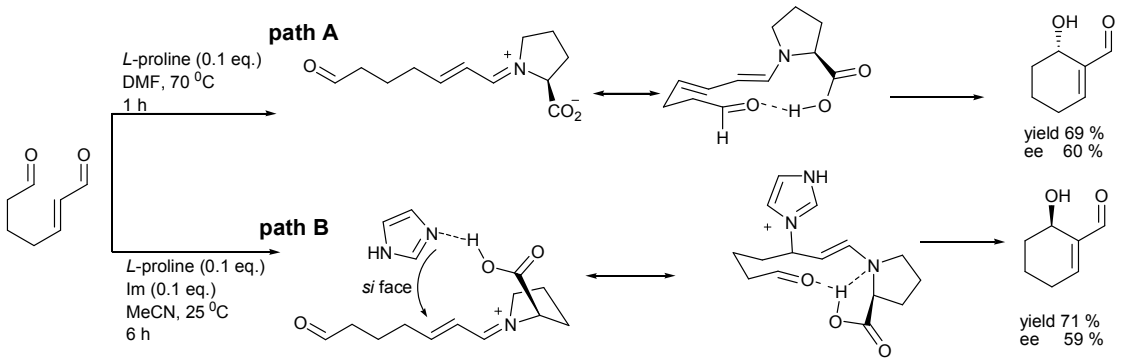
Scheme 17.



Scheme 18.

A breakthrough[28] for asymmetric IMBH with high and acceptable enantio selectivity was made by Miller and co-workers (Scheme 18). Working on co-catalytic system they found that combination of pipecolinic acid (20 mol %) and N methyl imidazole (NMI) (10 mol %) was effective in IMBH reactions, giving high ee of product. Further in order to enhance ee they carried out one pot IMBH reaction and kinetic resolution (*via* acylation (Ar = Ph)) to obtain final product with ee > 98 %. A peptide based catlalyst was used for the resolution of enantio enriched mixture of IMBH adduct.

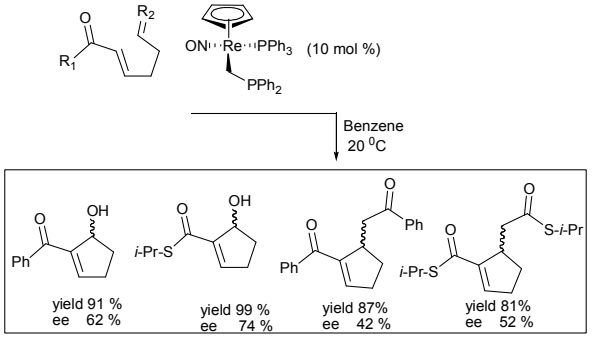
Working on enamine catalysis[29a] Hong and co-workers discovered key role of Imidiazole in reversing the selectivity of proline catalysed IMBH reaction (Scheme 19). In the proposed mechanism, proline leads to iminium ion which in absence of imidazole undergoes dienamine formation followed by ring closure (path A). However imidazole if present attacks the imminium ion and gives rise to mono enamine derivative which undergoes ring closure in different mode (path B). Thus two different reaction intermediates are formed giving different stereochemistry.



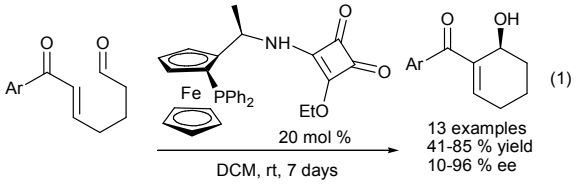
Scheme 19.

Latter Santos[29b] and co-workers performed the computational study of reaction mechanism which indicated water to be an important catalyst in the imine/enamine conversion. They found that selectivity of reaction happens to be outcome of electrostatic contacts between carbonyl oxygen atom and proline moiety.

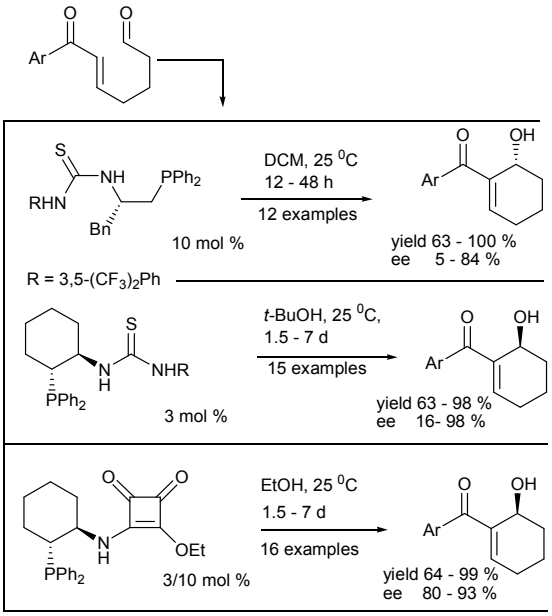
An organometallic phosphine for IMBH and IRC reaction of enone and thioacrylate was developed by Seidel and Gladysz (Scheme 20).[30] They used Rhenium containing phosphine catalyst for IMBH and IRC and obtained high yield with moderate selectivities. Subsequently[31] Chen, and co-workers used bifunctional Ferrocene based phosphine organocatalyst for IMBH reaction (eq 1).



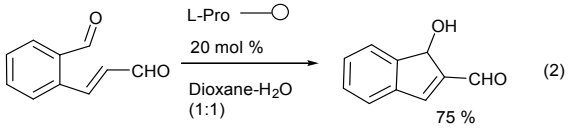
Scheme 20.



Wu and co-workers have developed a series of catalysts including amino acid[32a] derived phosphinothiourea catalyst, cyclohexane[32b] based chiral phosphinothiourea catalyst and squaramide[32c] based tertiary phosphine catalyst for asymmetric IMBH reactions (Scheme 21) and IRC reactions (scheme 39, vide infra). Reactions were applicable to a wide



Scheme 21.



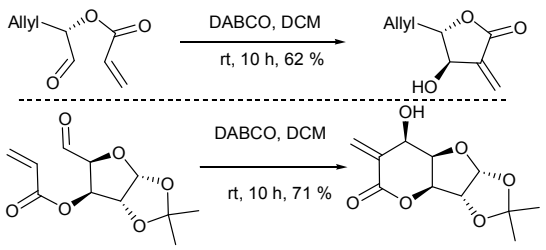
range of aryl enones including electronically deficient, rich and neutral aryl rings and provided high level of selectivity with access to both enantiomers.

Kudo and co-workers[33] (eq 2) have used resin supported proline in 1,4 dioxane-water, for the synthesis of indenes via IMBH reaction. An example is given.

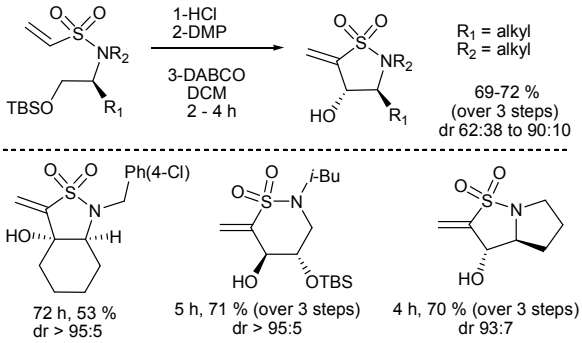
A DABCO catalysed distereoselective IMBH reaction[34] on sugar derived substrates was developed by Krishna and co-workers affording the corresponding α-methylene β-hydroxy lactones (Scheme 22).

Latter Hanson and co-workers generated a library of small molecules in distereoselctive fashion using vinyl

sulphonamide as activated alkene (Scheme 23).[35] Versatile precursors suitable for intramolecular versions of different reactions such as Heck, oxa-Michael, aza-Michael, RCM, Pauson Khand and IMBH were synthesized and applied. Selective examples of IMBH reactions are illustrated. Notably they also successfully carried out IMBH reaction using ketone as electrophile.

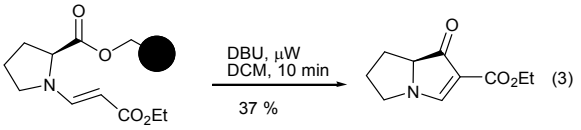


Scheme 22.



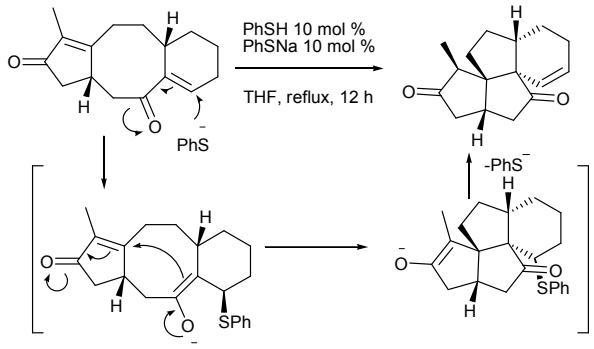
Scheme 23.

Eifler-Lima and co-workers carried out solid phase synthesis (eq 3) for obtaining Hyacinthacine core using Merrifield resin.[36] The key step was IMBH utilizing DBU as catalyst for cyclisation under microwave conditions, which also leads to cleavage of resin. In absence of DBU, reaction was low yielding (1.7 %). The reaction also exemplifies ester as electrophile in MBH reaction.



3. IRC-Fundamental developments

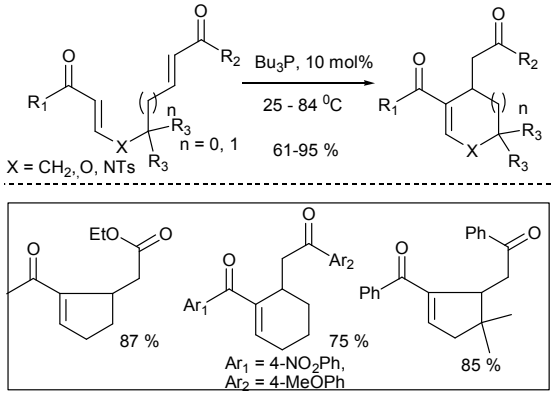
RC reaction which involves coupling of two homo or hetro alkenes is a useful protocol for C-C bond formation, but at times it lacks chemo selectivity and faces problem of dimer formation. In 1999, Erguden and Moore[37] in their studies towards transannular reaction demonstrated the application of IRC type cyclisation for synthesis of angularly fused polyquinanes (Scheme 24). They proposed Michael addition followed by tranannulation to give an intermediate



Scheme 24.

which undergoes elimination to give required precursor. Krische and Roush independently and simultaneously in their landmark discoveries utilised this reaction in the form of intramolecular version and found the reaction to be highly selective in terms of steric and electronic parameters. Reaction as expected prefers to start from a more electrophillic and sterically less hindered Michael acceptor. Thereafter several alkenes and alkynes for IRC have been documented, both in the form of starting and terminating partners. Phosphines are a preferred choice of catalysis.

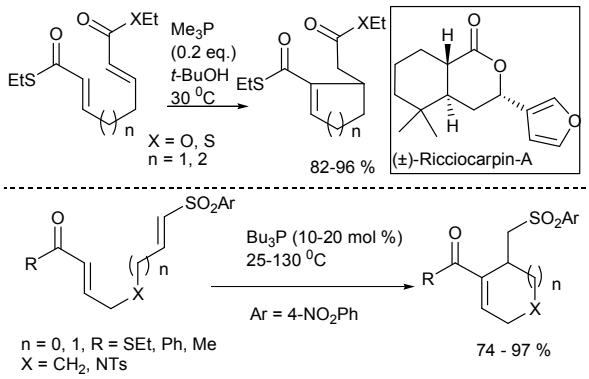
In their seminal work Krische and co-workers used Bu_3P as a catalyst and found wide substrate scope for cycloisomerisation reaction (Scheme 25).[38a] In case of unsymmetrical alkenes, reaction was sensitive to both steric and electronic parameters and gave regioselective formation of cyclic product. Representative examples illustrate high regio selectivity where other isomer was not detected.



Scheme 25.

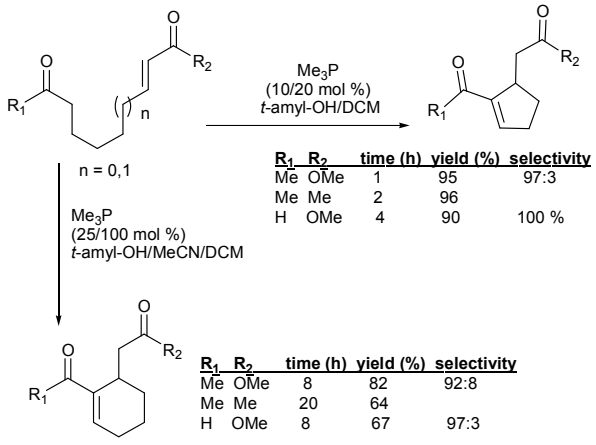
Further utilizing thioenoates[38b] as the initial Michael acceptor (Scheme 26) they carried out cycloisomerisation of both symmetrical (bis thioenoates) and non symmetrical (thioenoate and enoate) precursors. Reaction was selective on cross IRC reaction with thioenoate serving as superior Michael Acceptor. Protocol was applied for the synthesis of (±)-Ricciocarpin-A. The scope of reaction was further broadened by introducing vinyl sulphone[38c] as electrophilic

partner for trapping the enolate generated by enone and thioenoate in different solvents such as *t*-Amyl alcohol, MeCN, EtOAc, Acetone, *t*-BuOH. Reaction was selective and product utilizing vinyl sulfone as enolate source was not observed.



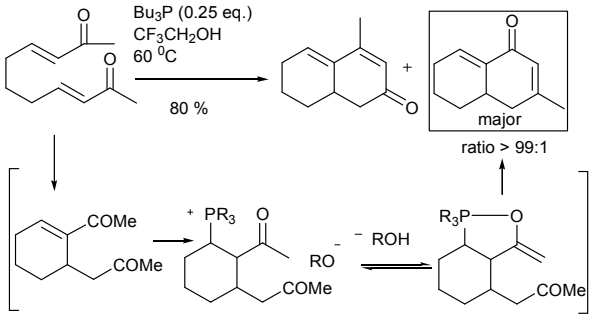
Scheme 26.

At the same time Roush and co-workers, using Me_3P and Bu_3P as promoter, carried out facile construction of 5 and 6 membered rings, utilizing both symmetrical and un symmetrical alkenes (Scheme 27).[39a] They obtained high regioselectiveity (upto 100 %) and found wide substrate scope of reaction in terms of nature of alkenes, substitutions around ring, and synthesis of carbocyclic/heterocyclic framework. Few examples are illustrated.



Scheme 27.

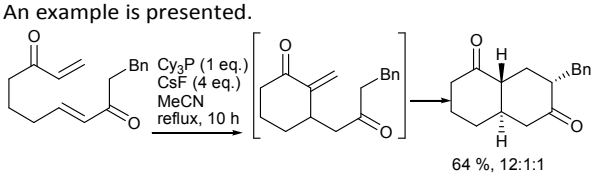
Phosphonium enolate intermediates have tendency to deprotonate alcoholic solvents, leading to generation of alkoxide anion.[39b] Roush used this concept in designing domino reaction involving one pot IRC reaction followed by highly regioselective aldol condensation (Scheme 28).[39c] They proposed cyclic phosphine intermediate which was responsible for selective enol formation and thus leading to highly regioselective aldol condensation. Various control



Scheme 28.

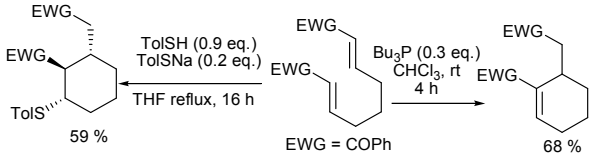
experiments were carried out to support the mechanism. In absence of phosphine reversal of selectivity was observed giving the linearly conjugated and thermodynamically more stable isomer as major product. Methodology was applicable to various substrates (yields 58-80 %). An example is presented.

Earlier Couturier et. al. have carried out one pot domino sequence of Rauhut currier and Michael addition[40] using phosphine and CsF for synthesis of decalin system (Scheme 29). Further they also discovered that phosphine itself can catalyze both steps by using protic solvent, or moist MeCN. An example is presented.



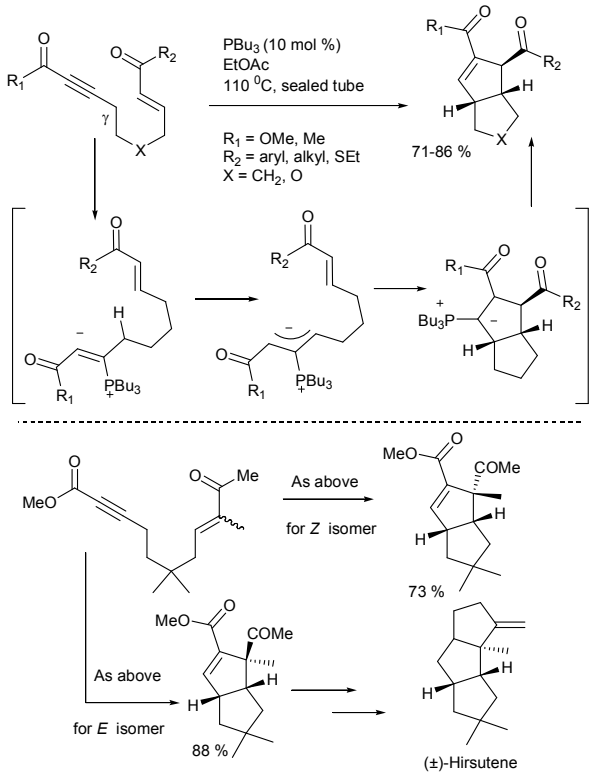
Scheme 29.

Murphy and co-workers[41] also investigated cycloisomerisation reactions using different catalysts (Scheme 30). With Bu_3P as catalyst they obtain IRC adduct. However TolSH and TolSNa gave non eliminated TolS-incorporated product. These observations were in accordance with their earlier studies for IMBH reactions (see scheme 2). An example is illustrated.



Scheme 30.

Activated alkynes with a γ carbon, allenes and MBH bromide, have been used as a source of 3 carbon centres which undergo cycloaddition reaction with a tethered activated alkene. The protocol thus happens to be complementary to classical IRC reaction, giving bicylic compounds rather monocyclic, with multiple stereocentres.



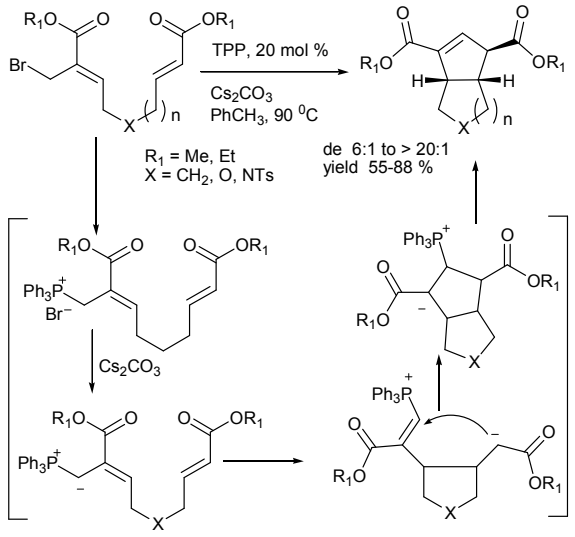
Scheme 31.

Extending and developing their reaction, further to ynoate as initial Michael acceptor,[42a] Krische and co-workers carried out phosphine catalysed synthesis of bicycle [3,3,0] ring system from electron deficient 1,7 enynes (Scheme 31). Ring closure took place from γ position and proceeds via [3+2] cycloaddition. Pleasingly they didn't observe any isomerization in product corresponding to 2,4- dienoate and selectivities observed were generally >95:5. They further established[42b] the stereospecific nature of protocol by exposing *E* and *Z* isomers separately, which delivered different distereoisomers and led to synthesis of (±)-Hirsutene.

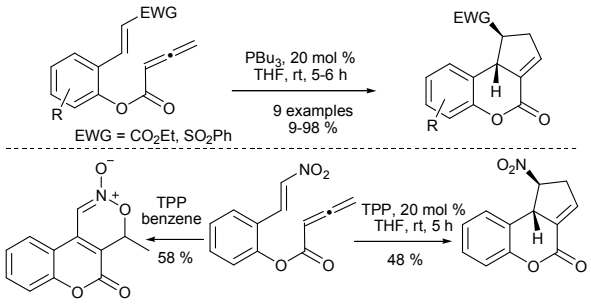
In an unconventional approach use of MBH bromide as initial Michael acceptor was demonstrated by Tang and co-workers.[43] Initial attack of TPP leads to salt formation (Scheme 32). Subsequently Cs_2CO_3 mediated ylid formation followed by [3+2] cycloaddition leads to bicyclic framework. Reaction was chemoselective with MBH bromide serving as superior electrophile for initial attack of TPP.

Another report for bicyclic construction using two tethered Michael acceptors was made by Henry and Kwon (Scheme 33).[44] They utilized 2-styrenyl allenoates under Bu_3P catalysis for synthesis of cyclopentene fused dihydrocumarins. Reaction was successful with acrylates and vinyl sulfone. Nitro styrene however gave a different [4+2] kind of product under TPP catalysis using benzene as a solvent.

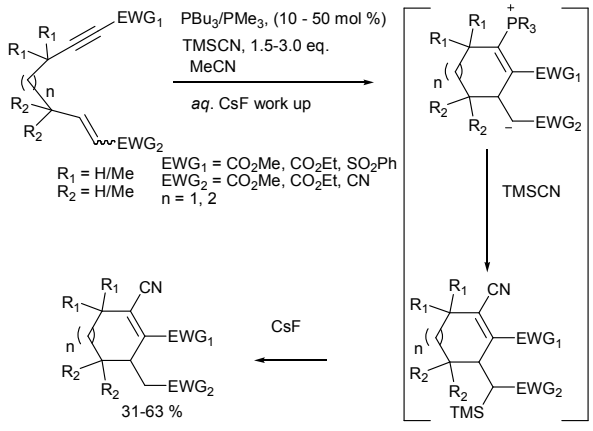
In a different and interesting kind of IRC reaction, MacKay et al. reported phosphine catalyzed ring closure along with addition of cynide across alkyne (Scheme 34).[45] Although end product resembles to be result of double Michael addition initiated by CN but reaction doesn't proceed in the absence of phosphine catalyst. In the proposed mechanism



Scheme 32.



Scheme 33.

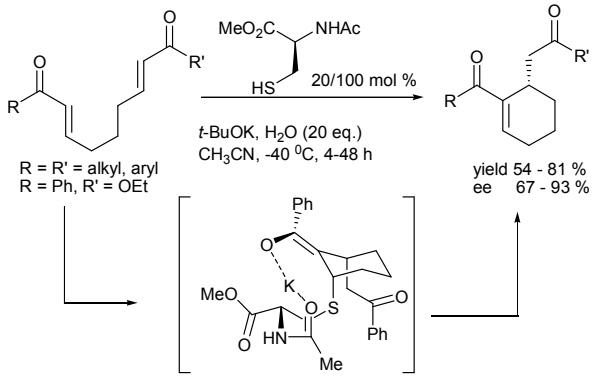


Scheme 34.

innital attack of phoshine across triple bond was followed by ring closure reaction. Subsequently release of catalyst, by substitution leads to completion of cycle. High regioselectivity was observed with alkynes serving exclusively as initial Michael acceptor. Even with steric hindrance as gem dimethyl substitution at γ carbon of alkyne, reaction was successful owing to high electrophilicity of alkynes. Asymmetric version was also explored but low enantiomeric ratios were observed.
For other examples of IRC see schemes 11 & 14.

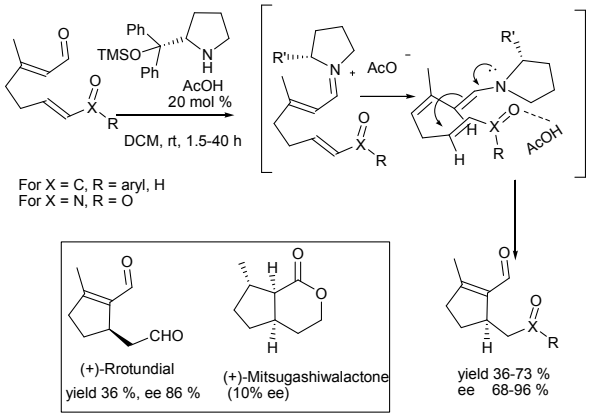
4. Asymmetric IRC

Asymmetric versions of IRC have been explored using chiral enolate, chiral enamine and chiral auxillary.
Miller and co-workers after their successful expedition in enantioselective IMBH reaction (Scheme 18) sparked the development in the area of asymmetric IRC catalysis (Scheme 35).[46a,b] They used cysteine based catalyst for the first enantioselective IRC reaction. Sequential, careful and extensive optimization of base, solvent, temperature, and additive led to optimum conditions which were employed to other substances. Mechanistic investigation revealed the importance of potassium ion chelation in transition state and that C-C bond formation was reversible. Elimination of cysteine after proton abstraction was proposed to be irreversible, rate determining and stereo determining step. Further computational studies[46c] also revealed elimination of thiol catalyst to be rate determining step.

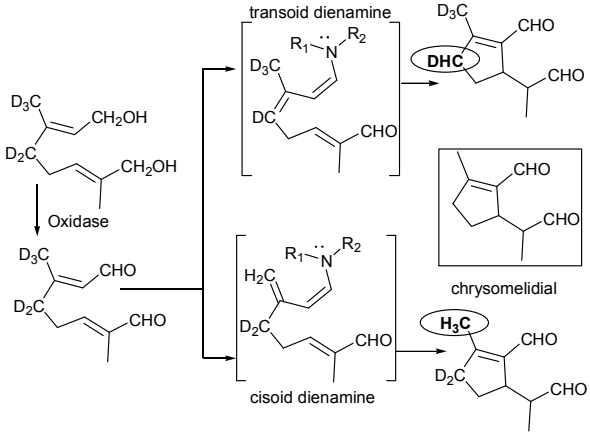


Scheme 35.

Unlikely with the most reports where chiral nucleophilic catalysts were used for Michael addition and thus generating a chiral enolate, Christmann and co-workers in their graceful approach have generated chiral dienamine (Scheme 36) as a source of chirality by using *L*-proline derived amine.[47] These chiral dienamine were used for cross IRC reaction and high ee with good yields were obtained. Authors have thus used successfully β-disubstituted activated alkene (a rarely used alkene) in MBH chemistry. Presence of methyl group at β position of RC donar aldehyde was important for reactivity and enantio selectivity. The mechanism was also supported by ESI-HRMS and NMR experiments. They also demonstrated the utility of protocol by total synthesis of (+)-Rotunidal and (+)-Mitsugashiwalactone (although there was a drop in ee in due course, in case of latter).



Scheme 36.

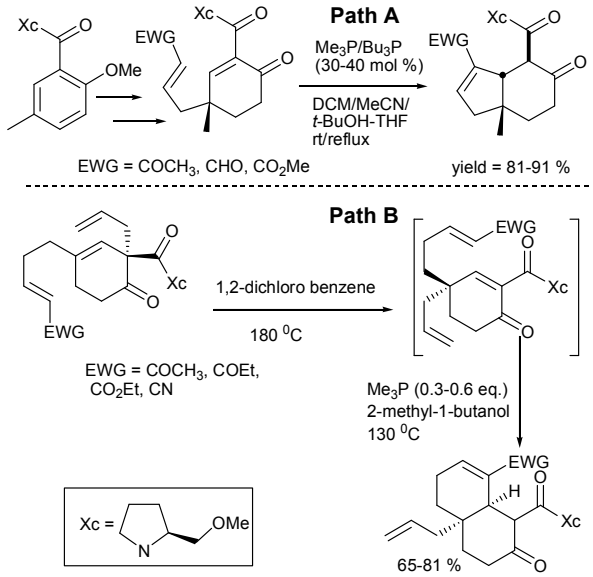


Scheme 37.

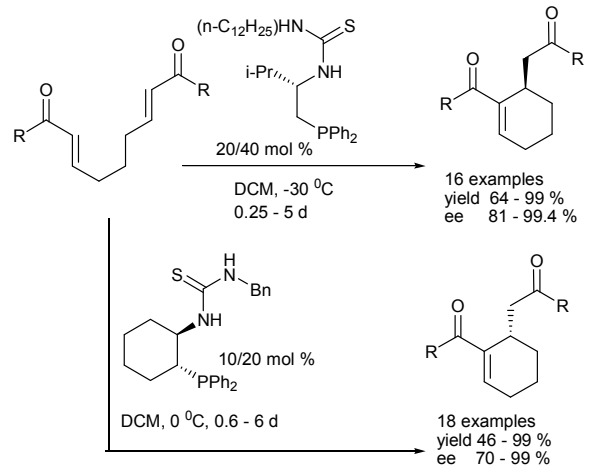
Further in an interesting piece of enamine catalysis[48] Boland and co-workers (Scheme 37) identified two different modes of cyclisations for synthesis of chrysomelidial between members of genus Gastrophysa. Using deuterated precursor authors found selective loss of deuterium from two different positions (either from methylene or methyl) suggesting formation of two different dienamines (transoid and cisoid respectively).
Use of chiral auxiliary in distereoselective IRC reaction was carried out by Malachowski and co-workers (Scheme 38). Initially (path A)[49a] they generated the precursor by Birch cope sequence and cross metathesis. This was subsequently transformed to bicarbocyclic skeleton *via* IRC pathway under the influence of Me_3P/Bu_3P. Latter (path B)[49b] they developed one pot domino sequence of Cope and IRC reactions for synthesis of decalin system. Interestingly although in both cases ring double bond was doubly activated, still it acted as terminal acceptor for enolate.

Wu and co-workers after successful demonstration of thiourea based catalysis in asymmetric IMBH (see scheme 21), further developed asymmetric IRC reaction of symmetrical bis enones and achieved excellent level of selectivities and yields (Scheme 39).[50] The two approaches for IRC using two different catalysts were complementary to each other in delivering opposite enantiomers.

Subsequently Zhang and Shi[51] utilized highly nucleophilic chiral phosphanes for asymmetric IRC and demonstrated the utility of catalyst for synthesis of both cyclohexene and cyclopentene scaffolds (Scheme 40).

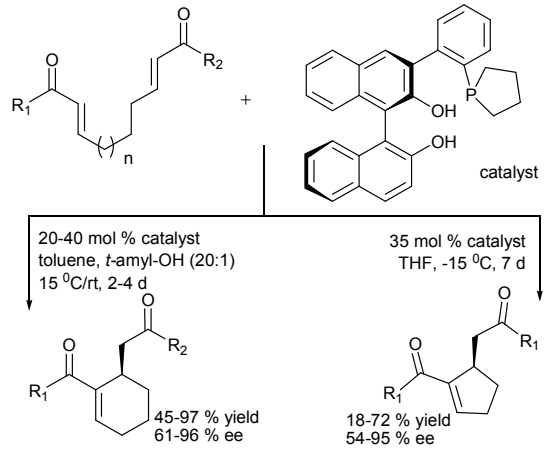


Scheme 38.

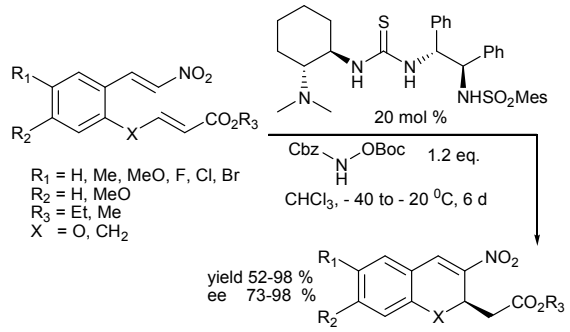


Scheme 39.

Xiao and co-workers have developed an asymmetric intramolecular crossed IRC reaction utilizing cooperative dual catalytic strategy (Scheme 41).[52] Reaction was completely chemoselective, with nitro alkene serving as initial Michael acceptor. Further they carried out



Scheme 40.

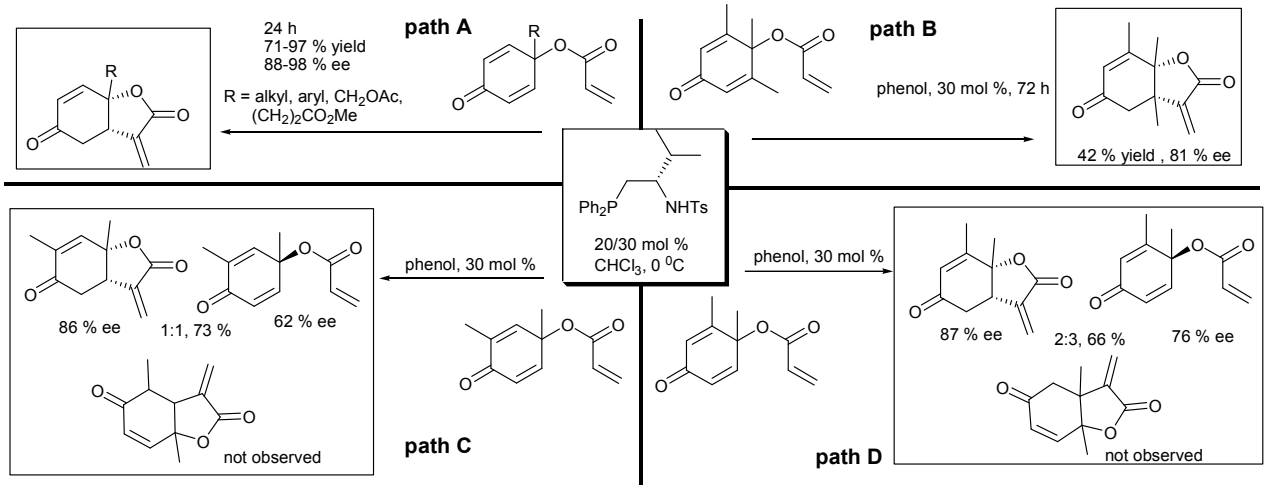


Scheme 41.

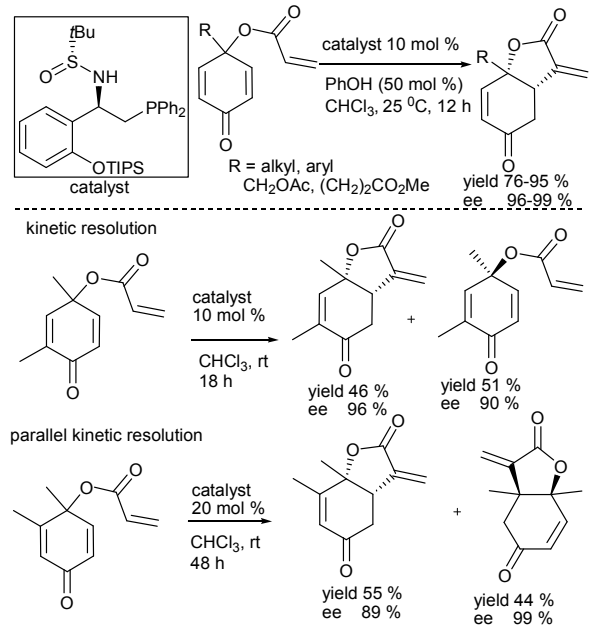
computational study which indicated that stereoselectivity was determined by intramolecular Michael addition and rate determining step of reaction was retro aza Michael addition step. Absolute configuration was found to be *R* which was in good agreement with their computational study.

In one of its kind of studies asymmetric desymetrization of symmetrical dienone was carried out by Sasai and co-workers (Scheme 42) using chiral acid/base organocatalysts, which resulted in the asymmetric synthesis of widely, occurring α methylene lactone skeleton (path A).[53] Protocol was applicable in constructing vicinal quaternary chiral centers (path B). They also investigated unsymmetrical substances and found that cyclization occured regioselectively at di substituted alkene and also led to resolution of racemic mixture (path C & D).

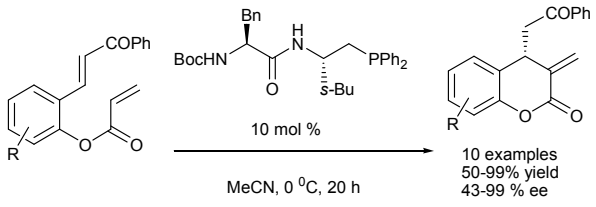
Subsequently Zhang and co-workers utilized above reaction as a template for testing the efficiency of a library of catalysts, which they were able to synthesize easily form commercially available *t*-butylsulfinamide (Scheme 43).[54] They also demonstrated the efficiency of selected catalysts on various substrates for IRC reaction. As an advantage catalyst was applicable for kinetic and parallel kinetic resolution too.



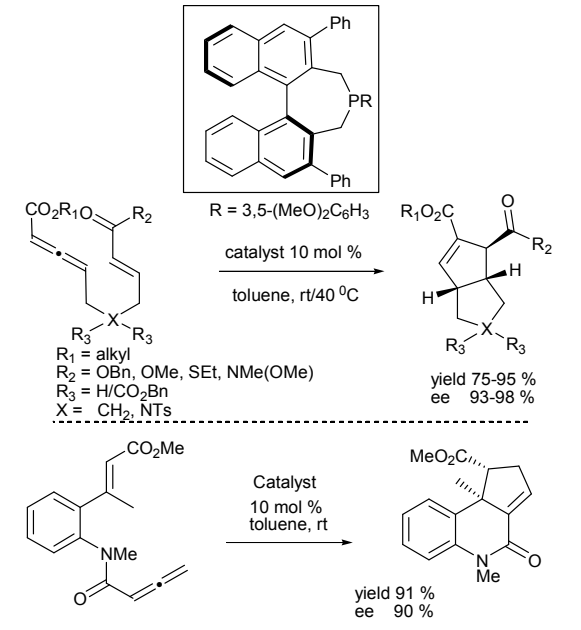
Scheme 42.



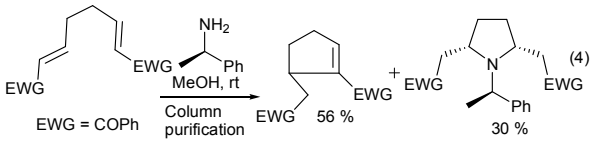
Scheme 43.



Scheme 44.



Scheme 45.



Spring and co-workers successfully demonstrated the use of salicaldehyde derived precursor for enantioselective IRC reaction (Scheme 44).[55] They used a peptide catalyst which was accessible in only 4 steps and delivered the product in high yields and high ee in most of the cases. Intramolecular Michael addition was proposed to be rate determining

step. Previously *O*-acryl Salicaldehyde derived substrate was used by Drewes also for IMBH reaction, but DABCO salt as major product was isolated (see scheme 1).

Building on the earlier reports by Krische and Kwon (see schemes 31&33), Fu and co-workers have carried out asymmetric stereo convergent intramolecular annulations using phosphepine catalyst for the synthesis of skeletons like diquinane, quinoline-2-one and others (Scheme 45).[56] Protocol was stereoconvergent as racemic allenes were converted to single stereoisomer. Mechanistic studies revealed β addition of phoshpepine to the allene to be turn over-limiting step of cycle.

During the course of their study for the synthesis of pyrrolidine alkaloids (eq 4),[57] Joseph and co-workers discovered the unusual primary amine cataylsed IRC reaction of bisenone. Tertiary amines have been the preferred choice of catalysis as they readily eliminate out from intermediate. This one thus happened to be an exception.

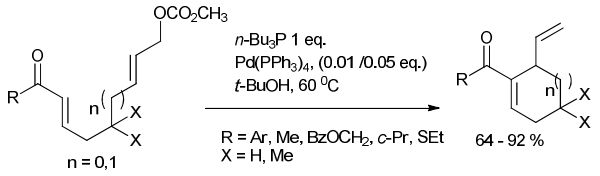
For other examples of asymmetric IRC see scheme 20.

5. Non conventional electrophiles

5.1 Leaving groups and metal complex

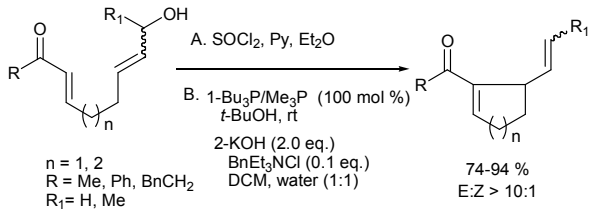
MBH reaction is basically a mild chemistry which involves π electrons where initial attack of catalyst occurs across π bond and gets terminated on another π bond. These bonds are relatively weaker in nature. Contrary σ bonds are stronger and difficult to break under normal conditions. Thus development of MBH reaction using electrophille with σ bond has been a challenge. This synthetic problem has been addressed in intramolecular fashion.

Krische and co-workers developed a fine combination of organo and metal catalysis for carbocycle generation via allylic substitution by tethered enone (Scheme 46).[58] Phosphine generated enolate was successfully trapped by Pd activated allyl carbonate (a combination of Morita Baylis Hillman and Trost-Tsuji reaction). Carbonate were found to be better electrophile over acetate, as it was proposed that liberated methoxide anion would help in final elimination of phosphines.

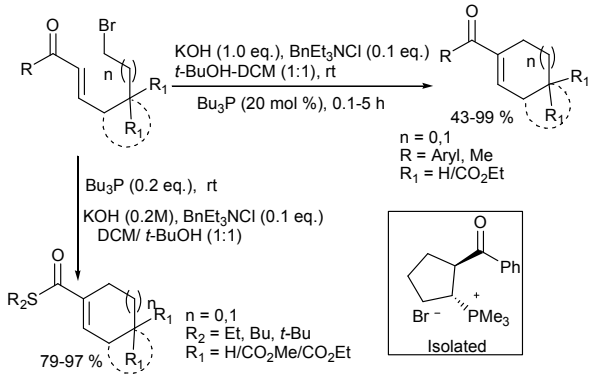


Scheme 46.

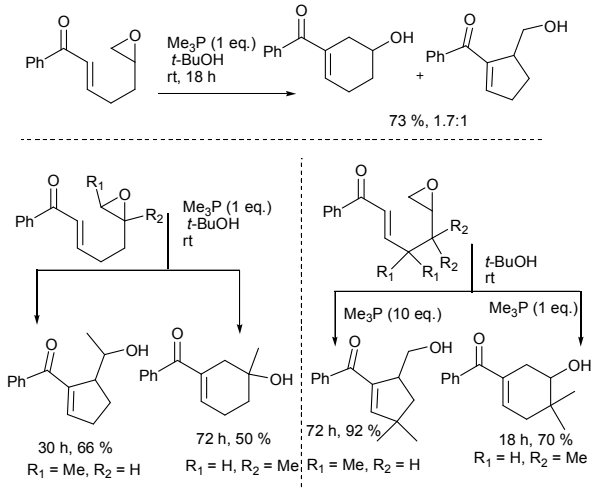
Further developments came from the laboratory of M. E. Krafft[59] where authors through a series of publications revealed a wide range of electrophiles like allylic chloride, bromide and epoxide in metal free conditions, for successful ring closure reaction. Initially subjecting isomeric mixture of allylic chlorides,[59a] to Bu_3P/Me_3P, both 5 and 6 membered rings were generated having mono and disubstitued exocyclic double bond (Scheme 47).



Scheme 47.



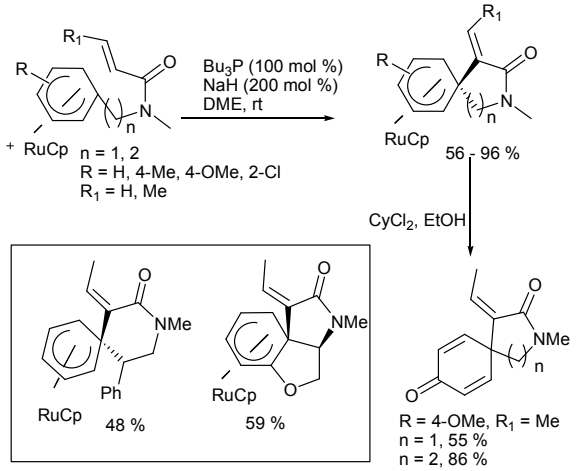
Scheme 48.



Scheme 49.

Assistance of base was required under phase transfer catalysis. Further, moving on to more challenging substrate they carried out nucleophilic displacement of non allylic alkyl bromide[59b-e] and were successful in applying it for the synthesis of mono and bicyclic products (Scheme 48). Bromide turned out to be a better choice then iodide which led to formation of phosphonium salt in control experiment. With the help of control experiments and NMR studies they were able to ascertain the corresponding roles of phosphine as nucleophile and base for elimination in IMBH reaction. Ultimate proof was obtained when they could isolate proposed salt[59d] as reaction intermediate

whose X-ray analysis revealed it to be cyclized product, resulting from displacement of bromide by generated enolate. The acyl and phpsphonium groups were found to be trans to each other.[59d,60] Subsequently Kraft utilized epoxide[59f] as another electrophile (Scheme 49) and Me_3P mediated cyclization via epoxide ring opening gave densely substituted carbocycle. Reaction was carried out without assistance of any base for elimination of phosphine. Unsubstituted epoxide gave a mixture of 5, and 6 memebered ring depending upon exo or endo mode of ring opening. However substitution at epoxide ring or gem dimethyl substitution on chain gave high selectivity.

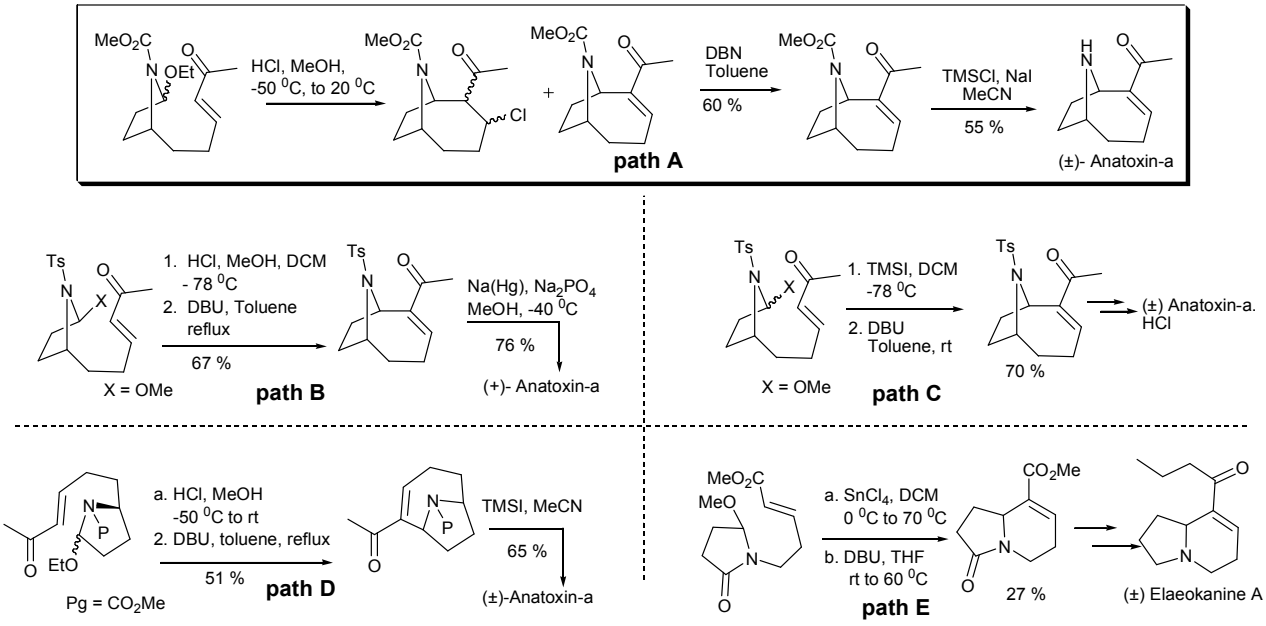


Scheme 50.

Discovering a very new source of electrophile (Scheme 50) Pigge et al. have utilized reactive ruthenium-arene complex as electrophile for trapping of enolate generated from acrylamide which are less rective in MBH chemistry.[61] The protocol delivered spiro product from which, ruthenium could be cleaved giving valuable spiro lactams. Protocol was subsequently extended for synthesis of various other bicyclic and tricyclic lactum. Few examples are shown.

5.2 Iminium ion as electrophile

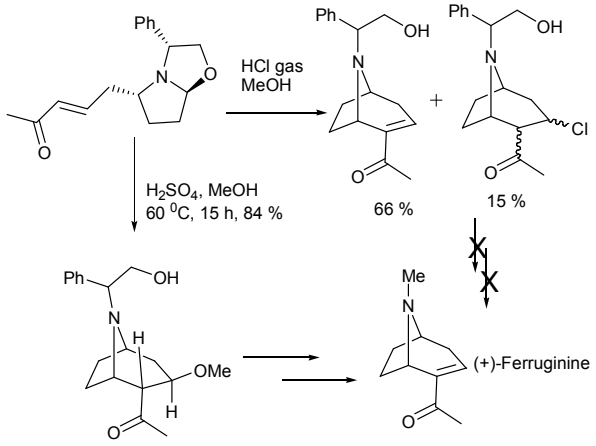
Hemiaminals have been used as a source for insitu generation of iminium ions under acidic conditions and have been subsequently trapped by tethered enolate. In an early study Speckamp and co-workers (Scheme 51) utilized intramolecular type MBH reaction using N-acyl imminium ion as electrophile.[62a] Treatment of precursor with HCl at -50 ^{0}C followed by gradual increase of temperature to 20 ^{0}C gave inseparable mixture of required IMBH adduct along with non eliminated chloride in 11 % and 47% yields respectively (determined by ^{1}HNMR) (path A). However refluxing the mixture with DBN in toluene led to elimination and gave pure enone. IMBH adduct was converted to (±)-Anatoxin-a. Similar approaches have been made by Somfai and Åhman[62b] (path B) for synthesis of (+)-Anatoxin-a and Stockman and co-workers for (±)-Anatoxin-a hydrochloride salt (path C).[62c,d] Tanner & coworker also attempted asymmetric total synthesis of Anatoxin-a (path D).[62e] However during the course of cylcization, complete racemisation was observed.



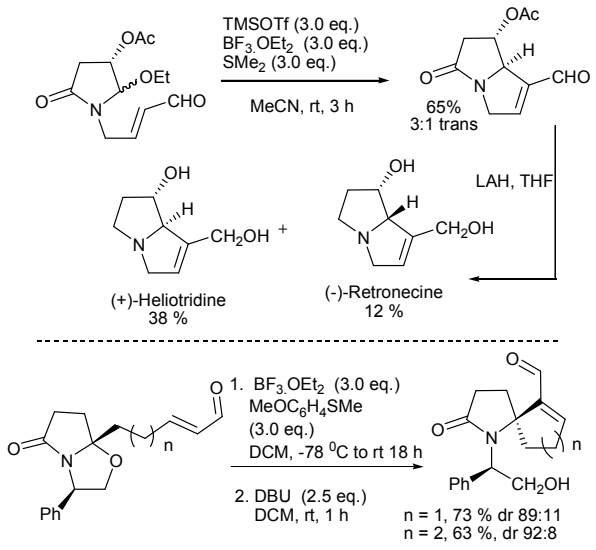
Scheme 51.

Latter Taber et al.[62f] utilized $SnCl_4$, DBU mediated ring closure of tethered acrylate with iminium ion towards synthesis of (±)-Elaeokanine A (path E). Iminium ions strategy was further applied for the synthesis of (+)-Ferruginine[63] (Scheme 52) by Husson and co-workers. Initially they used HCl mediated cyclization. However when they were unable to convert cyclized product to required target, they changed the protocol and used H_2SO_4 in MeOH to generate cyclized product as a single isomer which was eventually converted to (+) Ferruginine.

Using Lewis acid Aggarwal and co-workers[64a] (Scheme 53) developed one step IMBH reaction of N-Acyl iminium ion with a tethered enal using TMSOTf, BF_3OEt_2 and DMS. The cyclized product upon reduction gave (+) Heliotridine. They further modified and extended[64b] the application of protocol for the synthesis azaspirocycles.

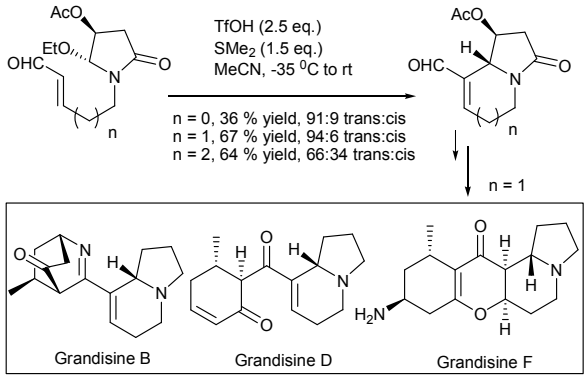


Scheme 52.

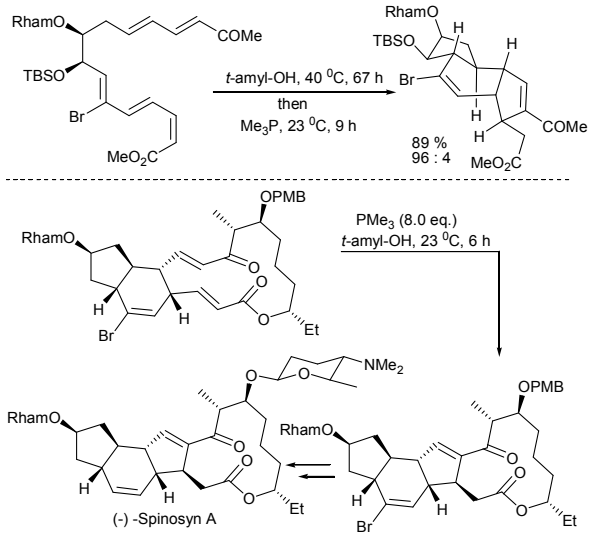


Scheme 53.

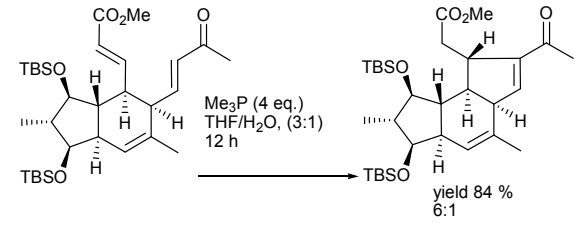
Tamura and co-workers (Scheme 54) made elegant use of iminium ions for synthesis of complex molecules such as Grandisines B, D and F.[65] The key step involved TMSOTf, Me_2S, catalyzed IMBH reaction of iminium ions which delivered the bicyclic precursor. Methodology was extendable for synthesis of 5 and 7 membered rings.



Scheme 54.



Scheme 55.



Scheme 56.

6. Applications in total synthesis

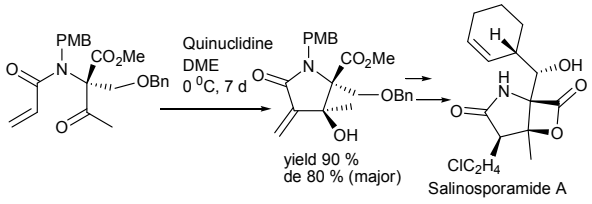
Total synthesis has always been the utmost application of any methodology. MBH reaction too has witnessed a number of reports for its application in synthesis of natural and bioactive products. Selected approaches featuring intramolecular pathways are discussed.

Roush and co-workers building upon their originally developed protocol for IRC reaction (see schemes 27 & 28) carried out its successful application for synthesis of natural products. They carried out one pot intramolecular Diels Alder and IRC reactions for the synthesis of tricyclic nucleus of Spinosyn A. The sequence generated five stereocenters with excellent selectivity.[66a] Latter they used this protocol for the synthesis of (-)-Spinosyn A[66c,d] and in their studies towards synthesis of FR 182877 (Scheme 55 & 56).[66b] Liu and co-workers also investigated enzyme mediated[66e] synthesis of Spinosyn A and found SpnF and SpnL enzymes to carry out ring closure in Diels Alder and IRC fashion respectively. Thus work of Roush was in support of their findings.

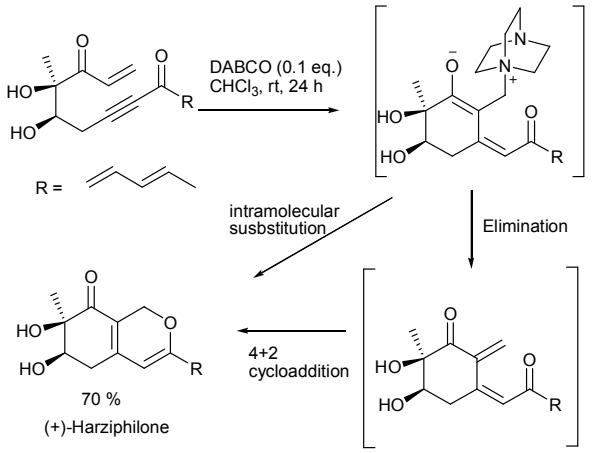
Corey and co-workers utilized IMBH as a key step during the total synthesis of Salinosporamide A (Scheme 57).[67] The reaction featured successful coupling of acrylamide with ketone, both of which happen to be sluggish reacting partners in field of MBH reactions. The product was obtained both in high yields and high de.

Sorensen and co-workers (Scheme 58) carried out DABCO catalysed cascade of reactions involving IRC and [4+2] cycloaddition/substitution on intelligently designed substrate, delivering natural product (+)-Harziphilone in 70 % yield.[68]

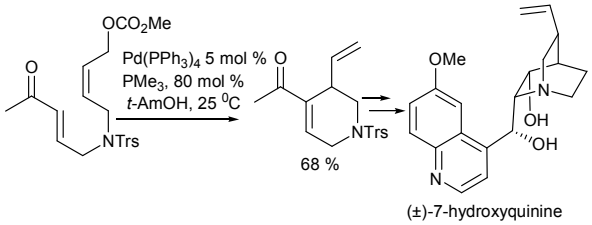
Making elegant use of their protocol using sp^3 electrophilic centre, Krische used IMBH and Tsuji-trost strategy for allylic substitution by enolate (Scheme 59 and also see scheme 46). The intermediate was used in the synthesis of (±)-7-Hydroxyquinine and formal synthesis of (±) Quinine.[69]



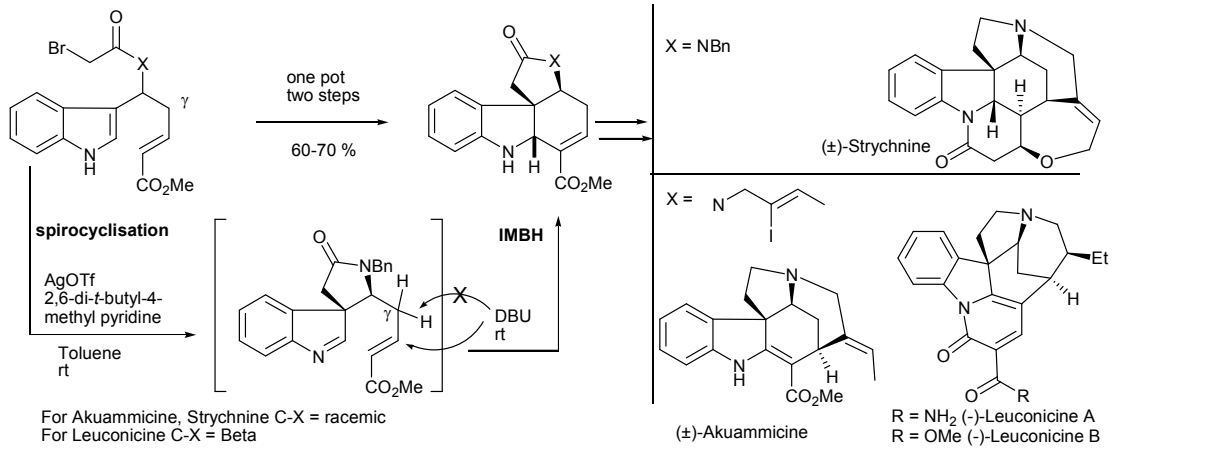
Scheme 57.



Scheme 58.

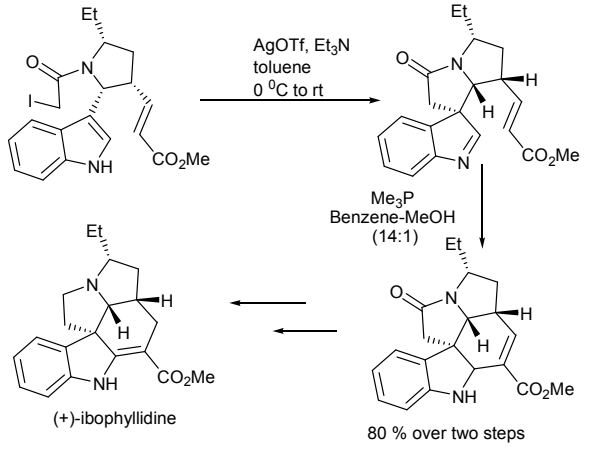


Scheme 59.



Scheme 60.

Andrade and co-workers in a series of reports[70] (Scheme 60) utilized intramolecular aza-MBH reaction for synthesis of various natural products. Towards the construction of ABCE tetracyclic framework of Strychnos alkaloids they developed one pot two consecutive key step sequences of AgOTf mediated spirocyclization followed by DBU catalyzed aza IMBH reaction.[70a] D_2O experiments strengthened the mechanism of nucleophilic attack of DBU to generate enolate rather γ-deprotonation and ring closure for the same. The application of protocol was then made[70b,c] for synthesis of complex polycyclic (±) Strychnine (±) Akuammicine and an asymmetric synthesis of (-)-Leuconicine A and B. Latter Andrews and Kwon also utilized spiro cyclisation and aza IMBH for the synthesis of (+)-ibophyllidine (Scheme 61).[71]



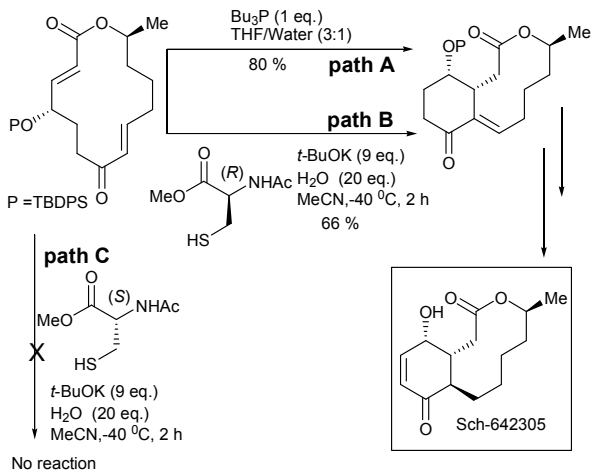
Scheme 61.

In their studies for total synthesis of Sch-642305 Miller and co-workers (Scheme 62)[72] carried out tributyl phosphine mediated IRC (path A) to obtain ring contracted product. In their quest to examine biomimetic pathways they investigated chiral cysteine based approach and found that only *R* isomer of catalyst was able to catalyse the reaction in 66 % yield (path B) while *S* enantiomer didn't give any product (path C) which could be attributed to principle of match and mismatch.

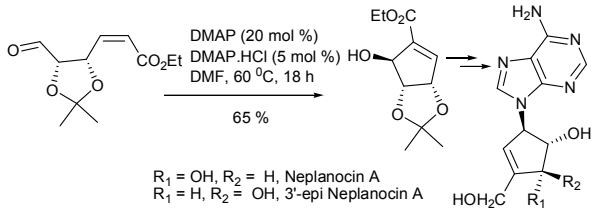
Tam and co-workers (Scheme 63) carried out DMAP catalysed distereoselective IMBH using substituted acrylate as activated alkene with *Z* configuration.[73] Interestingly corresponding *E* isomer failed to deliver cyclized product under optimized conditions. The cyclized precursor was latter used for synthesis of Neplanocin A and its 3'-epimer.

Li and co-workers used IRC type reaction for synthesis of 6,7,9,10- tetradehydroasteriscanolide. Their strategy relied on initial trans annulation by dual Michael addition followed by $BF_3.OEt_2$ mediated elimination of methanol (Scheme 64). [74]

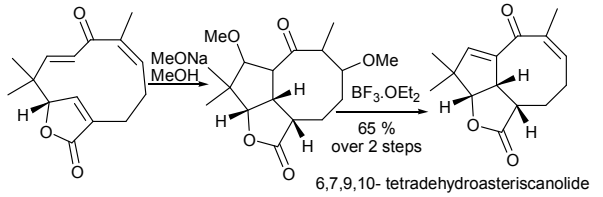
For other examples of total synthesis see schemes 26, 31, 36, 51-54.



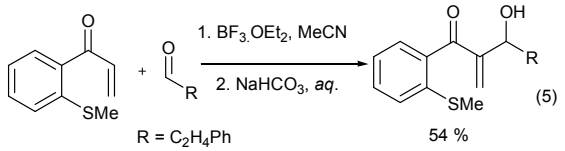
Scheme 62.



Scheme 63.



Scheme 64.



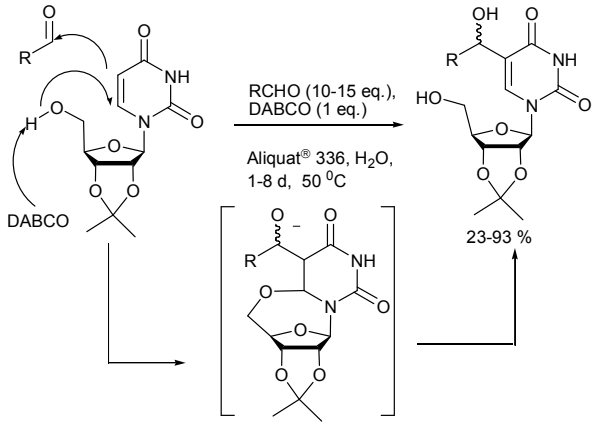
7. Miscellaneous reports

This section covers selected reports from literature, which are non conventional in IMBH reaction, but are interesting and give further understanding and application of reaction.

7.1 Internal nucleophile

Although IMBH reaction makes use of alkene and an elctrophile as part of the same molecular skeleton, there have been reports where an internal nucleophile has been used to promote reaction.

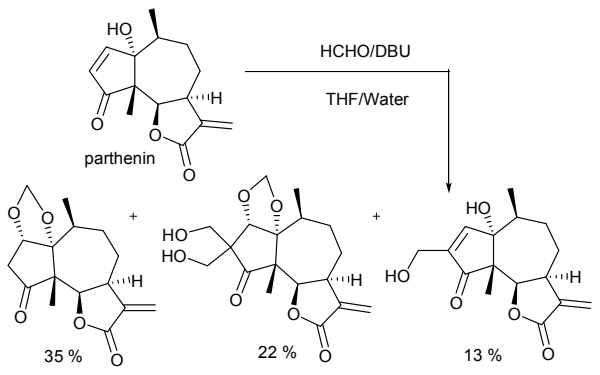
Kataoka et al. (eq 5)[75] utilized Lewis acid activation and facilitation by internal nucleophile (sulfur/selenium) for MBH reaction.



Scheme 65.

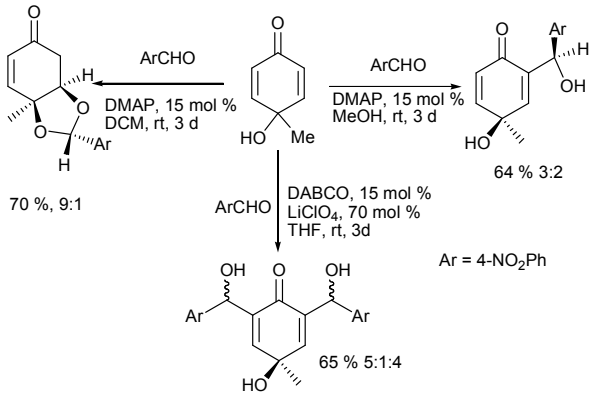
Hirota and co-workers carried out systematic investigation of MBH reaction on 5-position of uridine ring and showed its application to various aldehydes (Scheme 65).[76] They found the role of free hydroxyl group in assisting the reaction. Similar other uridine substrate with protected hydroxy/deoxy/unconstrained ring failed to give any MBH reaction. Reaction was also feasible using inorganic bases such as KOH. Clivio also investigated similar thio version and found role of sulphur for MBH reaction (eq 6).[77]

Taneja and co-workers[78] carried out MBH reaction of Parthenin (a sesquiterpene) and obtained a mixture of products featuring 1,3 dioxolane moiety which suggested key role of tertiary alcohol during the course of reaction. An example is presented in scheme 66.

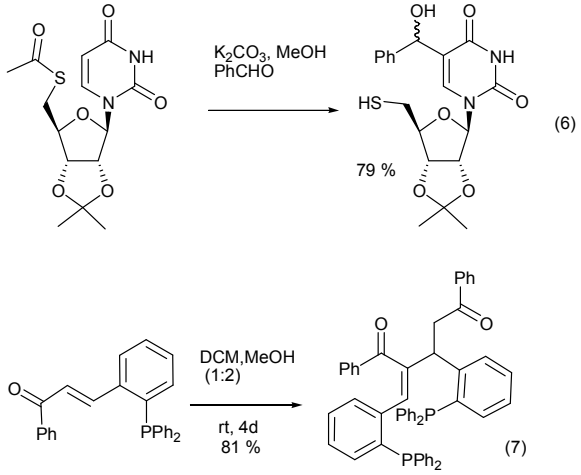


Scheme 66.

Carreño and co-workers investigated MBH reaction of *p*-Quinols, and obtained different products such as acetal, mono and di MBH adducts under different conditions (Scheme 67).[79] Role of hydroxyl moiety was validated by several control experiments. MBH reaction was faster while using non nucleophilic bases such as K_2CO_3 or Cs_2CO_3.



Scheme 67.



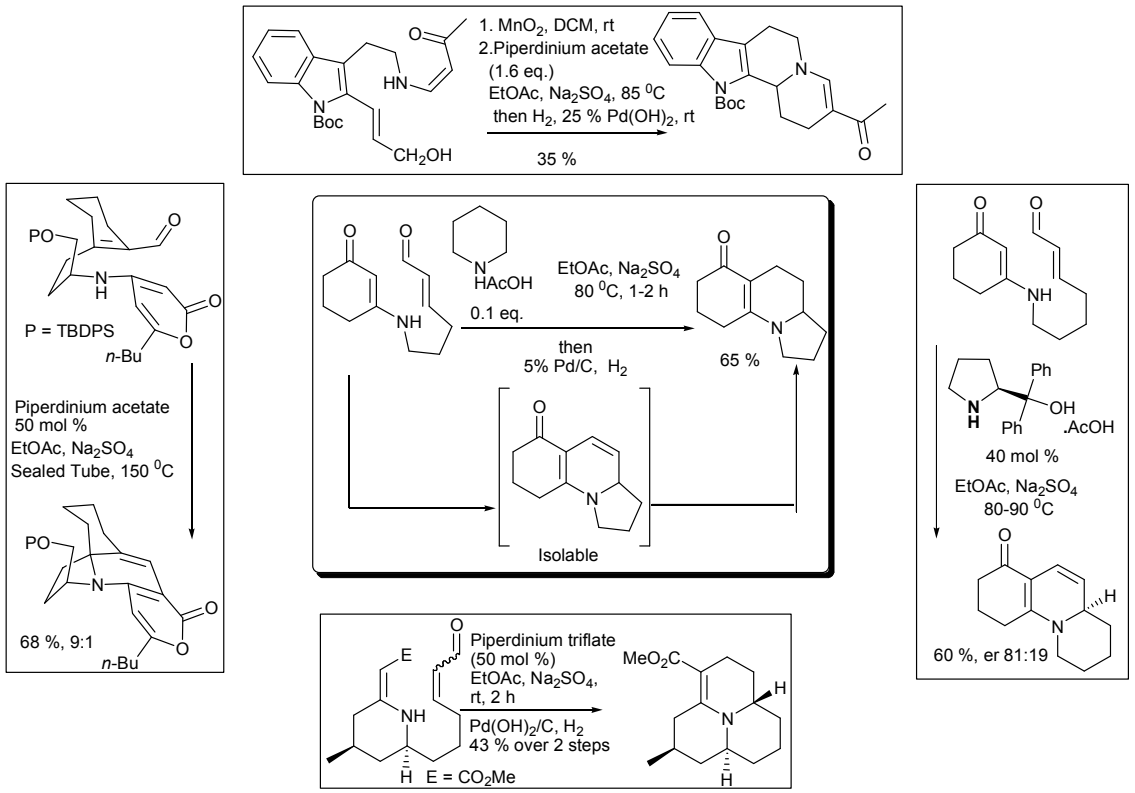
Further corresponding *p*-quinol methyl ether failed to undergo MBH reaction along with recovery of starting material.

In an example Lei (eq 7) and co-workers reported MBH reaction with no external assistance. The dimer of enone just crystallized out from a solution of enone in DCM and MeOH.[80]

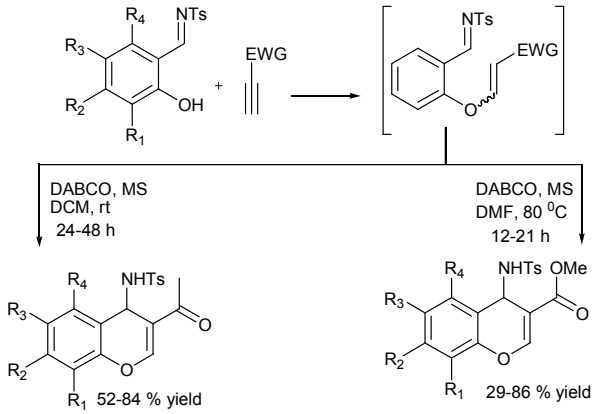
7.2 Cycloaddition approaches

Hsung and co-workers have developed successfully aza [3+3] annulations which also resemble to IMBH reaction.[81] After establishing the protocol they have developed many successful variants of the methodology. These protocols were also used for the synthesis of natural products. The concept has been highlighted by a few examples presented in scheme 68.

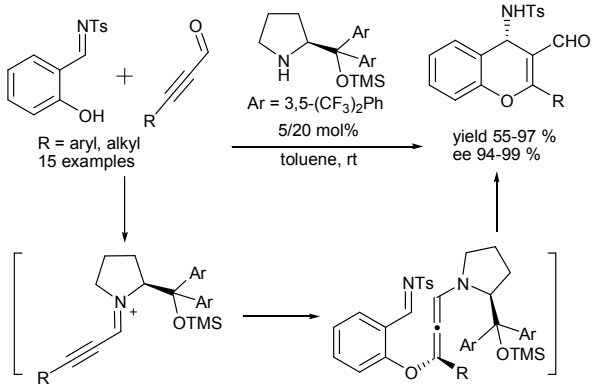
Y.-L. Shi and M. Shi carried out reaction between salicyl N-tosylimines with But-3-yn-2-one and Methyl propiolate to generate substituted chromenes (Scheme 69).[82] Of the different reaction pathways possible, NMR studies revealed the reaction to be going through initial Michael addition followed by IMBH reaction which was also suggested to be rate determining step.



Scheme 68.

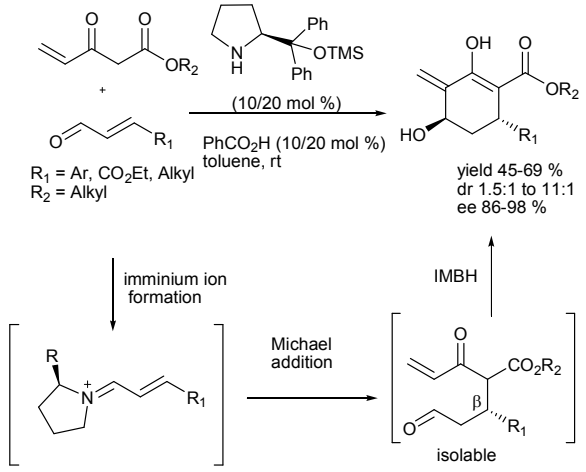


Scheme 69.



Scheme 70.

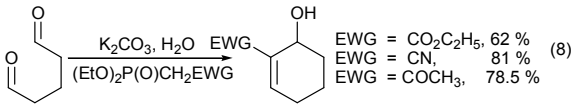
Alemán et al. utilized iminium ion approach to carry out asymmetric domino sequence of oxa Michael addition followed by intramolecular aza MBH reaction to deliver 4-amino-4H-chromene in high optical purity (Scheme 70).[83] Jørgensen and co-workers developed an interesting reaction of tandem catalysis (Scheme 71).[84] Starting from substituted acrolein and Nazarov reagent they carried out a cascade of reactions (Michael addition and IMBH reaction) to synthesize densely substituted carbocycle ring in high enantioselectivity. They proposed mechanism to be going through intermediate formed as a result of Michael addition which then underwent IMBH reaction. Cooling the reaction to 4 ^{0}C they were able to isolate the intermediate and further studies on intermediate revealed that enantioselectivty for IMBH reaction was dependent only on stereochemistry of β- position of aldehyde formed after Michael addition and remained uniform even after use of achiral catalyst on the isolated intermediate.



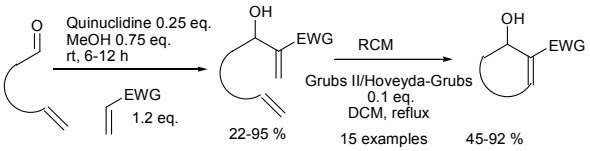
Scheme 71.

7.3 Other approaches

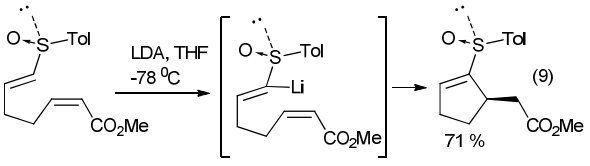
In a very early report (eq 8) Villieras et al. reported synthesis of cyclic IMBH alcohol, although in a non MBH pathway, using a domino sequence of Wittig and Aldol on dialdehyde.[85] In fact it has been method of choice for quick access to cyclic MBH adduct and its application.[86]



In another approach (Scheme 72) Krafft and co-workers carried out intermolecular MBH reaction of alkene tethered aldehyde followed by RCM which gave cyclic MBH adduct.[87] Reaction was applicable for the synthesis of variety of substrates including bicyclic and hetrocyclic adducts.



Scheme 72.



Tanaka and co-workers applied Michael addition of α-lithiated vinyl sulfoxides to enoate to synthesize IRC product (eq 9). (*Z*)-enoate gave better selectivity whereas (*E*)-enoate resulted in poor diasetreoselectivity. An example is presented.[88]

Conclusion and Future Projections

IMBH and IRC reactions have radiated out in several directions and continue to do so. The reaction has been tested continuously with the design of new substrates and use of new catalysts, with successful endeavours every time. Sustaining for almost 3 decades, itself adds testimony to the credit of reaction. During the period it has witnessed development of several alkenes, electrophiles and catalysts which has led to synthesis of several carbocycles and heterocycles both in achiral and chiral fashion. With so much work and discoveries in IMBH and IRC reaction, still there is plethora of opportunities and challenges which remain to be unfolded. IMBH and IRC have mostly witnessed enone as initial Michael acceptor, where as reports for other acryl systems and their asymmetric versions have been rather sporadic. Commonly used activated alkenes for IMBH and IRC reaction are mono or di substituted at double bond. Use of tri and tetra substituted is challenging and would add complexity and add additional functionalities to end product. This would also generate gateways for construction of quaternary stereocenters. Use of ketones and ketimines as electrophiles would also contribute towards this end. With the inflow of superior catalysts, asymmetric version offers many opportunities. Several chiral phosphines have been used for the reaction; however use of chiral tertiary nitrogen sources capable of achieving high selectivity needs to be developed. Use of lewis acids has been limited and their successful widely applicable use could be another milestone especially in the field of chiral versions. Synthesis of medium rings and larger rings by IMBH and IRC pathway is another unexplored area which would require extensive standardization to prevent intermolecular reaction over intramolecular. Domino/multiple IMBH and IRC still remains to be explored although individually they have been clubbed with other name reactions in domino fashion. Further the application of these IMBH derived adduct has not yet picked up. With so many functionalities embedded around a periphery, many synthetic manipulations can be tried for synthesis of complex molecules. Asymmetric substitution like that of intermolecular MBH derived adduct has to be explored as it opens the opportunity for optically active cyclic carbo/hetrocycles.

Acknowledgment

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References

1 (*a*) K. Morita, Japan Patent 6803364, 1968; *Chem. Abstr*., 1968, **69**, 58828s; (*b*) K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn*., 1968, **41**, 2815; (*c*) A. B. Baylis and

M. E. D. Hillman, German Patent, 2155113, 1972; *Chem. Abstr*., 1972, **77**, 34174q.
2 M. M. Rauhut and H. Currier, U. S. Patent, 1963, 3,074,999; [*Chem. Abstr*., 1963, **58**, 11224a].
3 For systematic discussion of literature till 2008 see (*a*) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447; (*b*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811; (*c*) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron,* 1996, **52**, 8001.
4 For excellent reviews on MBH see (*a*) P. Xie and Y. Huang, *Org. Biomol. Chem*., 2015, **13**, 8578; (*b*) Y. Wei and M. Shi, Chem. Rev., 2013, 113, 6659; (*c*) R. Rios, *Catal. Sci. Technol*., 2012, **2**, 267; (*d*) T.-Y. Liu, M. Xie and Y.-C. Chen, *Chem. Soc. Rev*., 2012, **41**, 4101; (*e*) V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev*., 2009, **109**, 1; (*f*) V. Singh and S. Batra, *Tetrahedron*, 2008, **64**, 4511; (*g*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem. Int. Ed*., 2007, **46**, 4614.
5 For excellent reviews on RC see (*a*) P. Xie and Y. Huang, *Eur. J. Org. Chem.* 2013, 6213; (*b*) C. E. Aroyan, A. Dermenci and S. J. Miller, *Tetrahedron*, 2009, **65**, 4069.
6 *(a)* X. Dong, L. Liang, E. Li and Y. Huang, *Angew. Chem. Int. Ed*., 2015, **54**, 1621; *(b*) R. M. Singh, K. C. Bharadwaj and D. K. Tiwari, *Beilstein J. Org. Chem.,* 2014**, 10**, 2975; (c) Y. Ma, G. Zhang, J. Zhang, D. Yang and R. Wang, *Org. Lett*., 2014, **16**, 5358; *(d*) A. Gradillas, E. Belmonte, R. F. da Silva and J. Pérez-Castells, *Eur. J. Org. Chem.,* 2014, 1935; *(e*) R. Zhou, J. Wang, J. Yu and Z. He, *J. Org. Chem*., 2013, **78**, 10596; *(f*) R. Kumar, T. Kumar, S. M. Mobin and I. N. N. Nambothiri, *J. Org. Chem*., 2013, **78**, 5073; *(g*) X.-J. Wu, X.-P. Xu, X.-M. Su, G. Chen, Y. Zhang and S.-J. Ji, *Eur. J. Org. Chem.,* 2009, 4963.
7 (*a*) Z. Dong, C. Yan, Y. Gao, C. Dong, G. Qiu and H.-B. Zhou, *Adv. Synth. Catal*., 2015, **357**, 2132; (*b*) L. Yao and C.-J. Wang, *Adv. Synth. Catal*., 2015, **357**, 384; (*c*) T. Milcent, J. Hao, K. Kawada, V. A. Soloshonok, S. Ongeri and B. Crousse, *Eur. J. Org. Chem*., 2014, 3072; (*d*) A. Lin, J. Wang, H. Mao, Y. Shi, Z. Mao and C. Zhu, *Eur. J. Org. Chem*., 2013, 6241; (*e*) Q.-L. Wang, L. Peng, F.-Y. Wang, M.-L. Zhang, L.-N. Jia, F. Tian, X.-Y. Xu and L.-X. Wang, *Chem. Commun*., 2013, **49**, 9422; (*f*) Z. Duan, Z. Zhang, P. Qian, J. Han and Y. Pan, *RSC Adv.*, 2013, **3**, 10127.
8 (*a*) D. Basavaiah, S. Pal, G. Veeraraghavaiah and K. C. Bharadwaj, *Tetrahedron*, 2015, **71**, 4659; (*b*) K. H. Kim, H. R. Moon, J. Lee, J. Kim and J. N. Kim, *Adv. Synth. Catal*., 2015, **357**, 1532; (*c*) F. Wei, H.-Y. Huang, N.-J. Zhong, C.-L. Gu, D. Wang and L. Liu, *Org. Lett*., 2015, **17**, 1688; (*d*) K. Yadav and L. D. S. Yadav, *Synlett*, 2015, **26**, 1026; (*e*) B. V. M. Teodoro, J. T. M. Correia and F. Coelho, *J. Org. Chem*., 2015, **80**, 2529; (*f*) M. Bakthadoss, D. Kannan, J. Srinivasan and V. Vinayagam, *Org. Biomol. Chem*., 2015, **13**, 2870; (*g*) C. R. Reddy, P. Kumaraswamy and K. K. Singarapu, *J. Org. Chem.*, 2014, **79**, 7880; (*h*) S. Madhavan, P. Shanmugam and R. L. Varma, *RSC Adv*., 2014, **4**, 26211; (*i*) D. T. Sreedharan and D. L. J. Clive, *Org. Biomol. Chem*., 2013, **11**, 3128; (*j*) L. Zhang, H. Yu, Z. Yang, H. Liu, Z. Li, J. Guo, Y. Xiao and H. Guo, *Org. Biomol. Chem*., 2013, **11**, 8235.
9 (*a*) A. Ilangovan and S. Saravanakumar, *Beilstein J. Org. Chem.*, 2014, **10**, 127; (*b*) S. Bhowmik and S. Batra, *Eur. J. Org. Chem.*, 2013, 7145; (*c*) P. R. Krishna, M. Alivelu and T. P. Rao, *Eur. J. Org. Chem.*, 2012, 616.
10 (*a*) R. E. Plata and D. A. Singleton, *J. Am. Chem. Soc*., 2015, **137**, 3811; (*b*) P. Verma, P. Verma and R. B. Sunoj, *Org. Biomol. Chem*., 2014, **12**, 2176.
11 S. E. Drewes, O. L. Njamela, N. D. Emslie, N. Ramesar and J. S. Field, *Synth. Commun*., 1993, **23**, 2807.
12 (*a*) G. P. Black, F. Dinon, S. Fratucello, P. J. Murphy, M. Nielsen, H. L. Williams and N. D. A. Walshe, *Tetrahedron Lett*., 1997, **38,** 8561; (*b*) F. Dinon, E. Richards, P. J. Murphy, D. E. Hibbs, M. B. Hursthouse and K. M. A. Malik, *Tetrahedron Lett*., 1999, **40**, 3279; (*c*) E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich and M. B. Hursthouse, *Tetrahedron*, 2001, **57**, 7771.
13 K. Yagi, T. Turitani, H. Shinokubo and K. Oshima, *Org. Lett*., 2002, **4**, 3111.
14 (*a*) B. Ressault, A. Jaunet, P. Geoffroy, S. Goudedranche and M. Miesch, *Org. Lett*., 2012, **14**, 366; (*b*) Y. Wang, A. Jaunet, P. Geoffroy and M. Miesch, *Org. Lett*., 2013, **15**, 6198.
15 G. E. Keck and D. S. Welch, *Org. Lett*., 2002, **4**, 3687.
16 J. E. Yeo, X. Yang, H. J. Kim and S. Koo, *Chem. Commun*., 2004, 236.
17 W.-D. Teng, R. Huang, C. K.-W. Kwong, M. Shi and P. H. Toy, *J. Org. Chem*., 2006, **71**, 368.
18 V. V. Trifonov, V. I. Goncharov and A. V. Aksenov, *Chem. Hetrocycl. Compd.*, 2006, **42**, 955.
19 D. Yin, W. Wang, Y. Peng, Z. Ge, T. Cheng, X. Wang and R. Li, *RSC Adv*., 2014, **5**, 17296.
20 C. K.-W. Kwong, R. Huang, M. Zhang, M. Shi and P. H. Toy, *Chem. Eur. J*., 2007, **13**, 2369.
21 F. O. Seidel and J. A. Gladysz, *Adv. Synth. Catal*., 2008, **350**, 2443.
22 (*a*) M. Ghandi, A. H. Bozcheloei, S. H. Nazari and M. Sadeghzadeh, *J. Org. Chem*., 2011, **76**, 9975; (*b*) M. Ghandi, S. Feizi, F. Ziaie and B. Notash, *Tetrahedron*, 2014, **70**, 2563.
23 K. Tong, J. Tu, X. Qi, M. Wang, Y. Wang, H. Fu, C. U. Pittman and A. Zhou, *Tetrahedron*, 2013, **69**, 2369.
24 P. S. Selig and S. J. Miller, *Tetrahedron Lett*., 2011, **52**, 2148.
25 (*a*) D. Basavaiah, G. C. Reddy and K. C. Bharadwaj, *Eur. J. Org. Chem.,* 2014, 1157; (*b*) D. Basavaiah, G. C. Reddy and K. C. Bharadwaj, *Tetrahedron*, 2014, **70**, 7991.
26 H. Mandai, K. Shimowaki, K. Mitsudo and S. Suga, *Asian J. Org. Chem*., 2014, **3**, 437.
27 F. Roth, P. Gygax and G. Fráter, *Tetrahedron Lett*., 1992, **33**, 1045.
28 C. E. Aroyan, M. M. Vasbinder and S. J. Miller, *Org. Lett*., 2005, **7**, 3849.
29 (*a*) S.-H. Chen, B.-C. Hong, C.-F. Su and S. Sarshar, *Tetrahedron Lett*., 2005, **46**, 8899; (*b*) F. J. S. Duarte, E. J. Cabrita, G. Frenking and A. G. Santos, *Chem. Eur. J*., 2009, **15**, 1734.
30 F. Seidel and J. A. Gladysz, *Synlett*, 2007, 986.
31 X. Zhang, P. Ma, D. Zhang, Y. Lei, S. Zhang, R. Jiang and W. Chen, *Org. Biomol. Chem*., 2014, **12**, 2423.
32 (*a*) J.-J. Gong, K. Yuan, H.-L. Song and X.-Y. Wu, *Tetrahedron*, 2010, **66**, 2439; (*b*) K. Yuan, H.-L. Song, Y. Hu, J.-F. Fang and X.-Y. Wu, *Tetrahedron: Asymmetry*, 2010, **21**, 903; (*c*) H.-L. Song, K. Yuan and X.-Y. Wu, *Chem. Commun*., 2011, **47**, 1012.
33 K. Akagawa, S. Sakamoto and K. Kudo, *Synlett*, 2011, 817.
34 P. R. Krishna, V. Kannan and G. V. M. Sharma, *J. Org. Chem*., 2004, **69**, 6467.
35 (*a*) A. Zhou and P. R. Hanson, *Org. Lett*., 2008, **10**, 2951; (*b*) A. Zhou, D. Rayabarapu and P. R. Hanson, *Org. Lett*., 2009, **11**, 531.
36 M. O. Duarte, G. Stedele, M. Pazinatto, E. R. de Oliveira and V. L. Eifler-Lima, *Lett. Org. Chem.,* 2009, **6**, 90.
37 J.-K. Erguden and H. W. Moore, *Org. Lett.,* 1999, **1**, 375.
38 (*a*) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang and M. J. Krische, *J. Am. Chem. Soc.,* 2002, **124**, 2402; (*b*) K. Agapiou and M. J. Krische, *Org. Lett.,* 2003, **5**, 1737; (*c*) A. L. Luis and M. J. Krische, *Synthesis,* 2004, 2579; (*d*) F.

Zanardi, G. Appendino and G. Casiraghi, *Chemtracts*: *Org. Chem*., 2002, **15**, 490.
39 (*a*) S. A. Frank, D. J. Mergott and W. R. Roush, *J. Am. Chem. Soc.,* 2002, **124,** 2404; (*b*) I. C. Stewart, R. G. Bergman and F. D. Toste , *J. Am. Chem. Soc.,* 2003, **125**, 8696; (*c*) R. K. Thalji and W. R. Roush, *J. Am. Chem. Soc.,* 2005, **127**, 16778.
40 M. Couturier, F. Ménard, J. A. Ragan, M. Riou, E. Dauphin, B. M. Andresen, A. Ghosh, K. Dupont-Gaudet and M. Girardin, *Org. Lett*., 2004, **6**, 1857.
41 (*a*) P. M. Brown, N. Käppel and P. J. Murphy, *Tetrahedron Lett.,* 2002, **43,** 8707; (*b*) P. M. Brown, N. Käppel, P. J. Murphy, S. J. Coles and M. B. Hursthouse, *Tetrahedron,* 2007, **63**, 1100.
42 (*a*) J.-C. Wang, S.-S. Ng, and M. J. Krische, *J. Am. Chem. Soc*., 2003, **125**, 3682; (*b*) J.-C. Wang and M. J. Krische, *Angew. Chem. Int. Ed.,* 2003, **42**, 5855.
43 (*a*) L.-W. Ye, X.-L. Sun, Q.-G. Wang and Y. Tang, *Angew. Chem. Int. Ed.,* 2007, **46**, 5951; (*b*) L.-W. Ye, X. Han, X.-L. Sun and Y. Tang, *Tetrahedron*, 2008, **64**, 1487; (*c*) X. Han, L.-W. Ye, X.-L. Sun and Y. Tang, *J. Org. Chem*., 2009, **74**, 3394; (*d*) Q.-G. Wang, S.-F. Zhu, L.-W. Ye, C.-Y. Zhou, X.-L. Sun, Y. Tang and Q.-L. Zhou, *Adv. Synth. Catal*., 2010, **352**, 1914.
44 C. E. Henry and O. Kwon, *Org. Lett*., 2007, **9**, 3069.
45 J. A. MacKay, Z. C. Landis, S. E. Motika and M. H. Kench, *J. Org. Chem*., 2012, **77**, 7768.
46 (*a*) C. E. Aroyan and S. J. Miller, *J. Am. Chem. Soc.,* 2007, **129**, 256; (*b*) C. E. Aroyan, A. Dermenci and S. J. Miller, *J. Org. Chem.,* 2010, **75**, 5784; (*c*) S. Osuna, A. Dermenci, S. J. Miller and K. N. Houk, *Chem. Eur. J.,* 2013, **19**, 14245.
47 (*a*) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo and M. Christmann, *Org. Lett.,* 2009*,* **11***,* 4116; (*b*) E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs and M. Christmann, *Synthesis,* 2013, **45**, 1016.
48 M. Kunert, P. Rahfeld, K. H. Shaker, B. Schneider, A. David, K. Dettner, J. M. Pasteels and W. Boland, *ChemBioChem,* 2013, **14**, 353.
49 (*a*) Y. Qiao, S. Kumar and W. P. Malachowski, *Tetrahedron Lett.,* 2010, **51**, 2636; (*b*) T. M. Ross, S. J. Burke and W. P. Malachowski, *Tetrahedron Lett*., 2014, **55**, 4616.
50 (*a*) J.-J. Gong, T.-Z. Li, K. Pan and X.-Y. Wu, *Chem. Commun*., 2011, **47,** 1491; (*b*) X. Zhao, J.-J. Gong , K. Yuan, F. Sha and X.-Y. Wu, *Tetrahedron Lett*., 2015, **56**, 2526.
51 X.-N. Zhang and M. Shi, *Eur. J. Org. Chem.,* 2012, 6271.
52 X.-F. Wang, L. Peng, J. An, C. Li, Q.-Q. Yang, L.-Q. Lu, F.-L. Gu and W.-J. Xiao, *Chem. Eur. J*., 2011, **17,** 6484.
53 (*a*) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders and H. Sasai, *Angew. Chem., Int. Ed.*, 2012, **51**, 5423; (*b*) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, M. Suzuki, D. Enders and H. Sasai, *Tetrahedron*, 2013, **69**, 1202.
54 X. Su, W. Zhou, Y. Li and J. Zhang, *Angew. Chem. Int. Ed*., 2015, **54**, 6874.
55 R. J. H. Scanes, O. Grossmann, A. Grossmann and D. R. Spring, *Org. Lett*., 2015, **17**, 2462.
56 S. Y. Lee, Y. Fujiwara, A. Nishiguchi, M. Kalek and G. C. Fu, *J. Am. Chem. Soc*., 2015, **137**, 4587.
57 Z. Amara, E. Drège, C. Troufflard, P. Retailleau and D. Joseph, *Org. Biomol. Chem*., 2012, **10**, 7148.
58 B. G. Jellerichs, J.-R. Kong and M. J. Krische, *J. Am. Chem. Soc.*, 2003, **125**, 7758.
59 (*a*) M. E. Krafft and T. F. N. Haxell, *J. Am. Chem. Soc.*, 2005, **127**, 10168; (*b*) M. E. Krafft, K. A. Seibert, T. F. N. Haxell and C. Hirosawa, *Chem. Commun.*, 2005, 5772; (*c*) M. E. Krafft and K. A. Seibert, *Synlett*, 2006, 3334; (*d*) M. E. Krafft, T. F. N. Haxell, K. A. Seibert and K. A. Abboud, *J. Am. Chem. Soc.*, 2006, **128**, 4174; (*e*) M. E. Krafft, K. A. Seibert and T. F. N. Haxell, *Synlett*, 2010, 2583; (*f*) M. E. Krafft and J. A. Wright, *Chem. Commun.*, 2006, 2977; (*g*) J. W. Cran, M. E. Krafft, K. A. Seibert, T. F. N. Haxell, J. A. Wright, C. Hirosawa and K. A. Abboud, *Tetrahedron*, 2011, **67**, 9922.
60 L. Zhao, X. Y. Chen, S. Ye and Z. X. Wang, *J. Org. Chem*., 2011, **76**, 2733.
61 (*a*) F. C. Pigge, R. Dhanya and E. R. Hoefgen, *Angew. Chem., Int. Ed.*, 2007, **46**, 2887; (*b*) F. C. Pigge, R. Dhanya and D. C. Swenson, *Organometallics*, 2009, **28**, 3869.
62 (*a*) K. H. Melching, H. Hiemstra, W. J. Klaver and W. N. Speckamp, *Tetrahedron Lett*., 1986, **27**, 4799; (*b*) P. Somfai and J. Åhman, *Tetrahedron Lett*., 1992, **33**, 3791; (*c*) S. J. Roe and R. A. Stockman, *Chem. Commun*., 2008, 3432; (*d*) S. J. Roe, D. L. Hughes, P. Aggarwal and R. A. Stockman, *Synthesis*, 2009, 3775; (*e*) T. Hjelmgaard, I. Søtofte and D. Tanner, *J. Org. Chem*., 2005, **70,** 5688; (*f*) D. F. Taber, R. S. Hoerrner and M. D. Hagen, *J. Org. Chem*., 1991, **56**, 1287.
63 I. Gauthier, J. Royer and H.-P. Husson, *J. Org. Chem.*, 1997**, 62***,* 6704.
64 (*a*) E. L. Myers, J. G. de Vries and V. K. Aggarwal, *Angew. Chem., Int. Ed*., 2007, **46**, 1893; (*b*) J. C. Killen, J. Leonard and V. K. Aggarwal, *Synlett*, 2010, 579.
65 (*a*) H. Kurasaki, I. Okamoto, N. Morita and O. Tamura, *Org. Lett.,* 2009, **11**, 1179; (*b*) H. Kurasaki, I. Okamoto, N. Morita and O. Tamura, *Chem. Eur. J.*, 2009, **15**, 12754.
66 (*a*) D. J. Mergott, S. A. Frank and W. R. Roush, *Org. Lett.,* 2002, **4**, 3157; (*b*) J. L. Methot and W. R. Roush, *Org. Lett.,* 2003, **5**, 4223; (*c*) D. J. Mergott, S. A. Frank and W. R. Roush, *Proc. Natl. Acad. Sci. U.S.A,* 2004, **101**, 11955; (*d*) S. M. Winbush, D. J. Mergott and W. R. Roush, *J. Org. Chem.*, 2008, **73**, 1818 (*e*) H. J. Kim, M. W. Ruszczycky, S.-h. Choi, Y.-n. Liu and H.-w. Liu, *Nature*, 2011, **473**, 109.
67 L. R. Reddy, P. Saravanan and E. J. Corey, *J. Am. Chem. Soc.*, 2004, **126**, 6230.
68 L. M. Stark, K. Pekari and E. J. Sorensen, *Proc. Natl. Acad. Sci. U.S.A,* 2004, **101**, 12064.
69 P. Webber and M. J. Krische, *J. Org. Chem*., 2008, **73**, 9379.
70 (*a*) G. Sirasani and R. B. Andrade, *Org. Lett*., 2009, **11**, 2085; (*b*) G. Sirasani, T. Paul, W. Dougherty, S. Kassel and R. B. Andrade, *J. Org. Chem*., 2010, **75**, 3529; (*c*) G. Sirasani and R. B. Andrade, *Org. Lett*., 2011, **13**, 4736.
71 I. P. Andrews and O. Kwon, *Chem. Sci*., 2012, **3**, 2510.
72 A. Dermenci, P. S. Selig, R. A. Domaoal, K. A. Spasov, K. S. Anderson and S. J. Miller, *Chem. Sci*., 2011, **2**, 1568.
73 Y. X. Tan, S. Santhanakrishnan, H. Y. Yang, C. L. L. Chai and E. K. W. Tam, *J. Org. Chem*., 2014, **79**, 8059.
74 J.-c. Han, F. Li and C.-c. Li, *J. Am. Chem. Soc*., 2014, **136**, 13610.
75 T. Kataoka, S. Kinoshita, H. Kinoshita, M. Fujita, T. Iwamura and S.-c. Watanabe, *Chem. Commun.*, 2001, 1958.
76 (*a*) H. Sajiki, A. Yamada, K. Yasunaga, T. Tsunoda, M. F. A. Amer and K. Hirota, *Tetrahedron Lett*., 2003, **44**, 2179; (*b*) Y. Monguchi, K. Yasunaga, T. Tsunoda, T. Ando, T. Maegawa, K. Hirota and H. Sajiki, *Heterocycles*, 2010, **80**, 537.
77 E. V. Velez, C. Desnous and P. Clivio, *J. Heterocycl. Chem.*, 2006, **43**, 1095.
78 (*a*) B. A. Shah, S. C. Taneja, V. K. Sethi, P. Gupta, S. S. Andotra, S. S. Chimni and G. N. Qazi, *Tetrahedron Lett*., 2007, **48**, 955; (*b*) B. A. Shah, R. Kaur, P. Gupta, A. Kumar, V. K. Sethi, S. S. Andotra, J. Singh, A. K. Saxena and S. C. Taneja, *Bioorg. & Med. Chem. Lett.*, 2009, **19**, 4394.

79 M. C. Redondo, M. Ribagorda and M. C. Carreño, *Org. Lett*., 2010, **12**, 568.
80 Q. Li, K. Wongkhan, X. C. Luo, A. S. Batsanov, J. A. K. Howard, Y. Lan, Y. D. Wu, T. B. Marder and A. W. Lei, *Chin. Sci. Bull.*, 2010, **55**, 2794.
81 (*a*) L.-L. Wei, R. P. Hsung, H. M. Sklenicka and A. I. Gerasyuto, *Angew. Chem. Int. Ed*., 2001, **40**, 1516; (*b*) H. M. Sklenicka, R. P. Hsung, M. J. McLaughlin, L.-l. Wei, A. I. Gerasyuto and W. B. Brennessel, *J. Am. Chem. Soc.*, 2002, **124**, 10435; (*c*) S. Luo, C. A. Zificsak and R. P. Hsung, *Org. Lett.,* 2003, **5**, 4709; (*d*) A. I. Gerasyuto, R. P. Hsung, N. Sydorenko and B. Slafer, *J. Org. Chem.*, 2005, **70**, 4248; (*e*) N. Sydorenko, C. A. Zificsak, A. I. Gerasyuto and R. P. Hsung, *Org. Biomol. Chem*., 2005, **3**, 2140; (*f*) J. J. Swidorski, J. Wang and R. P. Hsung, *Org. Lett*., 2006, **8**, 777; (*g*) A. I. Gerasyuto and R. P. Hsung, *Org. Lett*., 2006, **8**, 4899; (*h*) A. I. Gerasyuto and R. P. Hsung, *J. Org. Chem*., 2007, **72**, 2476; (*i*) Y. Zhang, A. I. Gerasyuto, Q. A. Long and R. P. Hsung, *Synlett*, 2009, 237.
82 Y.-L. Shi and M. Shi, *Chem. Eur. J*., 2006, **12**, 3374.
83 J. Alemán, A. Núñez, L. Marzo, V. Marcos, C. Alvarado and J. L. G. Ruano, *Chem. Eur. J*., 2010, **16**, 9453.
84 S. Cabrera, J. Alemán, P. Bolze, S. Bertelsen and K. A. Jørgensen, *Angew. Chem. Int. Ed*., 2008, **47**, 121.
85 J. Villieras, M. Rambaud and M. Graffa, *Syn. Commun*., 1986, **16**, 149.
86 (*a*) R. O. Saad, T. Turki and H. Amri, *Synthetic Commun*., 2005, **35**, 2921; (*b*) T. Nemoto, T. Fukuyama, E. Yamamoto, S. Tamura, T. Fukuda, T. Matsumoto, Y. Akimoto and Y. Hamada, *Org. Lett.,* 2007, **9**, 927.
87 M. E. Krafft, E.-H. Song and R. J. Davoile, *Tetrahedron Lett.*, 2005, **46**, 6359.
88 N. Maezaki, S. Yuyama, H. Sawamoto, T. Suzuki, M. Izumi and T. Tanaka, *Org. Lett*., 2001, **3**, 29.

