Chem Soc Rev

Cite this: *Chem. Soc. Rev.*, 2011, **40**, 4550–4562

www.rsc.org/csr

TUTORIAL REVIEW

Divergent reactions on racemic mixtures

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Received 16th March 2011
DOI: 10.1039/c1cs15069c

Methods that furnish enantioenriched products are crucial in modern organic synthesis. An underutilized strategy to arrive at enantioenriched products is to perform divergent reactions on racemic mixtures, where each enantiomer of the starting material reacts with a single chiral reagent to furnish two separable, non-enantiomeric products that are enantioenriched. Stereodivergent, regiodivergent and structurally divergent reactions on racemic mixtures are discussed in this *tutorial review*.

I. Introduction

Simple kinetic resolution[1–5] relies on a difference in reaction rate between enantiomers to obtain enantioenriched material. In this well-traveled resolution mode, a chiral, non-racemic agent reacts with one enantiomer (*e.g.*, E(*R*), Fig. 1) more quickly than with the antipode (*e.g.*, E(*S*)). The selectivity factor (*s*) is defined as the ratio of the rates of these two reactions (eqn (1)).

$$s = k_{fast}/k_{slow} \quad (1)$$

In the absence of selectivity ($s = 1$) in a simple kinetic resolution, a racemic mixture of products would be formed. In an ideal scenario, a large rate difference (*e.g.*, $s \geq 200$) would exist and one could obtain enantioenriched product in a 50% yield, as well as recover enantioenriched starting material in 50% yield. A disadvantage of this strategy is that to obtain high yields of each compound (~50%) with excellent enantioenrichment (≥95% *ee*), extremely high selectivity factors ($s \geq 200$), which are difficult to achieve, are required.[1]

One way to avoid the necessity for exquisite selectivity factors is to use a divergent reaction on a racemic mixture (divergent RRM).[6,7] In this strategy, both enantiomers of a substrate react with a chiral reagent (*e.g.*, **X***) at similar rates to form separable, non-enantiomeric products (*e.g.*, **P**(*R*) and **Q**(*S*), Fig. 1). With excellent reagent control, both products can be formed in high yields (up to 50%) and enantiomeric enrichment. Unlike simple kinetic resolutions, the relative rates do not matter as long as there is complete reagent control.[7] Following the convention of Kagan[6,8] and Vedejs,[7] parallel kinetic resolutions are defined as a special case of divergent RRM where two chiral agents, which each react preferentially with one enantiomer, are employed (*e.g.*, **X*** and **Y***, Fig. 1). There have been a variety of "parallel kinetic resolutions"

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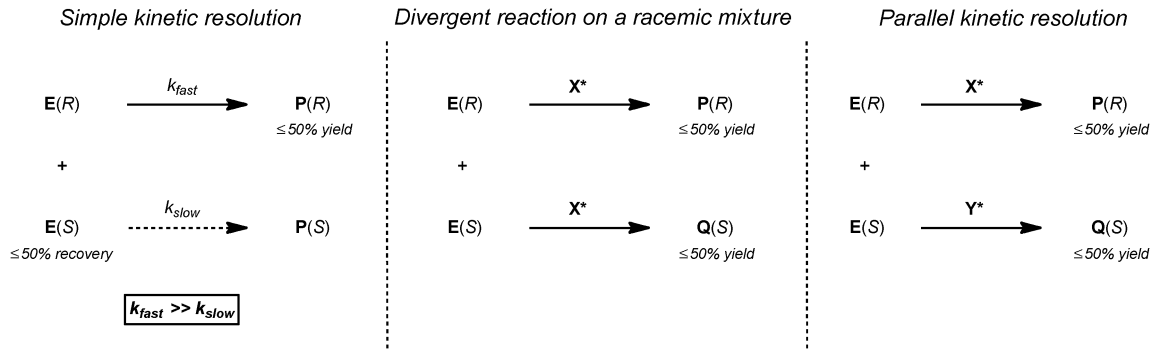


Fig. 1 Simple kinetic resolution compared to a parallel kinetic resolution and a divergent reaction on a racemic mixture.

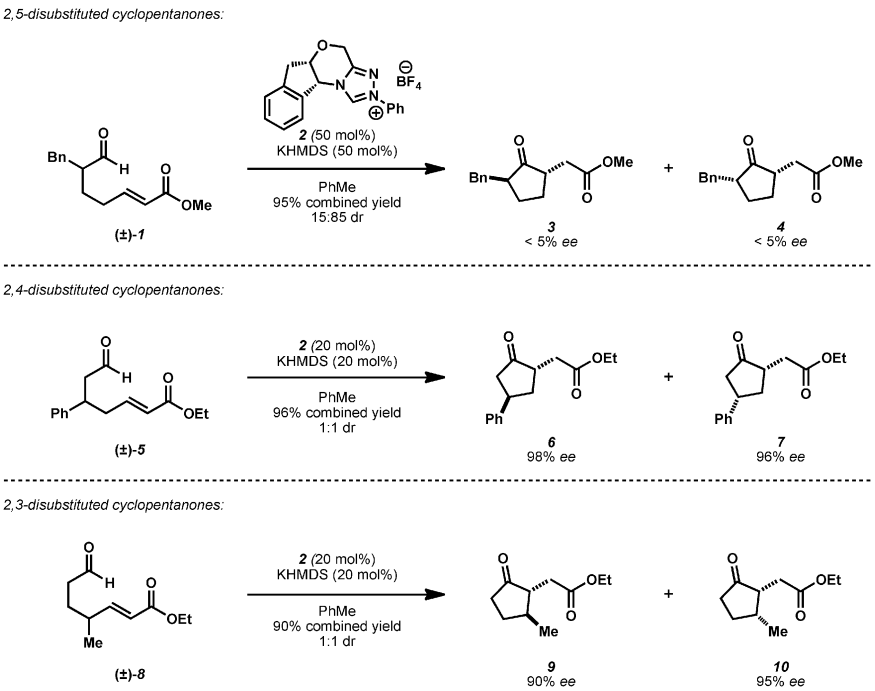
reported in the literature, including our own work,[9] that do not fit into this strict definition, but rather are more appropriately classified as divergent RRM. These definitions are more precise, and we will comply with them.

In this review we will focus on selected examples that have been reported since 2003 of divergent RRM using a single chiral reagent. It is important to note that this definition of divergent RRM encompasses a variety of transformations that do not necessarily involve a kinetic resolution, however only those reactions that utilize a kinetic resolution to determine the fate of each racemate will be covered in this review. Of the reactions that do employ kinetic resolutions, there are three general categories of divergent RRM: stereodivergent, regiodivergent and structurally divergent.

II. Stereodivergent reactions on racemic mixtures

A stereodivergent RRM strategy generally utilizes a racemic starting material possessing resident stereocenters. In the divergent step, a new stereocenter is introduced by reagent control independent of the resident stereocenters. The products formed are diastereomers and must be easily separable if the method is to be useful. However, in practice, separation can be difficult to achieve.

A recent example can be found in the work of Rovis. After their development of new catalysts (*e.g.*, **2**, Scheme 1) for the intermolecular asymmetric Stetter reaction,[10–12] the Rovis group applied their strategy to substrates with pre-existing stereocenters, setting the stage for a potential divergent reaction on a racemic mixture.[13] The cyclization to form 2,5-disubstituted cyclopentanones (*e.g.*, **3** and **4**) was found to be controlled by the stereocenter alpha to the aldehyde group, preferentially forming the *cis* product. The inherent substrate preference could not be overcome by the catalyst, which was also unsuccessful in producing an enantioenriched product. Conversely, steric bulk at the β- and γ-positions in the starting material (*e.g.*, **5** and **8**) imparted minimal substrate control, making a resolution possible in each of these scenarios. Thus both 2,4-disubstituted (*e.g.*, **6** and **7**) and 2,5-disubstituted cyclopentanones (*e.g.*, **9** and **10**) were successfully formed as

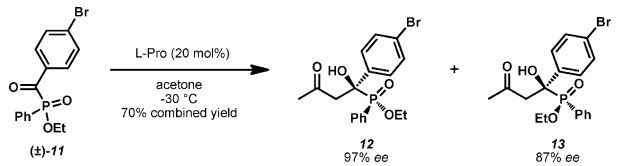


Scheme 1 Stereodivergent Stetter reaction to form enantioenriched cyclopentanones.[13]

enantioenriched diastereomers. Unfortunately, the diastereomeric cyclopentanones were inseparable, limiting the usefulness of the resolution strategy for these substrates.

Another pertinent example is that of Zhao and coworkers, who embarked on stereodivergent RRM in an effort to develop new strategies to synthesize enantioenriched α-hydroxyphosphinates.[14] Starting with a racemic α-hydroxyphosphinate (*e.g.*, **11**, Scheme 2), they performed a cross-aldol reaction in the presence of proline to furnish the enantioenriched diastereomeric products (*e.g.*, **12** and **13**).

The selectivity in the reaction is proposed to be derived from a transition-state that minimizes steric interactions between the phosphinate and the methyl group of the enamine (Fig. 2). For example, for the (*R*)-enantiomer, transition-state **14a** is preferred over **14b**, leading to formation of the observed product (**12**). A similar analysis can be considered for the (*S*)-enantiomer, where once again, the unfavorable configuration (**15b**) suffers from 1,3-diaxial interactions of the phosphinate and the methyl group. A weakness of the approach is that while a few of the α-hydroxyphosphinate diastereomers could be separated by selective recrystallization, most product mixtures in the work were inseparable.



Scheme 2 Divergent crossed-aldol to furnish α-hydroxyphospinates.[14]

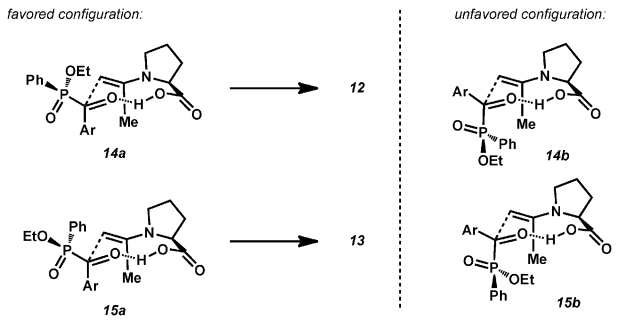


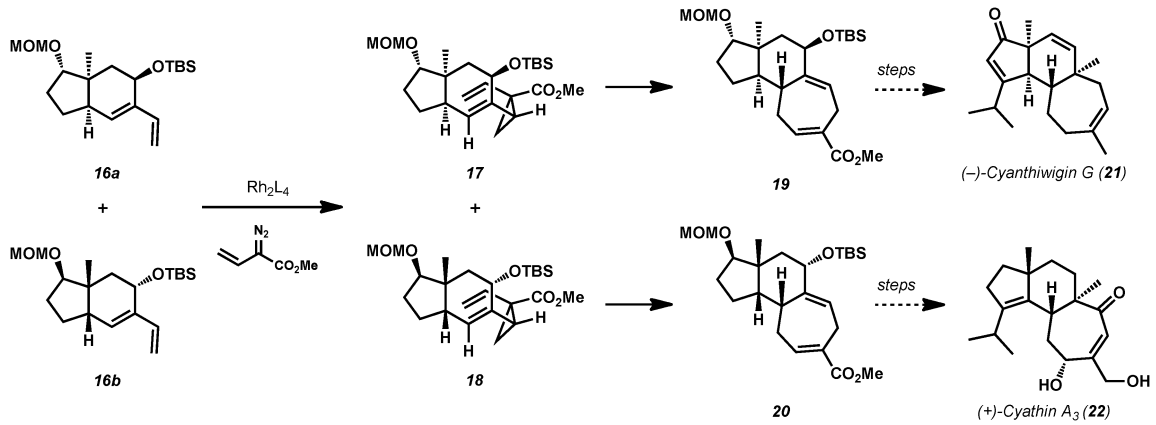
Fig. 2 Proposed transition state for the cross-aldol reaction.[14]

Because of the inherent difficulty in separating diastereomers possessing distal stereocenters, the ability to introduce new stereocenters by reagent control proximal to existing stereocenters in a substrate is powerfully enabling. An example is found in the work of Sarpong and coworkers, as they strove to develop a general approach to the cyanthiwigin and cyathane family of natural products, where a stereodivergent cyclopropanation-Cope rearrangement sequence was utilized (Scheme 3). Racemic diene **16** is cyclopropanated in a rhodium-mediated process, and the subsequent divinylcyclopropane intermediate (**17** or **18**) undergoes a stereospecific [*3*,*3*]-sigmatropic rearrangement to form tricycles **19** and **20**.[9] A unique feature of this strategy is that each product of the resolution, **19** and **20**, can be applied to the syntheses of the naturally-occurring antipodes of cyanthiwigins (*e.g.*, **21**) or cyathanes (*e.g.*, **22**), respectfully.

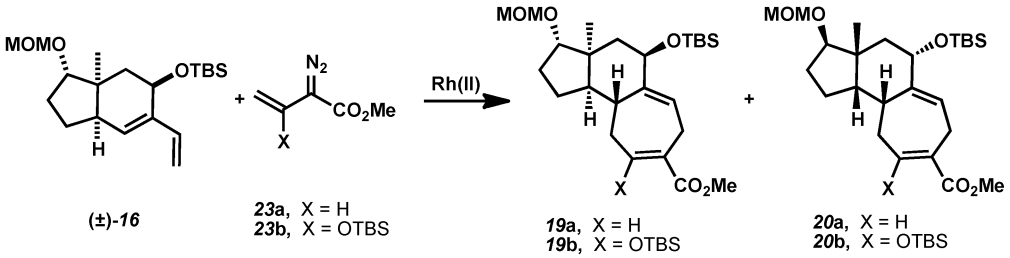
Initial efforts utilizing the $Rh_2(DOSP)_4$ catalysts[15,16] furnished a 1 : 1 ratio of separable products (**19** and **20**) in good *er* (entries 1-2, Scheme 4). Superior enantioenrichment and yields were achieved by the use of the adamantyl $Rh_2(PTAD)_4$ catalyst[17] along with silyl enol ether diazoacetate **23b** in a collaborative effort with the Davies group.[18] The resident stereocenters in diene **16** appear to be sufficiently distal and have minimal effects on the diastereomeric transition state enforced by the chiral rhodium catalyst.

Diastereomers created by virtue of olefin geometry have also been exploited in stereodivergent RRM. For example, in their total synthesis of pyranicin and pyragonicin, Rein and coworkers utilized a stereodivergent Horner–Wadsworth–Emmons reaction.[19–21] Previously Reiser, Rein and coworkers had achieved this transformation through a parallel kinetic resolution route, where a mixture of (*Z*)-selective **25** and the (*E*)-selective isopropoxy-phosphonate analog **26** were utilized (Scheme 5).[22]

However, in the course of the total synthesis of pyranicin and pyragonicin, Rein and coworkers found that a divergent RRM was possible through the slow addition of phosphonate **25** to 1.3 equivalents of racemic aldehyde **24** (Scheme 6). The strategy afforded dihydropyrans **27** and **28** with slightly improved diastereoselectivity, as well as an easier experimental set up. The (*R*)-aldehyde **24** reacts with the phosphonate to

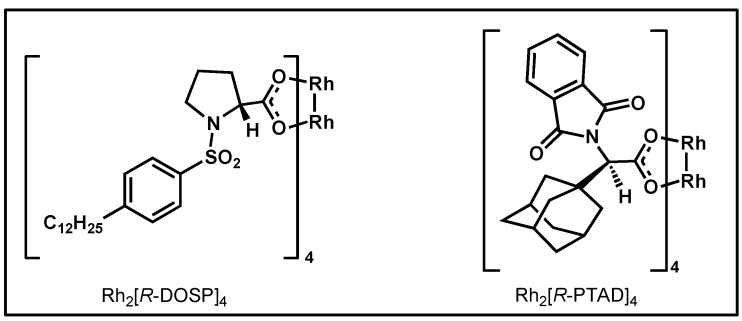


Scheme 3 Stereodivergent approach to the cyanthiwigin and cyathane cores.[9]

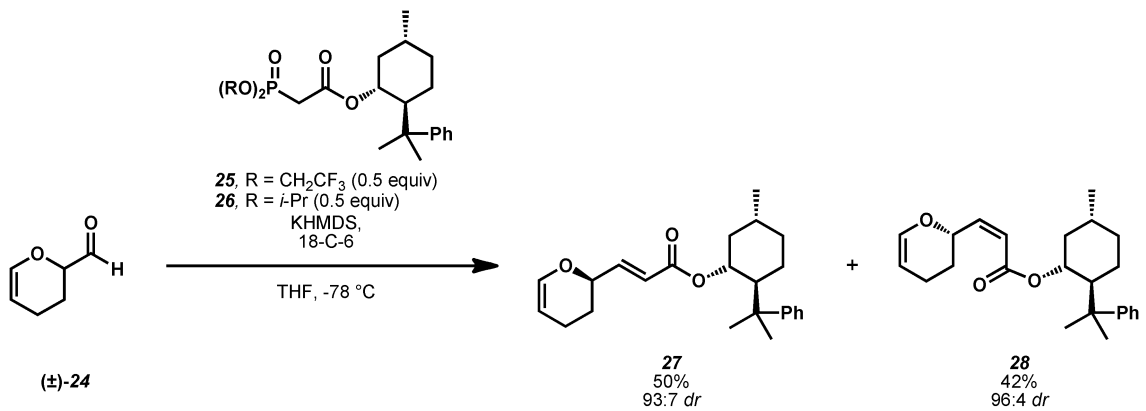


entry	catalyst	diazo	ratio (*19*/*20*)	yield (*19*+*20*, %)	*er* (+)-*19*:(-)-*19*	*er* (+)-*20*:(-)-*20*
1[a]	Rh_2(*R*-DOSP)$_4$	***23***a	1:1[b]	39[c]	12:88	88:12
2[a]	Rh_2(*S*-DOSP)$_4$	***23***a	1:1[b]	50[c]	89:11	15:85
3[d]	Rh_2(*R*-PTAD)$_4$	***23***b	2:1	64	5:95	99.5:0.5

[a] Reactions were conducted at 8 °C in pentane with 3.0 equivalents of ***23***a and 1 mol% catalyst; [b] Determined by ^{1}H NMR; [c] Isolated yields of the reduced ester protected as a *p*-nitrobenzoate; [d] Reactions were conducted at 0 °C in PhMe with 3.0 equivalents of ***23***b and 2 mol% catalyst.



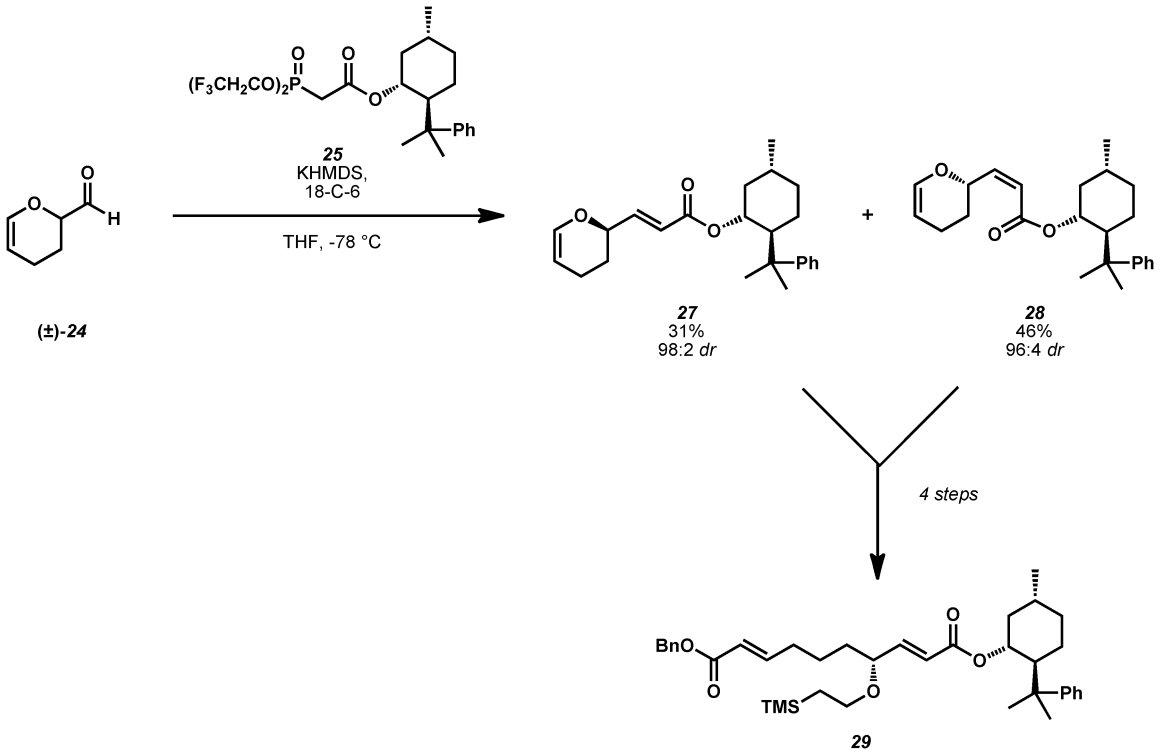
Scheme 4 Stereodivergent cyclopropanation-Cope rearrangement.[9,18]



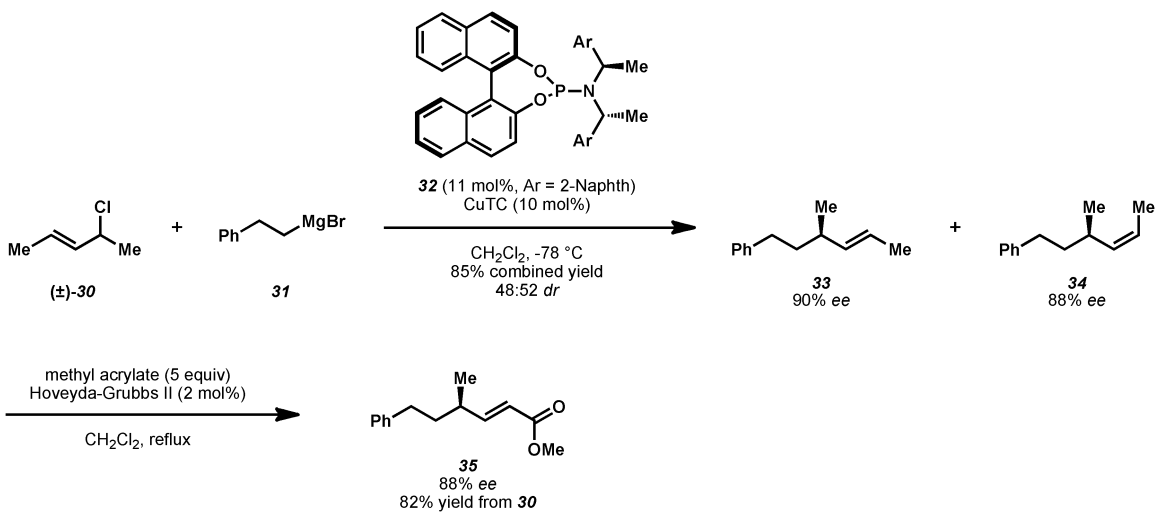
Scheme 5 Parallel kinetic resolution *via* a Horner–Wadsworth–Emmons reaction.[22]

form the (*E*)-product (**27**), whereas the antipode ((*S*)-**24**) affords the (*Z*)-alkene (**28**). The selectivity of this asymmetric HWE reaction has been studied computationally.[23] The facial selectivity is determined by the chiral auxiliary on the phosphonate and the stereocenter alpha to the aldehyde. The interplay between these two factors also determines the *E*/*Z* selectivity. Although dihydropyrans **27** and **28** are readily separable, Rein and coworkers carried the enantioenriched diastereomers forward as a mixture, and utilized a stereoconvergent allylic substitution mediated by palladium(0) at a later stage to convert the two stereoisomers to one enantioenriched product (**29**). Thus, overall, this strategy applied both products of the resolution to the syntheses of pyranicin and pyragonicin in a stereodivergent/stereoconvergent sequence.

In a recent example of stereodivergent RRM that also forms enantioenriched (*E*)- and (*Z*)-olefins, Alexakis and coworkers employed an asymmetric allylic alkylation of racemic allylic halides (*e.g.*, **30**, Scheme 7).[24] In the presence of phosphoramidite **32**, copper mediates an S_N2' addition of Grignard **31**. The (*S*)-enantiomer of **30** forms an (*E*)-alkene, whereas the



Scheme 6 Stereodivergent Horner–Wadsworth–Emmons sequence.[19–21]



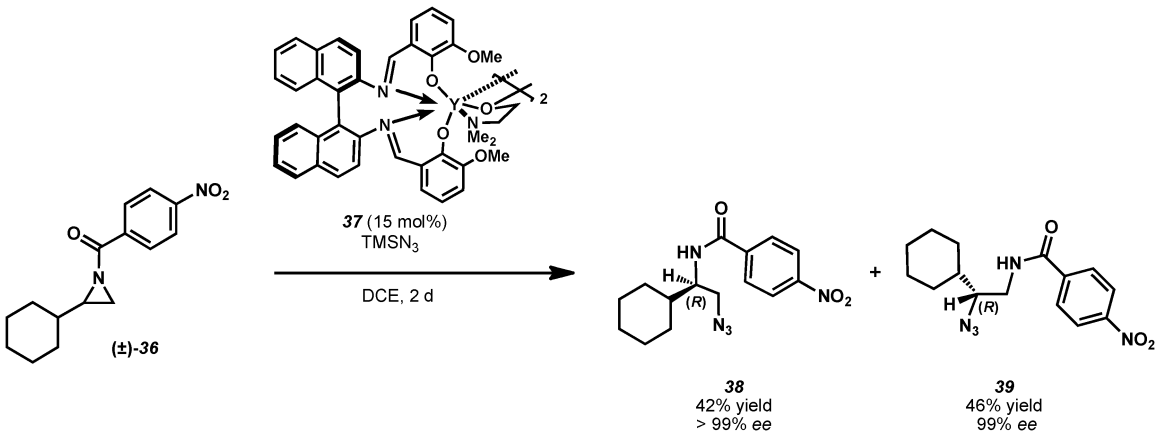
Scheme 7 Stereodivergent allylic alkylation.[24]

antipode forms the (*Z*)-alkene. The new stereocenter is installed with the same induction for both alkylated products, for example (*R*) in **33** and **34**. A number of transformations can converge the enantioenriched diastereomers to a single enantioenriched product, including cross-metathesis to form enoate **35**. Overall, an effective method to selectively install a tertiary stereocenter was achieved.

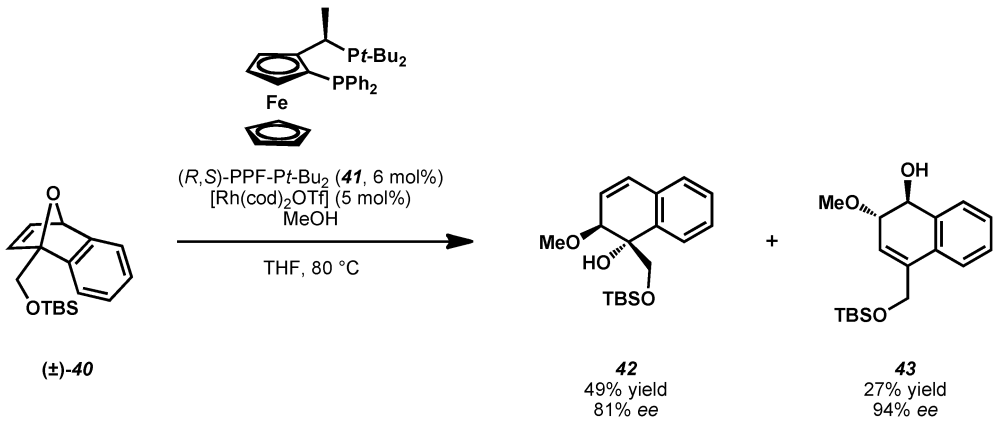
III. Regiodivergent reactions on racemic mixtures

Chiral non-racemic reagents can also promote the formation of enantioenriched regioisomers starting from a racemic substrate. Most of the examples from this class of divergent RRM occur through a ring-opening event. However, alternative strategies such as cycloadditions and aldol additions have also been employed. This is the category of divergent RRM that has been the most explored. Consequently, only selected recent examples will be discussed.

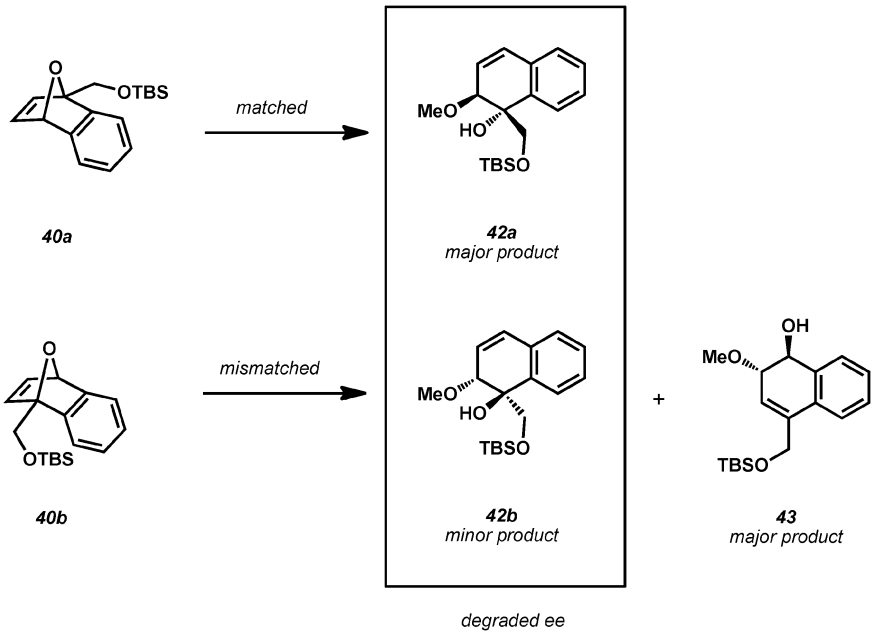
RajanBabu, Parquette and coworkers utilized a chiral non-racemic yttrium-salen complex (**37**) to promote the stereospecific addition of azides to racemic aziridines in excellent yields and selectivity (Scheme 8).[25] For example, the (*R*)-enantiomer of aziridine **36** was attacked at the less hindered position to afford azidoamide **38**, while the azide attacked the



Scheme 8 Regiodivergent aziridine-opening.[25]

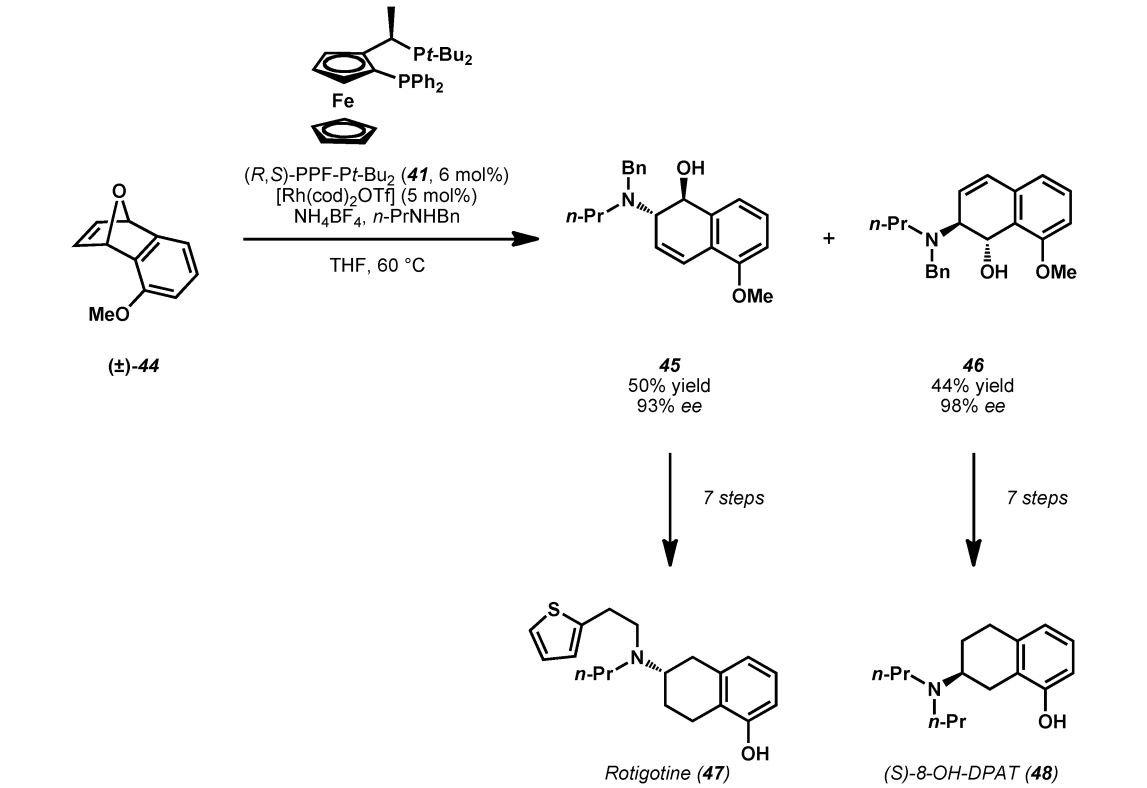


Scheme 9 S_N2' strategy to form hydroxy-naphthalenes.[27]

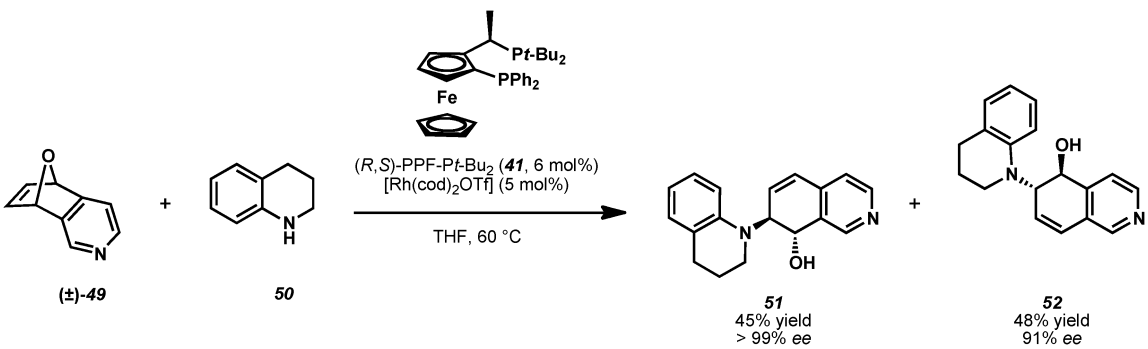


Scheme 10 Match/mismatch scenario (double diastereoselection) *p* leading to a matched product with lower enantioenrichment.[27]

(*S*)-enantiomer of **36** with inversion at the methine to provide **39**. Because the chiral center in each product is (*R*), the azidoamides could conceivably converge to a single diamine product through further synthetic transformations. Alternatively, the azidoamide products can be separated and utilized following the ring-opening step.



Scheme 11 Extension to substrates with unsymmetrical arene substitution.[28]

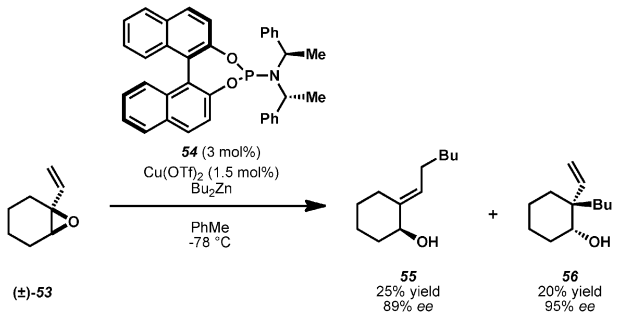


Scheme 12 Regiodivergent ring-opening of [2.2.1] hetaryne-furan Diels–Alder adducts.[29]

The Lautens group also utilized a strained ring system in a regiodivergent reaction, employing oxabenzonorbornene substrates rather than aziridines. Following the development of a method to form hydroxy-naphthalenes by substrate control,[26] Lautens and coworkers were inspired to develop a similar method that operated by reagent control (Scheme 9). To this end, a cationic rhodium(I) complex was utilized to promote ring-opening of substrates such as **40**.[27] The reaction proceeds by stereospecific oxidative addition of the rhodium complex to the C–O bond of the oxabicycle (**40**). Protonation of the rhodium alkoxide is followed by ring-opening by nucleophilic attack to form two enantioenriched hydroxy-naphthalenes (**42** and **43**). A variety of oxygen and nitrogen nucleophiles were effective in the transformation.

As in some previous examples, one product (*e.g.*, **43**) is formed in higher enantioenrichment than the other product (**42**). This can be explained by matched/mismatched considerations (double diastereoselection). In the matched case, both the substrate preference and the catalyst preference is to form hydroxy-naphthalene **42a** (Scheme 10). The mismatched pair has diminished selectivity, producing not only the catalyst-controlled product **43**, but also minor product **42b** due to the inherent substrate preference, leading to erosion of the *ee* of the matched product. Nevertheless, the products are still formed in good to excellent enantioenrichment.

Recently, Lautens and coworkers have extended this work to substrates with unsymmetrical substitution about the aryl moiety.[28] The use of NH_4BF_4 as a protic additive facilitated high yields and enantioselectivity, in accordance with the mechanistic proposal that protonation of the rhodium-alkoxide precedes nucleophilic attack.[29] The optimized reaction conditions were amenable to a variety of nitrogen and oxygen nucleophiles,

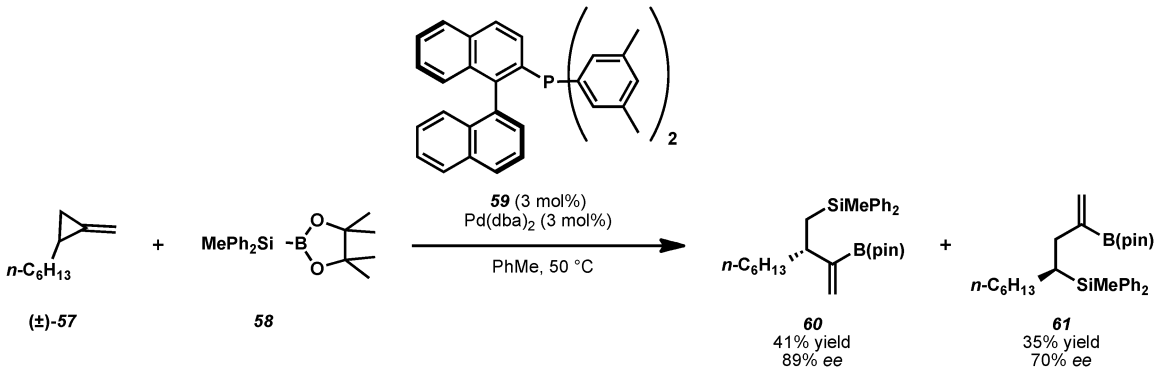


Scheme 13 Copper-phosphoramidite-catalyzed epoxide opening.[31]

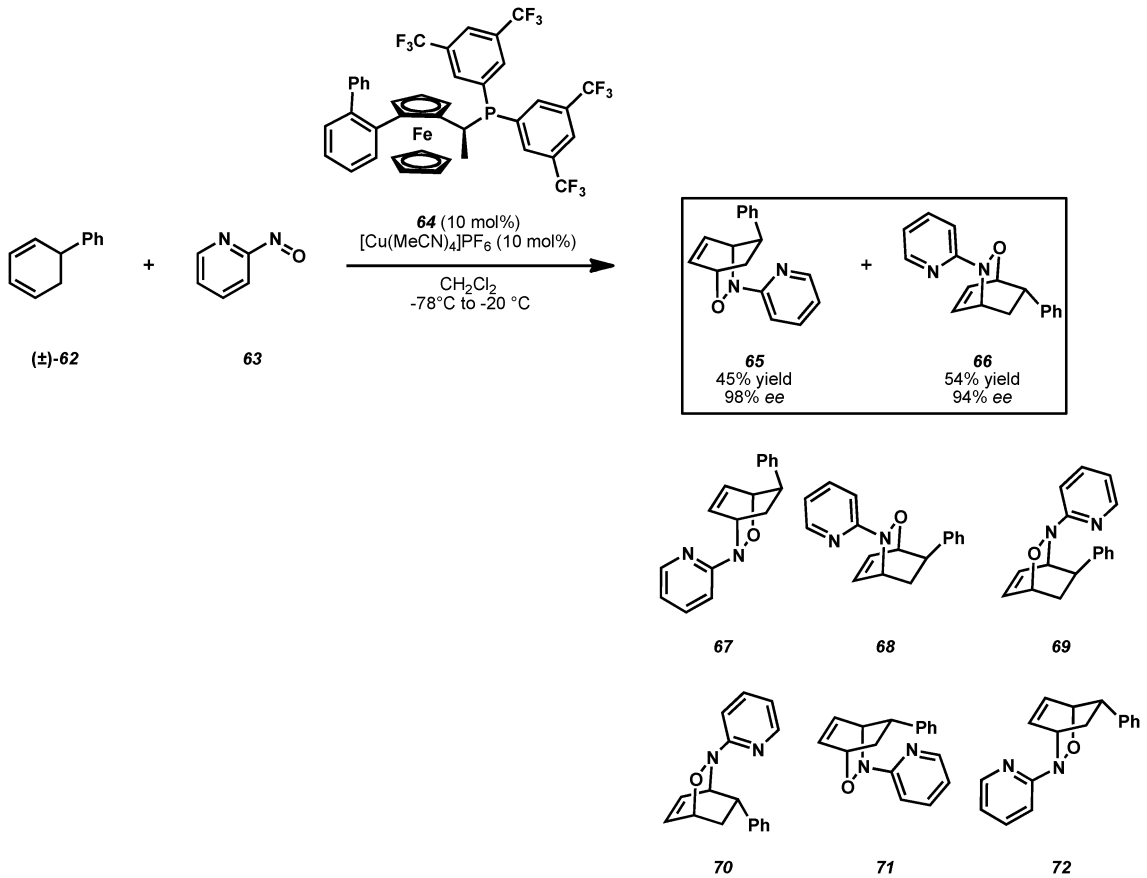
including the amine shown in Scheme 11, which furnishes aminotetralins **45** and **46**.

The Lautens group demonstrated the utility of enantio-enriched aminotetralins by completing the syntheses of rotigotine (**47**) and 8-(OH)-DPAT (**48**), two active pharmaceutical intermediates (Scheme 11). Regioisomers **45** and **46** were carried forward in seven steps, respectively, to the target compounds.

Recently, the group also established that the reaction is effective on a variety of related nitrogen-containing [2.2.1] heterocycles (*e.g.*, **49**, Scheme 12).[29] Despite the potential for catalyst poisoning due to the presence of basic nitrogen



Scheme 14 Regiodivergent silylborative C–C cleavage.[32]



Scheme 15 Regiodivergent nitroso Diels–Alder reaction.[33]

functionality, the reactions proceeded smoothly. The reaction is sensitive to the electronics of the substrate, and in some cases the nitrogen heterocycles imparted strong substrate control and resulted in lower enantioenrichment for one of the products. However, substrates such as bicycle **49** underwent ring-opening in the presence of the cationic rhodium(I) complex and dihydroisoquinoline **50** to form **51** and **52** in exceptional yield and enantioselectivity.

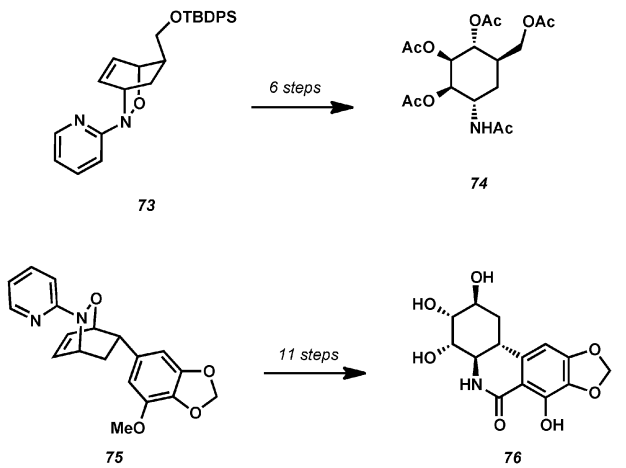
A related strategy employing S_N2 *versus* S_N2' reactivity in the regiodivergent step of a strained oxabicycle opening was used by Pineschi and coworkers to open epoxides.[30,31] In the presence of a copper-phosphoramidite catalyst, allylic epoxides (*e.g.*, **53**, Scheme 13) reacted with dialkylzinc reagents to form allylic alcohols (*e.g.*, **55**) or homoallylic alcohols (*e.g.*, **56**) in a C–C bond forming reaction. The method was most effective in substrates where the epoxide was fused to a ring, and could even be used to form all-carbon quaternary centers (*e.g.*, **56**), albeit in moderate yields.

Suginome and coworkers also utilized a strained ring in their regiodivergent synthesis of 2-boryl-3-silylmethyl-1-alkenes (*e.g.*, **60** and **61**) from methylenecyclopropanes (*e.g.*, **57**, Scheme 14).[32] A variety of ligands were surveyed, and **59** emerged as the most effective to provide each product in good yield and enantioselectivity. In the reaction, there are two selective steps: the insertion into the C=C bond, and the C–C bond cleavage in the β-carbon elimination step. Although each step taken individually has modest to good selectivity (in the range of 3 : 2 to 9 : 1), the additive effect of the steps provides products in high *ee*.

In most divergent reactions on racemic mixtures, the chiral reagent promotes the formation of two stereoisomers out of four possibilities. Studer and coworkers have been able to form two isomers (**65** and **66**) from a total of eight possible isomers (**65–72**) in a nitroso Diels–Alder reaction (Scheme 15).[33] Use of a copper catalyst with ligand **64** provided excellent yields and enantioselectivities. This method has been applied in a complex molecule synthesis, serving as the key step in the syntheses of peracetylated 2-*epi*-validamine (**74**, Scheme 16) as well as (+)-*trans*-dihydronarciclasine (**76**).[33,34]

Gansäuer and coworkers have employed a titanocene catalyst (**78**, Scheme 17) in their regiodivergent opening of epoxides.[35] In an electron-transfer event, the titanocene complex reductively opens unbiased epoxides (epoxides with substituents of similar steric bulk, *e.g.*, **77**) to furnish the corresponding enantioenriched alcohols **79** and **80** in good yields and selectivity. The strategy is advantageous over S_N2-based methods where poor selectivity or simple kinetic resolutions are often observed on similar systems.[36] The Gansäuer group later built on this regiodivergent reaction to develop a structurally divergent RRM (Scheme 23; see below).[37]

Krische and coworkers demonstrated a regiodivergent RRM to form enantioenriched fused bicycles (*e.g.*, **84** and **85**, Scheme 18).[38] The reaction commenced with an enantioselective rhodium-mediated conjugate addition of a boronic acid. The ensuing aldol cyclization is dictated by the absolute configuration of the intermediate, proceeding *via* a *Z*-enolate in a Zimmerman-Traxler transition state (**82** and **83**). The overall result is the formation of two fused bicycles (**84** and **85**) bearing four contiguous stereocenters in excellent yields and enantioenrichment.

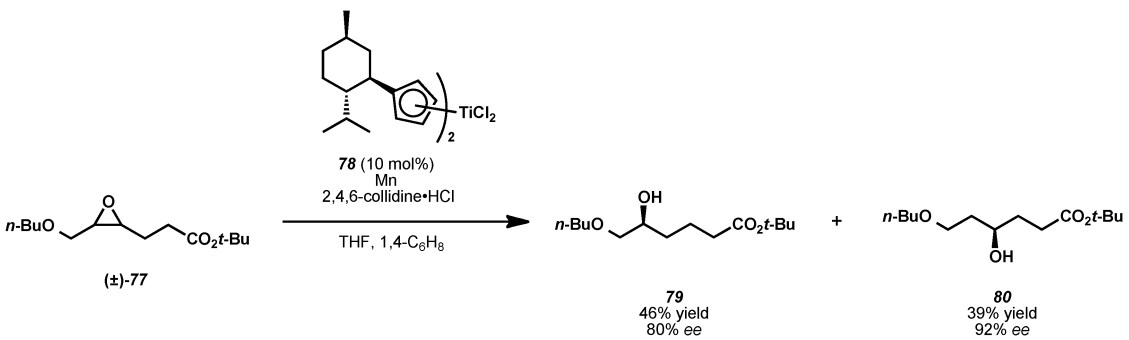


Scheme 16 Applications of Studer's regiodivergent RRM.[33,34]

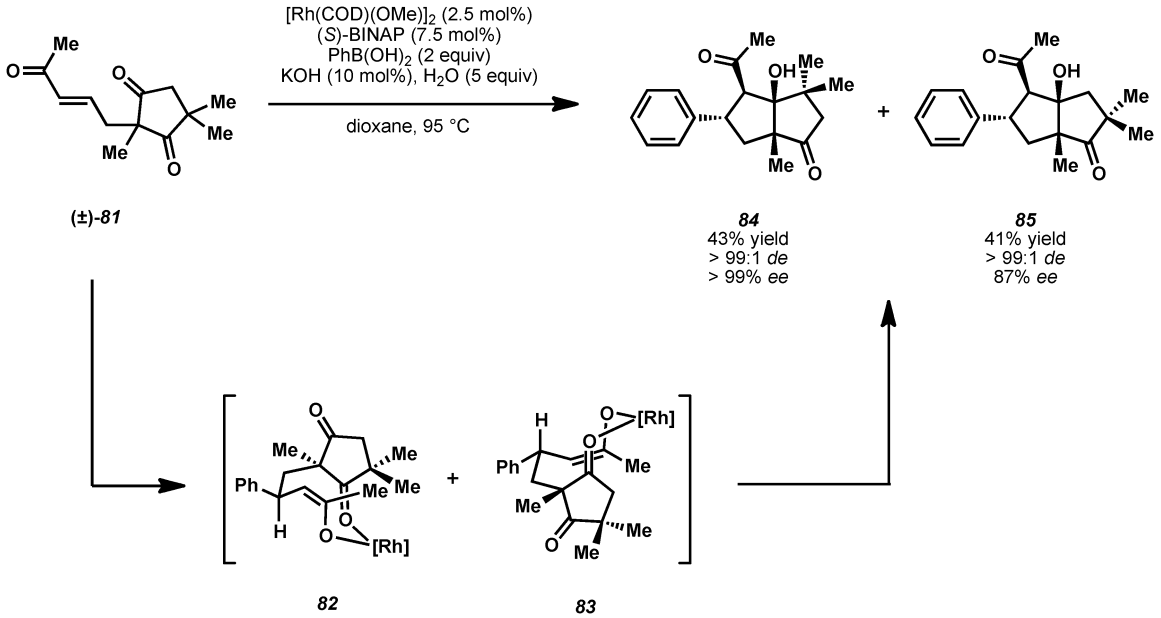
IV. Structurally divergent reactions on racemic mixtures

The final category of divergent RRM creates two distinct compounds from the racemic starting material. The enantioenriched products need not be isomers, and indeed in many cases are completely different with respect to structure connectivity.

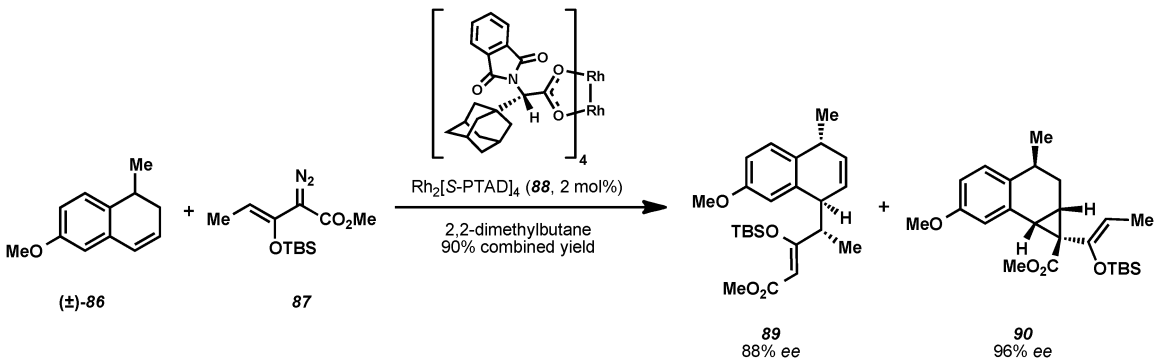
One example that provides constitutional isomers is that reported by Davies and coworkers (Scheme 19).[39] In a rhodium(II)-mediated diazo coupling reaction, the enantiomers



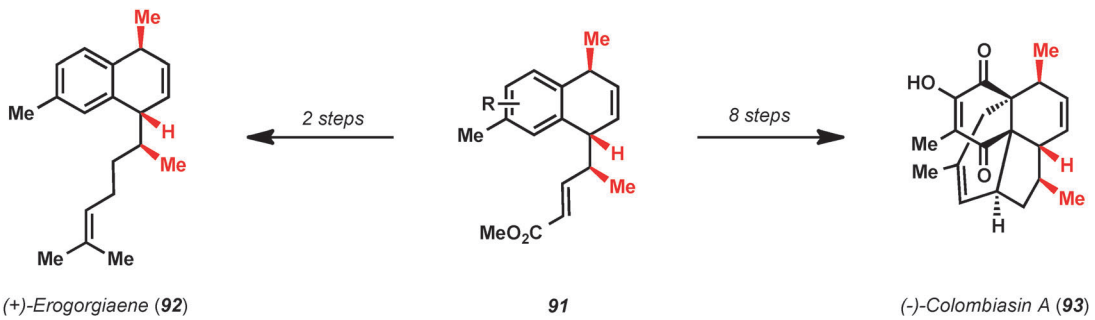
Scheme 17 Reductive ring-opening of epoxides catalyzed by titanocene.[35]



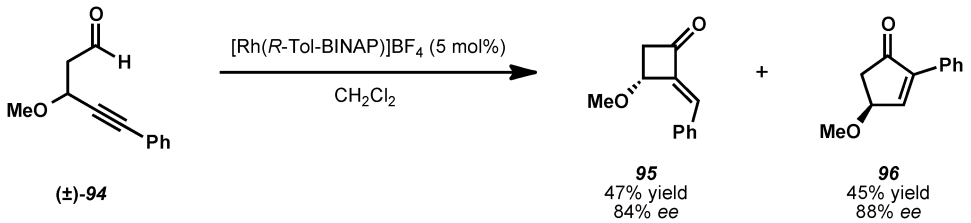
Scheme 18 Sequential conjugate addition-aldol cyclization.[38]



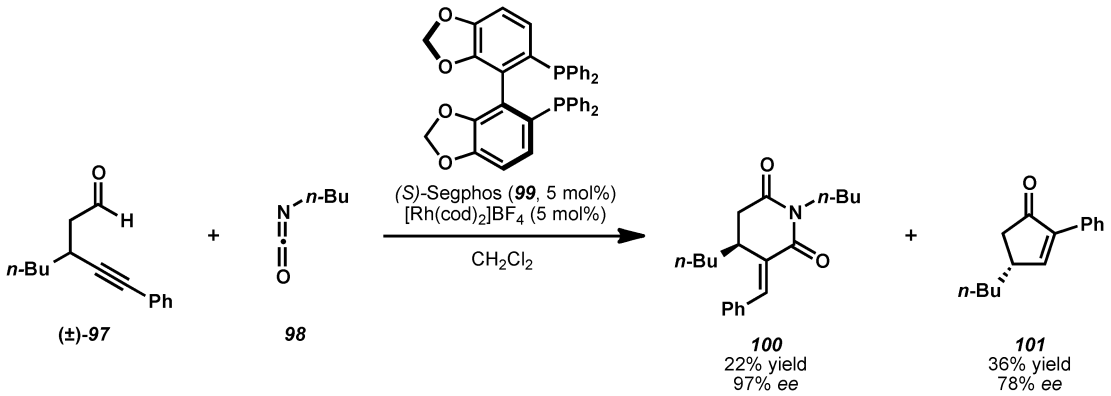
Scheme 19 Divergent C–H functionalization or cyclopropanation.[39]



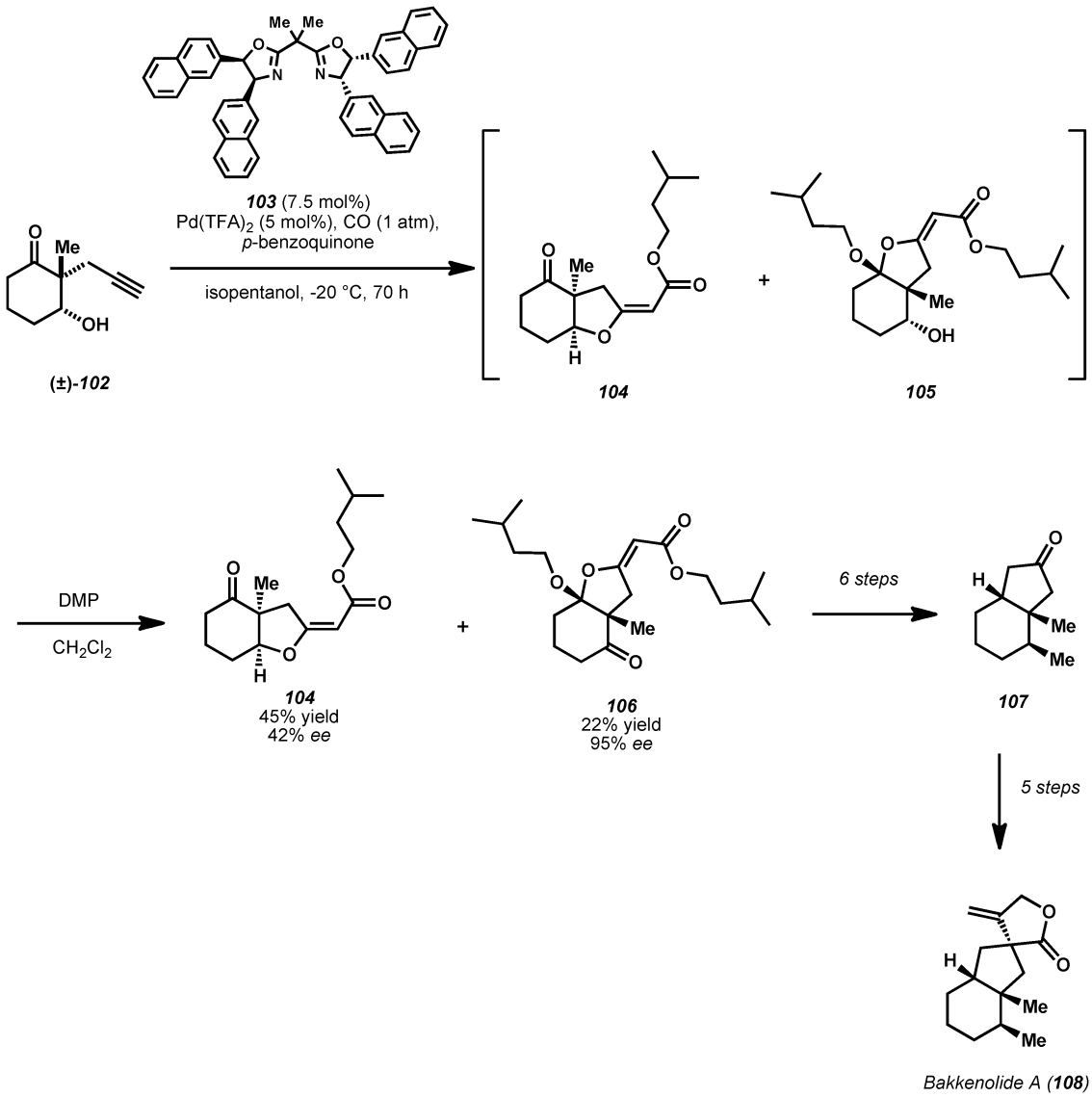
Scheme 20 Applications of a structurally divergent RRM to (+)-erogorgiaene[40] and (−)-colombiasin A.[41]



Scheme 21 Formation of cyclobutanones and cyclopentanones.[42]

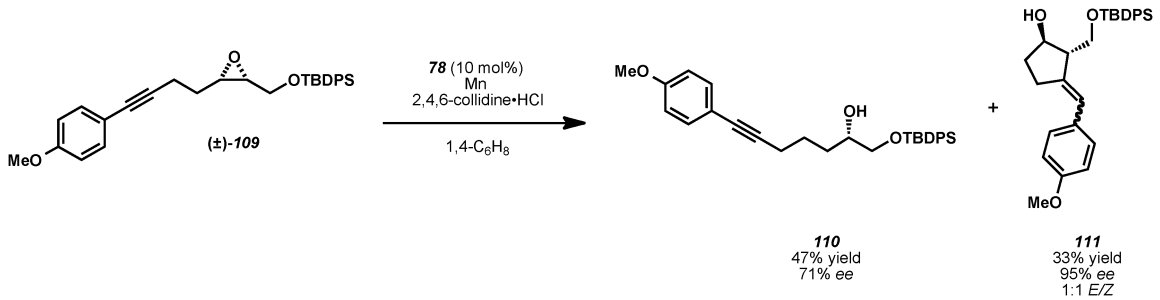


Scheme 22 Rhodium-mediated formation of alkylideneglutarimides and cyclopentenones.[43]



Scheme 23 Palladium-catalyzed cyclization-carbonylation reactions of propargyl ketols.[44]

of a dihydronaphthalene (*e.g.*, **86**) either reacted by a C–H activation/Cope rearrangement to provide enoate **89** or by a cyclopropanation to form **90**. The group applied this strategy to the total syntheses of (+)-erogorgiaene (**92**)[40] and (−)-colombiasin A (**93**)[41] (Scheme 20). Impressively, the divergent step establishes three stereocenters that are present in the natural products.



Scheme 24 Formation of enantioenriched alcohols or cyclopentanols.[37]

The structurally divergent reaction of 4-alkynals has been achieved by Tanaka and Fu.[42] Rhodium catalyzes a hydroacylative cyclization to form enantioenriched cyclobutanones (*e.g.*, **95**, Scheme 21) through a *cis* addition across the alkyne. The cyclopentanones (*e.g.*, **96**) are constructed through a net *trans* addition. This strategy provides a powerful method to form enantioenriched cyclobutanones.

Tanaka and coworkers have also reported a structurally divergent reaction of 3-substituted-4-alkynals.[43] Using a rhodium catalyst in the presence of (*S*)-Segphos (**99**), the alkynals (*e.g.*, **97**, Scheme 22) reacted to form enantioenriched 4-alkylidineglutarimides (**100**) and cyclopentenones (**101**). One enantiomer selectively underwent a [4+2] annulation with isocyanate **98**, whereas the antipode reacted by a hydroacylation to form the cyclopentenone product.

Kato and coworkers were able to utilize a structurally divergent reaction en route to their formal synthesis of (+)-bakkenolide A (**108**, Scheme 23).[44] One enantiomer of propargyl ketol **102** formed a hemiacetal, followed by a palladium catalyzed cyclization onto the alkyne and subsequent carbonylation to furnish bicycle **104**. In the antipode, the hydroxyl group in the starting material cyclized onto the alkyne and was then carbonylated to form bicycle **105**. The immediate products of the reaction, **104** and **105**, are difficult to separate. However, after Dess–Martin periodinane oxidation of **105** to the ketone **106**, the products are readily separable. Although a wide substrate scope has not yet been demonstrated, highly enantioenriched ketone **106** can be brought forward in six steps to compound **107**, which intersects with the Evans synthesis of bakkenolide A (**108**).[45,46]

Building on their regiodivergent RRM of epoxides (see Scheme 17), Gansäuer and coworkers extended their strategy to a structurally divergent RRM.[37] As in their previous example, titanium reagent **78** mediates a homolytic cleavage of the epoxide (**109**, Scheme 24), then one enantiomer undergoes a radical reduction to form acyclic alcohol **110**, while the radical intermediate of the antipode is positioned to cyclize onto the alkyne to furnish cyclopentanol **111**. The diastereomeric cyclopentanol products can be reduced with Crabtree's catalyst in a directed hydrogenation to furnish the corresponding enantionenriched cyclopentane derivative.

V. Conclusion

Divergent reactions on racemic mixtures have only begun to be developed. Most of the current examples are those of regiodivergent reactions, leaving much room for the exploration of stereodivergent and structurally divergent methods. The strategies established thus far have been shown to be useful in the context of complex molecule synthesis. Particularly exciting, and synthetically useful, are the strategies that utilize both enantioenriched products, either in the synthesis of two target compounds or in their convergence to a single enantioenriched product through further transformations. Divergent reactions on racemic mixtures promise to be a continuing fertile area of research.

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