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Nonenzymatic enantioselective synthesis of all-carbon quaternary centers through desymmetrization

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Abstract

The asymmetric desymmetrization of *meso* or prochiral compounds containing an all-carbon quaternary center is an attractive alternative to classical synthetic approaches aimed at the asymmetric formation of a new C—C bond. This review focuses on nonenzymatic desymmetrizations that utilize transition metal catalysts or organocatalysts to distinguish between enantiotopic groups to generate enantioenriched compounds containing all-carbon quaternary stereocenters.

Graphical Abstract

Keywords

desymmetrization; all-carbon quaternary center; asymmetric; organocatalysis; transition-metal catalysis

The stereoselective formation of all-carbon quaternary centers remains a significant challenge in synthesis due to the steric repulsion between the carbon substituents.¹ Most commonly, construction of stereocenters has focused on the asymmetric formation of a new C—C bond. Desymmetrization of prochiral or *meso* compounds offers an alternative approach, where the formation of a quaternary center is separate from the enantiodetermining step (Scheme 1). Here a chiral reagent or catalyst is used to distinguish between two enantiotopic groups. This approach is particularly attractive when the *meso* or achiral precursors are readily available and when low catalyst loadings can be utilized.

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While previous reviews have focused on enzymatic reactions,² this review focuses on catalytic nonenzymatic desymmetrization approaches for the enantioselective synthesis of compounds containing all-carbon quaternary centers. The review is divided into transition-metal catalyzed and organocatalyzed reactions.

Organometallic

Since the first reports of a homogeneous transition-metal complex catalyzing an asymmetric reaction in 1968, the field has grown in importance and scope.³ Traditionally, these types of enantioselective reactions depend on *in situ* formation of a tightly bound metal complex of a chiral ligand and transition metal precursor. More recently, formation of ion pairs have been invoked in asymmetric transition-metal catalysis.⁴ The reactions usually rely on the enantioselective formation of a new bond. Herein we will examine their use in desymmetrization strategies for the formation of enantioenriched quaternary carbon chiral stereocenters.

Cu

Recently, the desymmetrization of 2,2-dicarbon substituted 1,3-diols has successfully been achieved using a functionalized Cu(II)-pyridinebisoxazoline (Pybox) system.⁵ Monobenylation of diols such as **2** to benzoate esters **3** proceeded in overall excellent yield and generally good enantioselectivities following the pre-formation of the catalytic system using copper (II) chloride and Pybox **1** possessing 4-phenyl and 5,5-di-*n*-butyl substituents (Scheme 2). Remarkably, differentiation of R¹ = methyl and R² = ethyl (**2b** to **3b**) was accomplished in a greater than 10:1 enantiomeric ratio. The authors postulate an octahedral complex between the Pybox-Cu(II) catalyst, 1,3-diol and benzoyl chloride, which allows the two phenyl and oxazoline planes to cross vertically consequently allowing just enough space for the smaller R group to occupy (intermediate **I**).

Mikami and co-workers designed an asymmetric synthesis of highly functionalized five-membered-ring compounds bearing quaternary stereocenters through a desymmetrization strategy.⁶ Their strategy involves the conjugate addition of a zinc alkylating agent to a symmetric cyclopentene-1,3-dione **4** to yield enantioenriched compounds such as **5** using a copper (II) salt and phosphoramidite ligand in as low as 0.5 mol% (Scheme 3). Initial optimization identified Cu(OTf)₂ as the ideal copper salt and BINOL based phosphoramidite ligand **6** with a biaryl substituent at the 3 and 3' position. A broad range of substitution patterns were tolerated on precursor **4** including esters and protected alcohols and various alkyl zinc reagents were appropriate. The one pot reaction proceeded in excellent yield with generally good diastereo- and enantiocontrol. One notable exception was the silyl protected alcohol, **5I-Et**, which was formed in only 36% ee and as the opposite diastereomer. The methodology was utilized in the synthesis of a precursor of madindolines A and B.⁷

A method for the desymmetrization of 1,6-heptadiynes via click chemistry,⁸ Cu(I)-catalyzed azide alkyne cycloaddition (CuAAC) was recently reported (Scheme 4).⁹ This novel approach is only the second report of an asymmetric CuAAC reaction.¹⁰ Treatment of dialkynes such as **7** in the presence of CuCl and Pybox ligand **11** in the unusual solvent 2,5-hexanedione led to enantiomerically enriched chiral quaternary oxindoles bearing a 1,2,3-

triazole moiety **9**. In this methodology, generation of triazole **10** was a major side product, although it could generally be limited (typically <15%) through lowering of reaction temperature and increase of catalyst load. Simple manipulation of the resulting monoalkyne readily produced further substituted molecules (Scheme 5).

A Cu(I)-catalyzed azide alkyne cycloaddition was also used in the desymmetrization of succinimide-derived bis(alkynes **16** to yield 1,2,3-triazoles **18** with a quaternary center (Scheme 6).¹¹ When combined with novel chiral phosphine ligand **19**, CuF₂ was found to be the most effective catalytic system to limit unwanted bis(triazole) formation (yields 60%) and maximize enantiopurity (enantioselectivities 70%) of the reaction. The multifunctional nature of the catalyst was determined to be crucial to the success of the reaction. A variety of functional groups and substitution patterns were well tolerated on the aromatic ring of the succinimide (R¹) and incorporation of a *para*-OEt phenyl on the nitrogen (Ar, **18t–18x**) was found to have beneficial effects on the enantioselectivity of the reaction.

Cai and co-workers reported that 1,2,3,4-tetrahydroquinolines and 2,3,4,5-tetrahydro-1H-benzo[b]azepines with quaternary stereocenters could be prepared asymmetrically via a desymmetrization process utilizing a copper-catalyzed *N*-arylation in combination with binol-derived ligand **22** (Scheme 7).¹² Aryl iodides or bromides **20** yielded heterocyclic products **21** containing a cyano-bearing quaternary carbon in a remote position from the reaction center in good yields (47–91%) and enantioselectivities (76–94%). Although, no rationale was provided, the cyano group was essential to the reaction, with other functional groups such as methyl or esters giving lower yields and/or enantiopurity of product. The reaction was tolerant to functionalization of the aromatic ring such as ester substituents (**21k**) and less reactive halogens (**21g–21i**). A one carbon homologation of the substrate led to formation of a seven-membered ring heterocycle (**21n–21p**, *n* = 2). The origin of enantioselectivity is explained through a model involving coordination of an amine-copper(I) complex with the binol OH in the transition state (Figure 1).

As a follow-up to their copper-catalyzed asymmetric desymmetrization, which differentiates between two aryl halides, Cai and co-workers reported an analogous reaction that differentiates between two amide moieties (Scheme 8).¹³ This desymmetrization utilized diamide substrates **23** and a more nucleophilic 1,2-diamine catalyst **25** to control enantioselectivity. Quinolinone products **24** were generally formed in high yields and modest enantiopurity for a variety of substitution patterns.

Rh

Krische and co-workers utilized a rhodium catalyzed tandem conjugate addition-aldol cyclization of keto-enones to desymmetrize cyclic diones with high stereocontrol (Table 1).¹⁴ In this methodology, enone-diones **26** were treated with a phenyl boronic acid in the presence of an oxidation resistant methoxy-bridged rhodium dimer [Rh(COD)(OCH₃)₂]₂, (S)-BINAP (**28**), and KOH to yield bicyclic compounds **27**. The rhodium catalyzed conjugate addition was followed by a diastereoselective aldol addition invoking a *Z*-enolate and a Zimmerman–Traxler type transition state (**IV**). While the products formed have 4 continuous stereocenters, in all cases essentially a single relative stereoisomer (>99:1 dr) is

produced with high levels of enantiopurity (85% ee). The process efficiently forms diquinane, hydrindane and *cis*-decalone ring systems, however the reaction is limited to α,β -unsaturated ketone substrates (esters underwent conjugate addition but failed to undergo subsequent aldolization). Products such as **27ea** map nicely onto the ring system of the cardiotonic steroid digitoxin (Scheme 9).¹⁵

An enantioselective desymmetrization of boryl-substituted cyclobutanones **29** through cleavage of a carbon–carbon single bond to create 1-indanones **30** containing benzylic quaternary carbon centers was shown by Murakami and co-workers (Scheme 10).¹⁶ In this reaction, transmetalation of boron with rhodium (I) is followed by intramolecular addition of the arylrhodium species to the carbonyl. The resultant bicyclic structure undergoes an enantioselective β -elimination and protonolysis. Ideal conditions included the use of the chiral biaryl diphosphine ligand (*S*)-SEGPPOS (**31**) with a Rh (I) dimer and was shown to accommodate four different groups at the 3-position including the bulky isopropyl group (**29c**→**30c**) with excellent yields (81–96%) and enantioselectivities (79–95%). Indanone **30d** was then applied to the formal synthesis of α -herbertenol.¹⁷ A drawback of this methodology is that the synthesis of the boryl-substituted cyclobutanones which is quite laborious.

Recently, Dong and co-workers reported an enantioselective desymmetrization of cyclopropenes **33** bearing a quaternary carbon through an intermolecular Rh-catalyzed hydroacylation that is favored by the resulting release of strain energy to form cyclopropanes **34** with a quaternary stereocenter (Scheme 11).¹⁸ This methodology utilizes a rhodium (I) dimer and a ferrocene-based phosphine ligand **35** for the *in situ* formation of a chiral catalyst. Salicylaldehyde derivatives **32** were used as hydroacylation agents due to the known coordination of the phenolic oxygen to rhodium. Various arylaldehydes with electron-donating or electron-withdrawing substituents in the *ortho*-, *meta*-, or *para*-positions were readily oxidized. The cyclopropene structure could be modified to accommodate a wide range of aryl groups. The reaction favors formation of the *trans*-diastereomer of **34** (dr's range from >20:1–6:1) and the enantiopurity of both diastereomers is generally excellent (95%).

Prochiral γ,δ -unsaturated amides **36** were shown to undergo an enantioselective desymmetrization via a rhodium catalyzed asymmetric hydroboration (Table 2)¹⁹. The amide directs a *cis* addition of boron **39** and BINOL-derived phenyl phosphite **38** controlled the enantioselectivity of the reaction. Organoboronate intermediates were then oxidized to yield the alcohol products **37**. Alternatively, intermediates were converted into trifluoroborates **40** and underwent a palladium catalyzed cross-coupling reaction to yield arylated products **41**. Modest variation of the substituent α to the amide (R^1) and on the amide nitrogen was tolerated (R^2).

Pd

Asymmetric palladium-catalyzed coupling reactions have been an area of growing interest.²⁰ Other than nucleophilic substitutions pioneered by Trost and Stoltz, palladium-

catalyzed methods to generate enantioenriched quaternary carbons have been limited in scope.^{1c,21} Here the less prominent desymmetrization strategies are examined.

In 2004, Willis and co-workers developed an enantioselective Suzuki reaction that produces compounds with a quaternary carbon center utilizing a desymmetrization strategy (Scheme 12).²² The achiral 5-membered ditriflate **43** was selectively monocoupled with a variety of aromatic boronic esters in the presence of palladium diacetate and the monodentate phosphine ligand **45** to produce mono arylated products, **44**. Boronic acids with *para*, *meta*, and heterocyclic substitution patterns performed moderately well in the procedure (46–66% yield and 72–85% ee). The exception of *ortho*-substituted boronic acids (<5% yield, substrate **44c**) likely is due to steric factors. The consistent enantioselectivities over a range of boronic acid substrates may indicate that the enantiodetermining step is oxidative addition. While results are moderate, this is the first example of a Suzuki coupling that sets the absolute stereochemistry of quaternary carbon centers.

As a follow up to their desymmetrization of ditriflates through a Suzuki reaction, Willis and colleagues developed an asymmetric palladium catalyzed carbonylation reaction of prochiral six-membered ring 1,3-dienes **46** (Scheme 13).²³ Again, a monodentate phosphine ligand was utilized now featuring an electron-rich PCy₂ substituent, **49**. Unfortunately, the reaction produced a mixture of mono- and di-carbonylated product **47** and **48**. Enantioselectivities of the chiral products, monoester **47**, were seen to improve as a function of the yield of diester **48**, which led the authors to propose an *in situ* kinetic resolution mechanism.

Other

Jacobsen and co-workers report the desymmetrization of 3,3-disubstituted oxetanes with (salen)Co(III) complexes.²⁴ In this process oxetanes with a pendant hydroxy group such as **50** can undergo enantioselective ring opening to yield tetrahydrofurans with a quaternary center such as **51** using either monomeric or oligomeric (salen)Co(III) complexes **52** or **53** (Table 3). In general, both catalysts were found to be efficient in the transformation (yields 77% and ee's 96%); however the oligomeric catalyst **53** required lower catalyst loadings and often shorter reaction times.

The gold catalyzed desymmetrization of readily available 1,4-dynamides **54** to yield methylene pyrrolidines **55** (Scheme 14) was recently reported.²⁵ Following pre-formation of gold phosphonate complex **56** using binol derivative TRIP, cyclization of 1,4-dynamides in chlorinated solvents at –55 °C led to high yields (67%) of pyrrolidines with quaternary centers in good enantiopurity (ee 74%). In general, reactions were conducted using 5 mol% of catalyst and complete in less than 24 hours; however, when R was not an aryl group (**55f** and **55g**), 15 mol% of catalyst **56** and 7 days was required.

Optically active cyclic amines or imines **58** bearing a quaternary stereocenter were formed via an enantioselective hydroamination of dialkenes or dialkynes **57** with oxazolinyborate zirconium catalyst **59** (Table 4).²⁶ In the case of amino dialkenes (**58a–58g**), two stereocenters are formed in the reaction, one through the desymmetrization of a quaternary center and the other through C–N bond formation. By varying reaction conditions the authors were able to achieve reasonable diastereocontrol. Dilute conditions at room

temperature favored the formation of the shown *cis* diastereomer (under more concentrated conditions the *trans* isomer was favored). Piperidine formation (entry 6, ee = 32%) is much less selective than pyrrolidine formation (entries 1–5).

Organocatalytic

Chiral organic molecules have become attractive catalysts in the development of enantioselective reactions. In contrast to metal catalysts, organocatalysts are typically easier to handle and store, often involving non-inert reaction conditions.²⁷ Commercial availability and lower catalyst loadings have led to their widespread application.

Triazolium salt **62**, was utilized to induce an enantioselective Stetter reaction through the desymmetrization of substituted cyclohexadienone **60** available from 3,4,5-trimethylphenol (Scheme 15).²⁸ Product **61** containing a quaternary stereocenter adjacent to a tertiary ether was obtained in good yield and excellent enantioselectivity. While the methodology was thoroughly explored in regards to 2,4,6-trisubstituted phenols which produce neighboring tertiary centers, formation of quaternary carbons was limited to this single example. This was likely due to the lack of readily available starting materials.

Scheidt and co-workers reported an asymmetric synthesis of α,α -disubstituted cyclopentenones **65** via an intramolecular aldol reaction of prochiral diketones **63** catalyzed by chiral *N*-heterocyclic carbene **66** (Table 5).²⁹ For aryl ketones, the reaction proceeds through a β -lactone intermediate (**64**), which can eliminate CO₂ to generate the cyclopentene in good yield and enantiopurity (entries 1–8). When aliphatic ketones were used, the reaction stopped at the β -lactone (entries 9–10). The resulting enantioselectivities dropped slightly when larger substitution patterns were used at R¹ (entries 5–8).

Spinol-derived phosphoric acid **70** was found to catalyze an intermolecular sulfur nucleophile ring-opening of achiral 3-substituted oxetanes **67** (Scheme 16).³⁰ This desymmetrization process was effective for the formation of highly enantioenriched tertiary stereocenters (R² = H), but less stereoselective for the formation of alcohols such as **69a** and **69b** with quaternary carbons (enantiopurity of 71 and 77%). A plausible transition state **V** is suggested wherein the larger substituent (R_L) is positioned away from the catalyst to minimize steric interactions.

An organocatalytic desymmetrization of diynoic acids **71** through a bromolactonization was recently reported by Hennecke and co-workers.³¹ Enantioenriched bromoenol lactones **72** containing a tetrasubstituted alkene and a quaternary center were prepared using dimeric chinchona alkaloid derivative **73** and NBS (Table 6). Internal alkynes generally yielded products with higher enantiopurity. Mechanistically, the catalyst is proposed to activate the carboxylic acid through one of the pyridazine nitrogens and potentially also stabilize the forming intermediate halirenium ion (transition state **VI**, Figure 2).

Spirocyclohexadienoneoxindoles **74** were shown to undergo desymmetrization via an organocatalyzed asymmetric sulfa-Michael addition (Table 7).³² This reaction utilizes aminethiourea catalyst **77** and generates spirocyclic oxindoles such as **76** bearing an all-carbon quaternary center with an adjacent chiral sulfur containing stereocenter as a single

diastereomer (>20:1 dr). The process tolerates a variety of aryl thiols (entries 1–11) and some modest substitution on the oxindole ring (entries 12–14). Overall yields were excellent (77%) and enantioselectivities good (82%).

The desymmetrization of *meso* diols such as **78** through selective acylation was recently described by Chuzel, Bressy co-workers (Scheme 17).³³ This process, which utilizes ferrocenyl Fu based chiral dialkylaminopyridine derivative **80**³⁴ as a catalyst yields monoesters such as **79** bearing 5 contiguous asymmetric centers, including 2 all-carbon quaternary stereocenters with up to 94% enantioselectivity. The authors explored two different sets of conditions. The first condition (A) consisted of standard Fu protocols using *t*-AmOH as the solvent and led to high enantioselectivity. The second condition (B) utilized a C₆F₆/CHCl₃ solvent mixture and generally gave yields. Mechanistically, the authors postulate that in C₆F₆ π - π complexation between solvent and the chiral DMAP catalyst led to a standard desymmetrization event. In *tert*-amyl alcohol however, a desymmetrization reaction followed by a kinetic resolution may have been responsible for the enantioselectivities seen. Manipulation of monoacetate products led to complex polyketide fragments **81** (Scheme 18).

Desymmetrization of 2,2-disubstituted 1,3-diols via a chiral phosphoric acid catalyzed oxidative cleavage of benzylidene acetals was recently realized (Scheme 19).³⁵ Dimethyldioxirane (DMDO) was used in combination with catalyst **85** (TRIP) to selectively oxidize benzylidene acetals **82** to esters such as **84** via the proposed intermediate **83** in excellent yields and good enantiopurity. DFT calculations showed that the rate determining step was oxidation by DMDO and that aryl-aryl interactions between the substrate and catalyst are responsible for the high enantioselectivities seen.

We have recently reported the desymmetrization of prochiral diesters **87** through a Brønsted acid catalyzed intramolecular cyclization with phosphoric acid **85** to yield lactones **88** containing an all-carbon quaternary center.³⁶ Desymmetrization substrates were prepared in 3 steps and high yields from commercially available *tert*-butyl malonate (**86**). Lactonization yields were generally high and enantioselectivities of products excellent (90% ee for γ -lactones and 86% ee for δ -lactone). Recently, we have found that catalyst loading could be reduced to 1 mol% and reaction times lowered through the use of toluene at 80 °C with only minimal loss in yield and no loss in enantioselectivity (**88a** was prepared in 95% yield and 98% ee).³⁷ Lactone **88a** readily underwent synthetic transformations to yield new useful building blocks with little to no loss in enantioselectivity (Scheme 21).

Asymmetric synthesis of cycloalkanones with an α -quaternary stereocenter such as **95** was accomplished through a chlorination/ring expansion cascade (Table 8).³⁸ Desymmetrization of cyclic substrates **93** was accomplished using 1,3-dichloro-3,3-dimethylhydantoin (**94**) as a chlorine source in combination with organocatalysts (DHQD)₂PHAL and *N*-boc-L-phenylglycine. Choice of solvent had a large impact on the enantioselectivity of the reaction, with toluene performing the best and the addition of molecular sieves led to decreased reaction times. Halogens and alkyl groups in the *meta* or *para* position were tolerated on the aromatic ring, and notably, this was the first time oxa-cyclobutanol substrates (**93h–93l**) were used as ring expansion substrates en route to dihydrofuran-4-(2*H*)-ones.

Olefinic 1,3-diols **96** were shown to undergo a desymmetrization event through bromoetherification catalyzed by C_2 -symmetric sulfide **98** to yield substituted tetrahydrofurans with 3 stereogenic centers, including a quaternary carbon such as **97** by Yeung and co-workers (Table 9).³⁹ *N*-Bromosuccinimide (NBS) was used as the halogen source and key to the reaction was addition of 1 equivalent of MsOH (other acids were less effective). In general the reaction proceeded with good diastereoselectivity, the exceptions being for *meta*-substituted aromatics (entry 8, **96h**→**97h**) and when a methyl replaces the benzyl group at the diol stereocenter (entry 13, **96m**→**97m**). Enantioselectivities for the reaction range from 64–92%. The nature of the substituent on the aromatic ring did not significantly affect the reaction. Notably, the reaction required 3 days at –78 °C for completion. The bromocyclization is thought to go through active species **99** which could deliver Br to olefin **96** through a transition state such as **VII** (Scheme 22).

Yeung and co-workers expanded upon their desymmetrization of diols through bromoetherification by utilizing diolefinic substrates **100** to yield tetrahydrofuran substrates with two quaternary stereogenic carbon atoms such as **101** (Scheme 23).⁴⁰ This cyclization utilized chiral amino-thiocarbamate catalyst **102** and *N*-bromophthalimide (NBP) as the bromine source. Substrates with symmetric diolefins (i.e.; $R^1 = R^2$) were first examined and yielded heterocycles with reasonable dr and enantioselectivities. Diols with unsymmetric diolefins ($R^1 \neq R^2$), usually favored cyclization onto the phenyl olefin (**100h**, **100i**, **100k**, and **100l**); however, when the mixed methyl olefin was used, cyclization occurred at the less hindered olefin (**100j**). Interestingly, several of the tetrahydrofuran substrates were able to undergo a second halocyclization of the intermediate olefin to yield spirocyclic compounds **103**.

Prochiral 2,2-disubstituted cyclopentene-1,3-diones **104** underwent an enantioselective desymmetrization via a formal $C(sp^2)$ -H alkylation to substituted products **106** which contain a quaternary carbon (Table 10).⁴¹ The reaction is catalyzed by tertiary amino-urea-based catalyst **107** and utilizes readily available nitroalkanes **105** as the alkylating agents. The reaction presumably proceeds via an addition reaction followed by an *in situ* elimination and isomerization. Choice of the external base, Na_2CO_3 , was carefully examined such that the base would not participate in the conjugate addition (only facilitate the elimination). The substrate scope for the reaction is quite general, accommodating a wide array of substitution on the dione **104** and the nitroalkane **105**. Yields were generally good and enantioselectivities of up to 96% were seen for this process. Manipulation of products into more complicated structures was explored and reactions were generally diastereoselective (products **109–111**, Scheme 24). A second alkylation of **106aj** gave compound **112** which is the core of the antibiotic natural product (+)-madindoline B.⁴²

The asymmetric synthesis of bicyclo[3.2.1]octanes and bicyclo[3.3.1]nonanes containing an all-carbon quaternary center such as **114** and **115** was achieved via the desymmetrization of 2,2-disubstituted cyclic 1,3-diketones **113** (Table 11).⁴³ The process involves a chiral phosphoric acid (TRIP, **85**) promoted reversible enolization followed by an intramolecular Michael addition. The major product for the reaction is a bicyclic compound with the

substituent in the equatorial position. Yields and enantioselectivities were good to excellent, although slightly lower for the bicyclo[3.3.1]nonanes **115** ($n = 2$).

Conclusion and outlook

The asymmetric formation of all-carbon quaternary centers continues to be of significant interest to the synthetic community as seen by the vast number of publications in recent years. Desymmetrization is an increasingly attractive method for the enantioselective preparation of these challenging stereocenters. Advantages to this strategy are that one can influence stereocenters remote from the reaction site and often set multiple stereocenters in a single operation. The utility of desymmetrizations are best highlighted when the prochiral starting material is readily available and the commercially available catalyst can be used in low loadings. As seen from this review, many of the most efficient desymmetrizations involve an intramolecular process. We expect the future of this field to be in the development of more generalized intermolecular processes.

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Scheme 1.

General desymmetrization strategy to set all-carbon quaternary stereocenters

2a/3a: R ¹ = Me, R ² = allyl
98% yield, 89% ee	2l/3l: R ¹ = Me, R ² = (<i>E</i>)-C(Me)=CHCOOEt
95% yield, 98% ee
2b/3b: R ¹ = Me, R ² = Et
95% yield, 84% ee	2m/3m: R ¹ = Me, R ² = CH ₂ C(Br)=CH ₂
93% yield, 92% ee
2c/3c: R ¹ = Me, R ² = <i>i</i> -Pr
96% yield, 94% ee	2n/3n: R ¹ = Me, R ² = (CH ₂) ₂ CH=CH ₂
98% yield, 94% ee
2d/3d: R ¹ = Me, R ² = Bn
99% yield, 95% ee	2o/3o: R ¹ = Et, R ² = Ph
98% yield, 49% ee
2e/3e: R ¹ = Me, R ² = Ac
85% yield, 95% ee	2p/3p: R ¹ = CH=CH ₂ , R ² = Bn
88% yield, 84% ee
2f/3f: R ¹ = Me, R ² = Ph
98% yield, 83% ee	2q/3q: R ¹ = CH ₂ CH=CH ₂ , R ² = CH ₂ C(Me)=CH ₂
91% yield, 51% ee
2g/3g: R ¹ = Me, R ² = CN
73% yield, 99% ee	2r/3r: R ¹ = CN, R ² = Et
67% yield, 98% ee
2h/3h: R ¹ = Me, R ² = CH=CH ₂
91% yield, 54% ee	2s/3s: R ¹ = CN, R ² = CH ₂ CH=CH ₂
72% yield, 98% ee
2i/3i: R ¹ = Me, R ² = CH=CBr ₂
99% yield, 97% ee | 2t/3t:

92% yield, 87% ee |
| 2j/3j: R ¹ = Me, R ² = C(Me)=CH ₂
97% yield, 96% ee | |
| 2k/3k: R ¹ = Me, R ² = (<i>E</i>)-CH=CHCOOEt
95% yield, 85% ee | |

Scheme 2.

Desymmetrization of diols using a Cu-Pybox complex

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Scheme 4.
Desymmetrization of dialkynes via CuAAC

Conditions: (a) *N*-Hydroxy-4-methylbenzimidoyl chloride (2.5 equiv), Et₃N (2.5 equiv), CH₂Cl₂, 10 h.; (b) PhI (1.5 equiv), Pd(PPh₃)₄ (5 mol%), CuI (5 mol%), Et₃N (10.0 equiv), DMF, 4 h.; (c) Raney Ni, MeOH, H₂, 4 h.; (d) Lindlar's catalyst, quinine (10.0 equiv), MeOH, H₂, 5 h.

Scheme 5.
Synthetic manipulation of alkyne product

Scheme 6.

Asymmetric copper catalyzed azide-alkyne click cycloaddition

Scheme 7.
Desymmetrization by copper-catalyzed *N*-arylation

Figure 1.
Origin of enantioselectivity for **21q**

Scheme 8.
Asymmetric desymmetrization of diamides

Scheme 9.
Products as precursors to steroids

Scheme 10.

Desymmetrization of boryl-substituted cyclobutanones

Scheme 11.
Hydroacylation of prochiral cyclopropenes

Scheme 12.
Enantioselective Suzuki reaction

- 47a/(48a):** R = CH₂Ph
34(57)% yield, 95% ee
- 47b/(48b):** R = CH₂Ar (4-OMeC₆H₅)
34(47)% yield, 94% ee
- 47c/(48c):** R = CH₂Ar (4-CNC₆H₅)
44(32)% yield, 89% ee
- 47d/(48d):** R = CH₂Ar (4-CF₃C₆H₅)
40(15)% yield, 85% ee
- 47e/(48e):** R = CH₂Ar (4-FC₆H₅)
35(36)% yield, 95% ee
- 47f/(48f):** R = CH₂Ar (2-CH₃C₆H₅)
36(28)% yield, 80% ee
- 47g/(48g):** R = CH₂-2-Naphthyl
44(33)% yield, 93% ee
- 47h/(48h):** R = CH₂-1-cyclohexene
41(20)% yield, 74% ee
- 47i/(48i):** R = Pr
32(38)% yield, 87% ee
- 47j/(48j):** R = Et
31(38)% yield, 61% ee

Scheme 13.
Desymmetrization via carbonylation reaction

Scheme 14.
Enantioselective cyclization of diynamides

Scheme 15.
Desymmetrization via an intramolecular Stetter reaction

Scheme 16.
Desymmetrization of 3,3-disubstituted oxetanes

Figure 2.
Possible transition state

Scheme 17.

Enantioselective desymmetrization of *meso* primary diols

Scheme 18.
Synthesis of polyketides

Scheme 19.
Asymmetric synthesis of 1,3-diols

Scheme 20.
Enantioselective desymmetrization of diesters

Scheme 21.
Synthetic transformations

Scheme 22.
Plausible mechanism for bromocyclization

Scheme 23.
Desymmetrization diolefinic diols

Scheme 24.
Synthetic transformations of alkenes

Table 1

Conjugate addition-aldol cyclization of prochiral diones

Entry	Substrate	Product	Results
1	26a	27aa	83% yield >99:1 dr, 90% ee
2	26a	27ab	87% yield >99:1 dr, 90% ee
3	26a	27ac	88% yield >99:1 dr, 94% ee
4	26b	27bb	94% yield >99:1 dr, 87% ee
5	26c	27ca	97% yield >99:1 dr, 90% ee
6	26c	27cb	87% yield >99:1 dr, 91% ee
7	26c	27cc	77% yield >99:1 dr, 92% ee

Entry	Substrate	Product	Results
8			86% yield >99:1 dr, 85% ee
9			80% yield >99:1 dr, 86% ee
10	26e		82% yield >99:1 dr, 85% ee
11	26e		85% yield >99:1 dr, 88% ee
12			65% yield >99:1 dr, 88% ee
13			93% yield >99:1 dr, 88% ee
14			95% yield >99:1 dr, 87% ee

Table 2

Desymmetrization via catalytic asymmetric hydroboration

entry	R ¹	R ²	product	yield	ee
1	Me	Ph	37a	65	92
2	Ph	Ph	37b	72	92
3	CF ₃	Ph	37c	78	94
4	Me	Bn	37d	62	84
5	Ph	Bn	37e	70	86
6	CF ₃	Bn	37f	71	92
7	Ph	(<i>R</i>)-CH(Me)Ph	37g	76	76
8	Ph	(<i>S</i>)-CH(Me)Ph	37h	74	60

Table 3

Desymmetrization of oxetanes with (salen)Co(III) complexes

entry	substrate	product	catalyst (mol%)	time (h)	yield (%)	ee (%)
1	50a	51a	52 (1)	6	87	99
2			53 (0.01)	6	88	96
3	50b	51b	52 (1)	24	96	98
4			53 (0.01)	24	98	99
5	50c	51c	52 (1)	2	93	99
6			53 (0.01)	12	97	99
7	50e	51e	52 (1)	5	88	97
8			53 (0.01)	5	98	99
9	50f	51f	52 (10)	8	77	96
10			53 (1)	8	95	98

Table 4

Zirconium catalyzed enantioselective desymmetrization of dienes

entry	substrate	product	[substrate]	time	yield (%)	cis:trans	ee (%)
1			5.45 mM	6 h	94	8.9:1	96
2			5.45 mM	2d	84	4.2:1	93
3			5.45 mM	3 h	95	8:1	95
4			65.4 mM	48 h	78	>20:1	97
5			10.9 mM	8d	75	8:1	92
6			5.45 mM	4 d	76	6.6:1	32
7			16.4 mM	6d	74	7:1	89

entry	substrate	product	[substrate]	time	yield (%)	cis:trans	ee (%)
8			5.45 mM	2 h	95	n.a.	91
9			5.45 mM	48 h	94	n.a.	77
10			5.45 mM	72 h	89	n.a.	89

Table 5

Enantioselective synthesis of cyclopentenones

entry	R	R ¹	cyclopentenone	yield (%)	ee(%)
1	Ph	Me (63a)	65a	80	93
2	4-Cl-Ph	Me (63b)	65b	76	94
3	4-Me-Ph	Me (63c)	65c	60	94
4	3-Me-Ph	Me (63d)	65d	65	93
5	Ph	Et (63e)	65e	73	90
6	Ph	allyl (63f)	65f	70	83
7				69	83
8				64	82
9				65	93
10				51	96

Table 6

Desymmetrization of alkynes via bromolactonization

entry	acid	R ¹	R ²	yield (%)	ee (%)
1	71a	CO ₂ Me	H	72a, 79	72
2	71b	CO ₂ Me	Me	72b, 91	90
3	71c	CO ₂ Me	Et	72c, 90	76
4	71d	CO ₂ Me	Ph	72d, 83	96
5	71e	CO ₂ Me	4-ClC ₆ H ₄	72e, 92	96
6	71f	Ph	H	72f, 90	70
7	71g	Ph	Me	72g, 98	92
8	71h	Ph	Ph	72h, 94	84
9	71i	Ph	4-ClC ₆ H ₄	72i, 92	92
10	71j	4-FC ₆ H ₄	Me	72j, 98	92
11	71k	3-ClC ₆ H ₄	Me	72k, 90	90
12	71l	CH ₂ O(4-BrBz)	H	72l, 82	94

Table 7

Asymmetric synthesis of spirocyclic oxindoles

entry	R ¹	R ²	R ³	76	yield (%)	ee (%)
1	H	Me (74a)	Ph (75a)	76aa	92	84
2	H	Me (74a)	2-Me-C ₆ H ₄ (75b)	76ab	85	83
3	H	Me (74a)	4-Me-C ₆ H ₄ (75c)	76ac	85	82
4	H	Me (74a)	3-Me-C ₆ H ₄ (75d)	76ad	83	82
5	H	Me (74a)	2-F-C ₆ H ₄ (75e)	76ae	77	88
6	H	Me (74a)	4-F-C ₆ H ₄ (75i)	76af	85	88
7	H	Me (74a)	3-F-C ₆ H ₄ (75g)	76ag	84	85
8	H	Me (74a)	4-Cl-C ₆ H ₄ (75h)	76ah	95	86
9	H	Me (74a)	1-Naphthyl (75i)	76ai	86	92
10	H	Me (74a)	2-Naphthyl (75j)	76aj	89	88
11	H	Me (74a)	2-Thienyl (75k)	76al	83	95
12	MeO	Me (74b)	2-Naphthyl (75j)	76bj	85	84
13	Cl	Me (74c)	2-Naphthyl (75j)	76cj	80	84
14	Me	Me (74d)	2-Naphthyl (75j)	76dj	81	82
15	H	Bn (74e)	2-Naphthyl (75j)	76ej	82	92

Table 8

Enantioselective desymmetrization through chlorination/ring expansion

entry	X	R	product	time (h)	temp (°C)	yield (%)	ee
1	CH ₂	H	95a	96	−40	76	96
2	CH ₂	3-Me	95b	96	−40	82	97
3	CH ₂	4-Me	95c	96	−40	70	93
4	CH ₂	4- ^t Butyl	95d	96	−40	75	91
5	CH ₂	3-F	95e	96	−40	55	92
6	CH ₂	4-F	95f	96	−40	80	96
7	CH ₂	4-Cl	95g	96	−40	72	95
8	0	H	95h	72	−40	73	93
9	0	3-Me	95i	72	−40	67	93
10	O	4-Me	95j	72	−40	72	90
11	0	4-F	95k	120	−20	73	91
12	O	4-Cl	95l	120	−20	63	87
13	CH ₂ CH ₂	H	95m	96	−40	58	77
14			95n	96	−40	70	93
15			95o	96	−40	70	94
16			95p	96	−40	53 <i>cis/trans</i> = 4.5:1	94, 92

entry	X	R	product	time (h)	temp (°C)	yield (%)	ee
17			95q	96	-40	76 dr > 35:1	75

Table 9

Asymmetric bromoetherication and desymmetrization of diols

entry	diol. R^1, R^2	product	yield (%)	dr	ee
1	96a , Ph, H	97a	92	93:7	87
2	96b , 4-Me- C_6H_4 , H	97b	96	>99:1	80
3	96c , 2-naphthyl, H	97c	97	92:8	64
4	96d , 4-F- C_6H_4 , H	97d	91	95:5	86
5	96e , 4- CF_3O - C_6H_4 , H	97e	93	85:15	60
6	96f , 4-Cl- C_6H_4 , H	97f	86	89:11	88
7	96g , 4-Et- C_6H_4 , Ph	97g	96	92:8	90
8	96h , 3-MeO- C_6H_4 , Ph	97h	99	71:29	95
9	96i , 4-Ph- C_6H_4 , Ph	97i	98	91:9	92
10	96j , 4-F- C_6H_4 , Ph	97j	94	>99:1	82
11	96k , 4- CF_3O - C_6H_4 , Ph	97k	93	>99:1	84
12	96l , Ph, Et	97l	99	>99:1	85
13	96m	97m	73	75:25	82

Table 10

Enantioselective desymmetrization of cyclopentene-1,3-diones

Reaction scheme showing the enantioselective desymmetrization of cyclopentene-1,3-diones (**104**) with a nitro compound (**105**) using catalyst **107** (10 mol%), Na_2CO_3 (1.5 equiv), PhCF_3 (0.5 M), at $-10\text{ }^\circ\text{C}$ to yield product **106**.

entry	R ¹	R ²	product	time (h)	yield (%)	ee
1	CH ₂ Ph (104a)	Me (105a)	106aa	48	88	94
2	CH ₂ -4-Me-C ₆ H ₄ (104b)	Me (105a)	106ba	48	83	93
3	CH ₂ -2-Me-C ₆ H ₄ (104c)	Me (105a)	106ca	48	79	88
4	CH ₂ -1-naphthyl (104d)	Me (105a)	106da	60	83	94
5	CH ₂ -2-naphthyl (104e)	Me (105a)	106ea	48	90	94
6	CH ₂ -4-Cl-C ₆ H ₄ (104f)	Me (105a)	106fa	48	84	88
7	CH ₂ -3-Cl-C ₆ H ₄ (104g)	Me (105a)	106ga	48	88	90
8	CH ₂ -2-Cl-C ₆ H ₄ (104h)	Me (105a)	106ha	70	80	74
9	CH ₂ -4-Br-C ₆ H ₄ (104i)	Me (105a)	106ia	48	82	87
10	 (104j)	Me (105a)	106ja	48	85	93
11	 (93k)	Me (105a)	106ka	72	84	84
12	 (104l) 4-Cl-C ₆ H ₄	Me (105a)	106la	72	73	95
13	<i>i</i> Bu (104m)	Me (105a)	106ma	72	78	80
14	CH ₂ OTBS (104n)	Me (105a)	106na	72	82	92
15	Ph (104o)	Me (105a)	106oa	48	90	67
16	CHPh ₂ (104p)	Me (105a)	106pa	70	86	96
17	CH(4-Cl-C ₆ H ₄) ₂ (104q)	Me (105a)	106qa	48	83	96
18	CH ₂ Ph (104a)	<i>n</i> Bu (105b)	106ab	70	82	70
19	CH ₂ Ph (104a)	CH ₂ Ph (105c)	106ac	72	86	88
20	CH ₂ Ph (104a)	CH ₂ -4-Me-C ₆ H ₄ (105d)	106ad	70	78	88
21	CH ₂ Ph (104a)	CH ₂ CH ₂ Ph (105e)	106ae	70	88	85
22	CH ₂ Ph (104a)	CH ₂ CH ₂ -2-furyl (105f)	106af	56	51	86
23	CH ₂ Ph (104a)	CH ₂ CH ₂ NHPh (105g)	106ag	72	72	80
24	CH ₂ Ph (104a)	CH ₂ CH ₂ NBzPh (105h)	106ah	72	90	82
25	CH ₂ Ph (104a)	CH ₂ CH ₂ OH (105i)	106ai	60	82	55

entry	R ¹	R ²	product	time (h)	yield (%)	ee
26	CH ₂ Ph (104a)	CH ₂ CH ₂ OTBS (105j)	106aj	72	92	88
27	CH ₂ Ph (104a)	Et (105k)	106ak	60	74	90
28	CH ₂ -2-naphthyl (104e)	Et (105k)	106ek	60	79	85

Table 11

Enantioselective desymmetrizing Michael cyclizations

entry	n	R ¹	R ²	product	yield (%)	ee
1	1	Me	Ph	114a	93	91
2	1	Me	4-Me-C ₆ H ₄	114b	91	92
3	1	Me	4-MeO-C ₆ H ₄	114c	92	91
4	1	Me	4-Cl-C ₆ H ₄	114d	80	94
5	1	Me	3-Cl-C ₆ H ₄	114e	79	86
6	1	Me	2-Naphthyl	114f	97	91
7	1	Me	^t Bu	114g	96	95
8	1	Me	2-Pyridyl	114h	76	87
9	1	Me	2-Furyl	114i	80	88
10	1	Me	2-Thienyl	114j	97	92
11	1	Et	Ph	114k	95	93
12	2	Me	Ph	115a	77	82
13	2	Me	4-Me-C ₆ H ₄	115b	95	86
14	2	Me	4-MeO-C ₆ H ₄	115c	94	87
15	2	Me	4-F-C ₆ H ₄	115d	82	86
16	2	Me	4-Cl-C ₆ H ₄	115e	73	87
17	2	Me	4-NO ₂ -C ₆ H ₄	115f	85	72
18	2	Me	3-CF ₃ -C ₆ H ₄	115g	68	86
19	2	Me	2-MeO-C ₆ H ₄	115h	60	83
20	2	Me	2-Cl-C ₆ H ₄	115i	75	92
21	2	Me	2-Naphthyl	115j	96	87
22	2	Me	2-Pyridyl	115k	75	82
23	2	Me	CH ₂ CH ₂ OBn	115l	35	92
24	2	Allyl	Ph	115m	89	86
25	2	Allyl	4-Cl-C ₆ H ₄	115n	94	88
26	2	Ph	Ph	115o	68	94
27	2	Ph	2-Thienyl	115p	50	97
28	2	PMP	Ph	115q	63	94
29	2	PMP	2-Thienyl	115r	49	92