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# Enantioselective Syntheses of Indanes: From Organocatalysis to C—H Functionalization



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# Enantioselective Syntheses of Indanes: From Organocatalysis to C—H Functionalization

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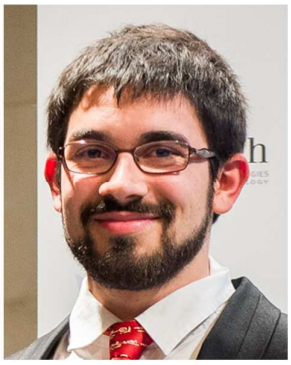
The indanyl core is ubiquitous in a large variety of drugs and natural products. Importantly, the ever-increasing demand for chiral catalysts bearing this scaffold calls for state of the art methods allowing for a step-economical enantioselective access to this structural motif. We herein summarize the asymmetric syntheses of indanes with a particular focus on asymmetric catalysis, covering the literature of the last decade until July 2015.



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*Malek Nechab studied chemistry at Paris 12 University (France) and graduated in 2003. He then joined Jacques Einhorn's group at Grenoble University and received his PhD in 2006. He worked on novel C2-symmetric and axially chiral N-hydroxyphtalimides as catalysts for enantioselective oxidations. This work has been awarded by the "Société Chimique de France" (Prix de Thèse Fournier). He moved to Marseille as a CNRS postdoctoral fellow in Gérard Gil's and Michele Bertrand's groups where he worked on dynamic kinetic resolution of amines. He was then appointed as an assistant professor in 2007 in Marseille. His current research interests include asymmetric synthesis, memory of chirality and chirality transfer in radical and polar cascade reactions*

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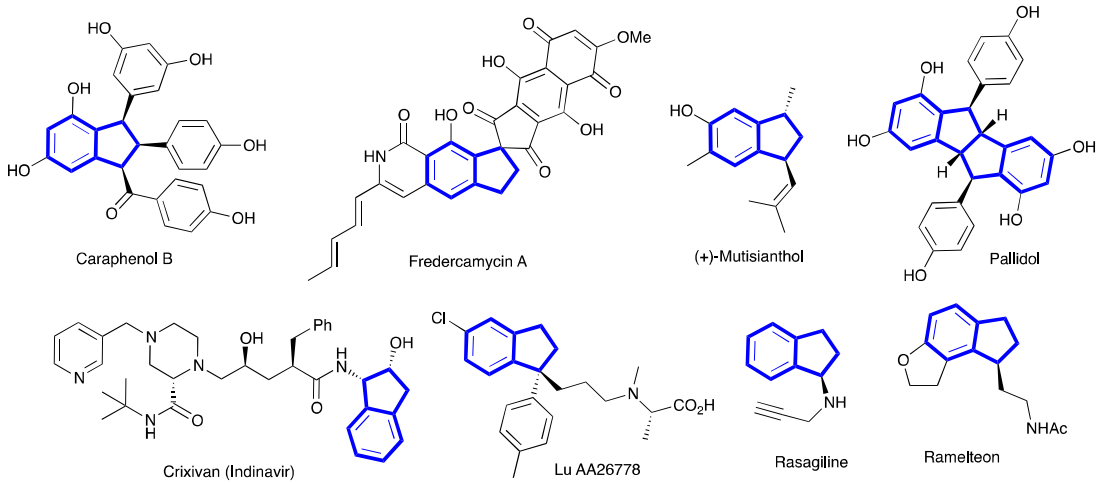


Figure 1 Selected examples of natural products and drugs possessing the indanyl architecture

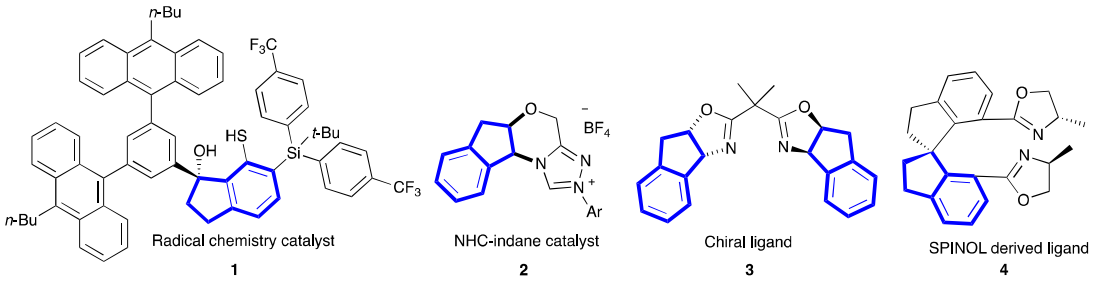


Figure 2 Examples of chiral catalysts and ligands with the indanyl core

## 1. Introduction

The indanyl core is present in numerous natural products, or drugs (Figure 1) and is also essential as the key motif in ligands for chiral catalysts (Figure 2). Particularly, indanes bearing *cis*-vicinal substituents were found as efficient catalysts as well as bioactive compounds.[1] Crixivan, an HIV protease inhibitor developed by Merck, is one of the best-selling drugs for AIDS treatment. The development of such chiral drugs in their single enantiomeric form is of prime importance. The enantioselective synthesis of drugs is a prerequisite for their approval. Thus, it is well established that an enantiomer can exhibit different biological activities than its mirror image. For this reason the challenging asymmetric synthesis of enantiopure indanes continues to be a highly active research area. Importantly, in the last decade the progress in stereoselective C-C bond formation enabled a plethora of methods to construct the indanyl architecture. To illustrate their synthetic utility, we listed selected representative indanes that have been used as organocatalysts,[2] NHC catalyst **2**,[3] chiral ligand **3**,[4] or chiral thiol **1**, the latter of which for enantioselective radical chemistry[5] (Figure 2). For example, SPINOL **4**, a spiro bis-indane ligand reported by Zhou has proved its efficiency in a wide range of applications.[6,7] Likewise, the Rovis catalyst **2** has shown to be versatile in different asymmetric reactions. From a historical perspective, the chirality induction in the synthesis of the indanyl core uses direct functionalization of indenes including hydrogenation,[8] epoxidation[9] or aziridination.[1] Asymmetric additions,[10] reduction of indanones,[11] addition to imine derivatives[12] and kinetic resolution of indanols (or amino-indane)[13,14] have also been reported. Already in 1984, the Merck Company was

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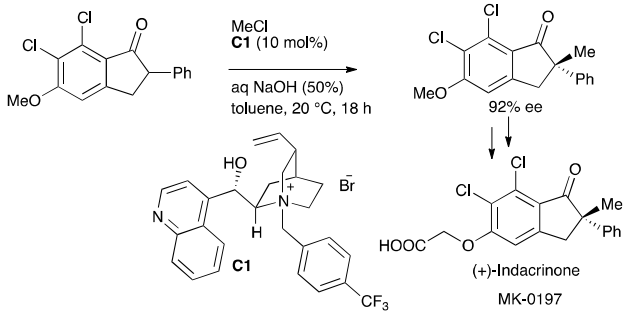
probing the asymmetric synthesis of (+)-indacrinone *via* chiral phase transfer catalysis (Scheme 1).[15]

Despite the importance of this architectural motif there is a lack of a review regarding the stereoselective synthesis of indanes.[16] Hence, asymmetric synthesis of this class of compounds has not been summarized in the literature. Therefore, this review will highlight the recent progress that has been achieved in the last decade exploiting modern asymmetric methodologies to access chiral indanes.[17]



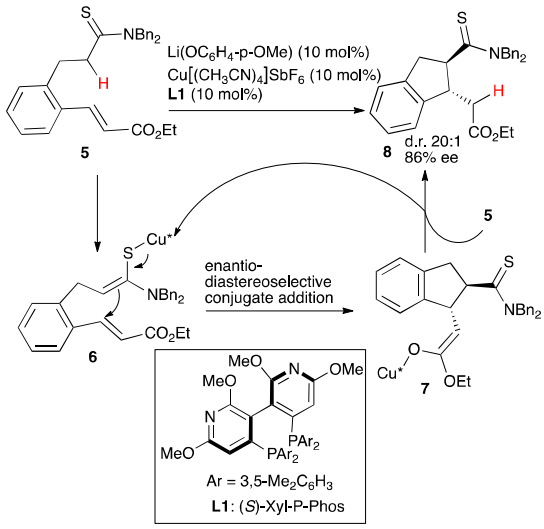

Scheme 1 Asymmetric synthesis of (+)-Indacrinone

This review is classified into two main parts: a) Enantioselective synthesis of the indanyl architecture through a carbocyclization and b) Asymmetric catalysis involving an existing indanyl scaffold. In the first section a selection of the state of the art in asymmetric conjugate addition is discussed, followed by the construction of indanes through a transition-metal catalyzed cyclization. A particular attention will be paid to this strategy because metal-catalyzed reactions hold a significant place in the arsenal of synthetic methods offering a facile access to the indanyl skeleton. The development and availability of commercial chiral ligands provided many opportunities to target this class of molecules in an enantio-enriched form.

## 2. Enantioselective synthesis of the indanyl architecture through a carbocyclization

### 2.1. Asymmetric conjugate additions

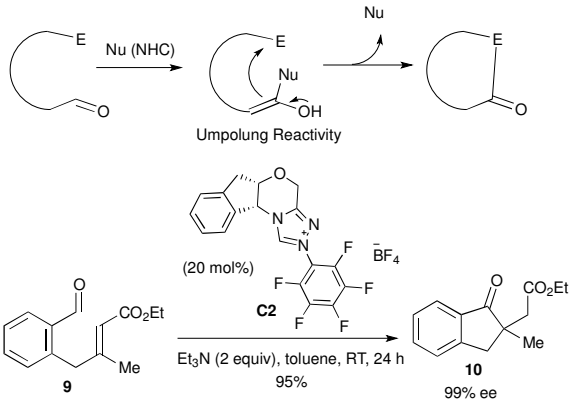
Investigations led by Kumagai and Shibasaki revealed that thioamidates could act as pronucleophiles through soft Lewis acid (LA)/hard BrØnsted base cooperative catalysis.[18] The sulfur atom in substrate **5** is a soft Lewis base that should undergo soft-soft interactions with the copper LA. However, LiOAr served as a Brønsted base, which is able to "enolize" the substrate generating the thioamide enolate **6**. Selective intramolecular cyclization of the latter would afford the 1,4-adduct (Scheme 2).[19] The use of (*S*)-Xyl-P-Phos **L1** as a chiral ligand allowed a high dia- and enantiocontrol in this step. Proton transfer from substrate **5** to the 1,4-adduct **7** made this reaction catalytic. The authors have also been able to use a catalytic amount of mesytil copper and (*S*)-Xyl-P-Phos, in the absence of the lithium base to achieve successful enantioselective cyclization. However, the sole use of Li(O-$C_6H_4$-*p*-OMe) afforded the desired product with *cis* stereochemistry.




Scheme 2 Asymmetric intramolecular conjugate addition of thioamide to α,β-unsaturated esters

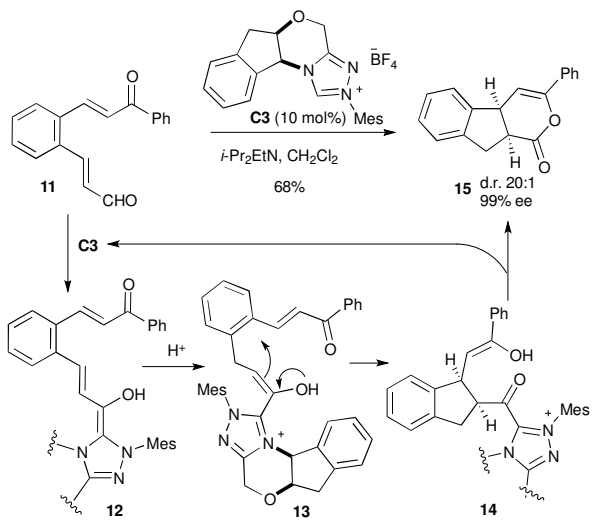
It is important to mention that the intermolecular 1,4-addition according to this strategy that is ArOLi/Copper/phosphine catalysis, has as of yet not met with success.

Enantioselective copper-catalyzed reductive Michael cyclization of substrates containing α,β-unsaturated ketones was reported by Lam as well.[20]




Scheme 3 Enantioselective synthesis of indanes via asymmetric Stetter reaction

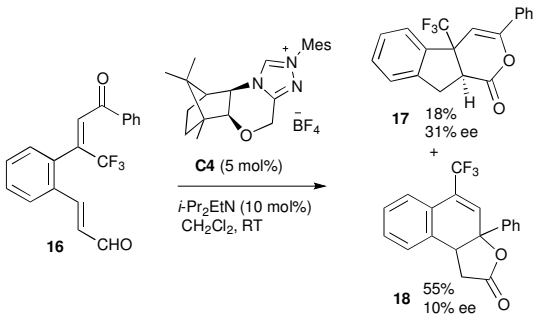
Enders and co-workers have elegantly devised the first asymmetric Stetter reaction using a chiral triazolium catalyst.[21] From this pioneering study, several NHC catalysts have been developed.[22,23] This approach is based on an Umpolung reactivity of the carbonyl function that becomes nucleophilic upon NHC activation (Scheme 3). Based on this strategy, the Rovis group developed **C2**-Catalyzed intramolecular Stetter reaction of benzaldehyde tethered to β,β-disubstituted Michael acceptor **9** with excellent enantioselectivity.[3]




Scheme 4 Enantioselective intramolecular conjugate addition catalyzed by NHC

In 2007, Scheidt and co-workers developed a new route to fused indanes in which a chiral NHC catalyst **C3** triggered an intramolecular Michael addition with excellent dia- and enantiocontrol (Scheme 4).[24] The strategy is based on Umpolung reactivity of conjugated aldehydes **11** that become nucleophilic in the presence of NHC.[25,26] The key step is the enol nucleophilic addition to the pendant Michael acceptor to construct the indanyl skeleton **14** with high *cis*-selectivity. Intramolecular acylation of the resulting adduct **14** afforded the desired product **15** in 68% yield and 99% ee.

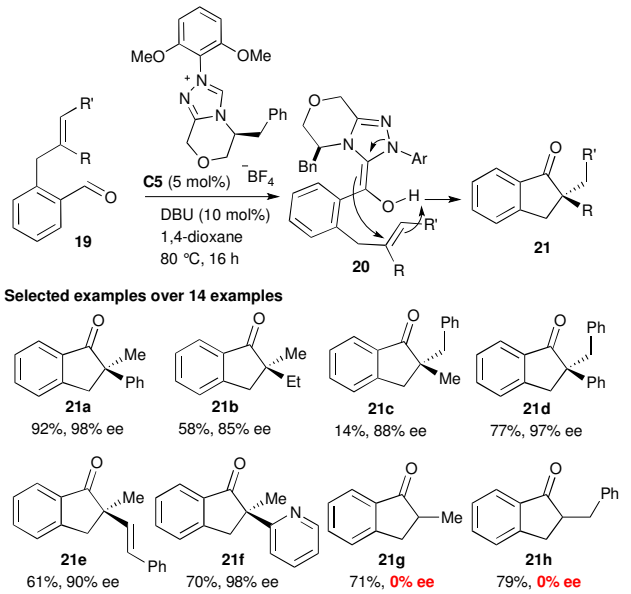
An improvement of this route was reported by You using only 1 mol% camphor-derived triazolium catalyst **C4** (Scheme 5).[27] However in this study, the use of substrate **17** with a trifluoromethyl substituent at the β–position of the enone led to γ–Butyrolactone **18** in 55% yield, along with the Michael adduct **19** as a minor by-product. Unfortunately, both products were obtained with relatively low ee's of 10% and 31%, respectively. The presence of the $CF_3$ group is not beneficial since it introduces a competition in the intramolecular aldehyde-ketone crossed-benzoin condensation.




Scheme 5 Enantioselective intramolecular Michael reaction catalyzed by camphor-derived NHC

The NHC-based strategy was also applied by Studer to furnish indane analogues bearing three contiguous stereocenters upon intermolecular malonate addition.[28]

*In situ* organocatalytic generation of chiral enolate is also possible from carboxylic acid analogues of substrate **11**. Thus, isothiourea has been found as an effective catalyst to induce, similarly to the mechanism outlined in Scheme 4, intramolecular enolate-Michael addition followed by a lactonization to reach analogues of **15**.[29]




Scheme 6 Enantioselective hydroacylation of unactivated alkenes

This intramolecular hydroacylation catalyzed by *N*-heterocyclic carbenes was limited to activated-olefins until Glorius reported the enantioselective reaction of substrates bearing electron-neutral olefins **19** (Scheme 6).[30] Although this example is out of scope of this section, it is however important to highlight the capacity of catalyst **C5** to allow good to excellent enantioselectivities (85-98% ee), except for products **21g,h** in which racemic forms were obtained. This result was attributed to the racemization (enolization) of the product under the basic reaction conditions. DFT Studies of an analogous version of this reaction supported a concerted but asynchronous transition state from intermediate **20** through a Conia-ene type reaction.[31]

Within their program on developing organocatalytic reactions, List and coworkers had, in 2005, associated the MacMillan imidazolidinium salt **C6** and Hantzsch ester to generate the active chiral enamine **24** allowing intramolecular Michael addition with excellent diastereoselectivity (*anti*:*syn* > 50:1) and good enantiomeric excess (86%).[32] The use of the Hantzsch ester was critical in this strategy (Scheme 7). Indeed, hydride transfer revealed the nucleophilic ability of intermediate **24**. The scope of the reaction was extended to aliphatic and aromatic Michael acceptors.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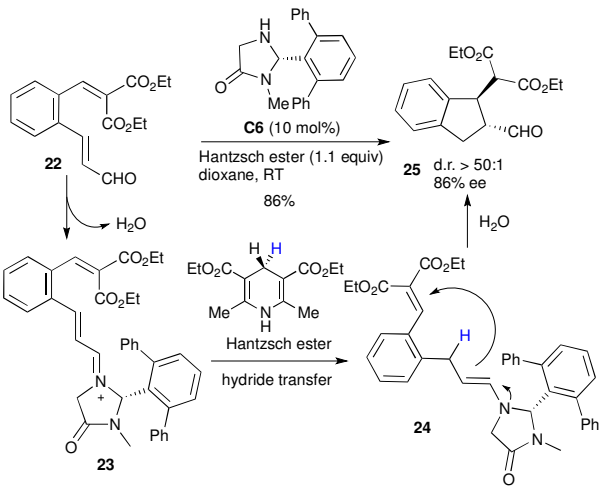
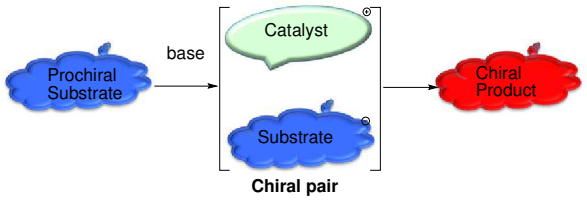



Scheme 7 Organocatalyzed reductive Michael cyclization

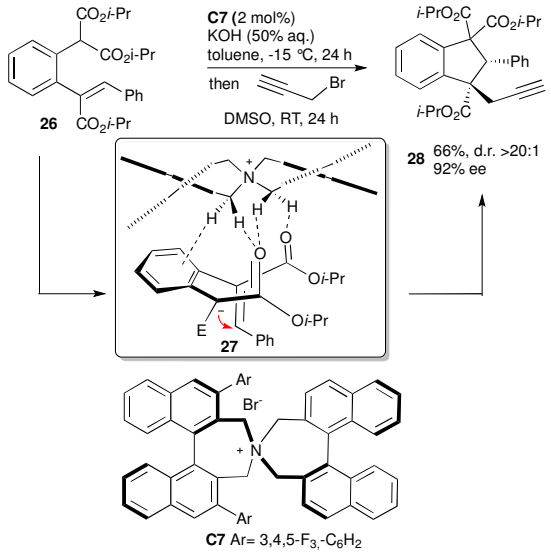
A chiral counterion strategy,[33,34] which normally consists on non-covalent association of a chiral cationic catalyst with an anionic substrate, has been applied by Smith and co-workers to obtain chiral indanes (Scheme 8).[35]



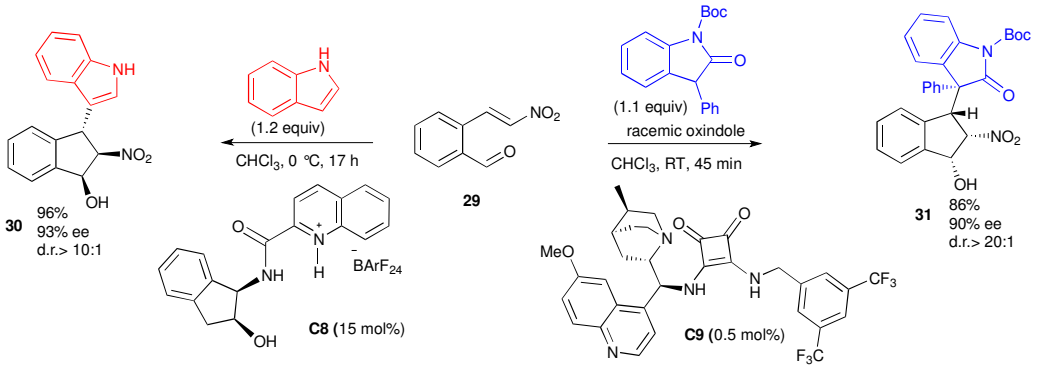

Scheme 8 chiral counterion concept

They reported a disfavoured 5-*endo-trig* Michael cyclization, in highly enantio- and diastereoselective fashion, to provide indane bearing all-carbon stereocenter **28**. Malonate deprotonation by aqueous potassium hydroxide would afford the chiral ion pair **27** (Maruoka catalyst **C7** and enolate of **26**), being responsible for the stereoinduction of the 5-*endo*-adduct. In the predictive model (box of Scheme 9), non-bonding CH–π and CH–O interactions between the substrate and the catalyst could be involved in the transition state. This may contribute to the preferred facial attack and explain the high enantioselectivity. Trapping of an external electrophile (propargyl bromide in this example) allowed the construction of quaternary carbon stereocenter.[36] Quantum chemical calculations showed that this process is under kinetic and thermodynamic control.

However, it is important to highlight the fact that when the substrate is bearing a single electron-withdrawing group, the reaction proceeded through 5-*exo-trig* cyclization, according to the Baldwin rules,[37] to afford the Dieckman adduct. The computational calculations supported a more favorable kinetic control in this case.

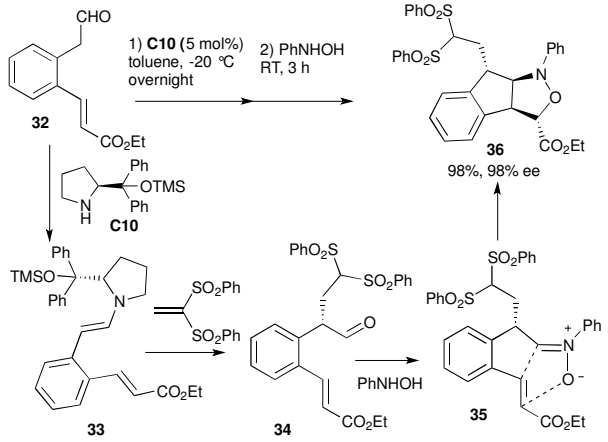



Scheme 9 5-endo-trig Michael cyclization catalyzed by chiral ammonium salt




Scheme 10 Asymmetric synthesis of indanes through an organocatalyzed Michael/Henry domino reactions

A Michael/Henry tandem reaction was reported by Enders and co-workers to construct the indanyl framework possessing three contiguous stereocenters connected to oxindole. Following their first report with indole as the pro-nucleophile to reach product **30**,[38] the authors extended the methodology to include racemic oxindole as the nucleophile (Scheme 10).[39] Despite the broad scope of this reaction, a limitation was detected in the necessity of the presence of an aryl group in the oxindole moiety; which is critical for the stabilization of the C3-carbanion. Chiral catalyst **C9**-assisted Michael addition of the latter to the nitro olefin created two stereocenters. The cascade further evolved through intramolecular Henry condensation. The whole process is very fast and allows the formation of the nitroindanol **31** with excellent yield, diastereomeric ratio and enantioselectivity.



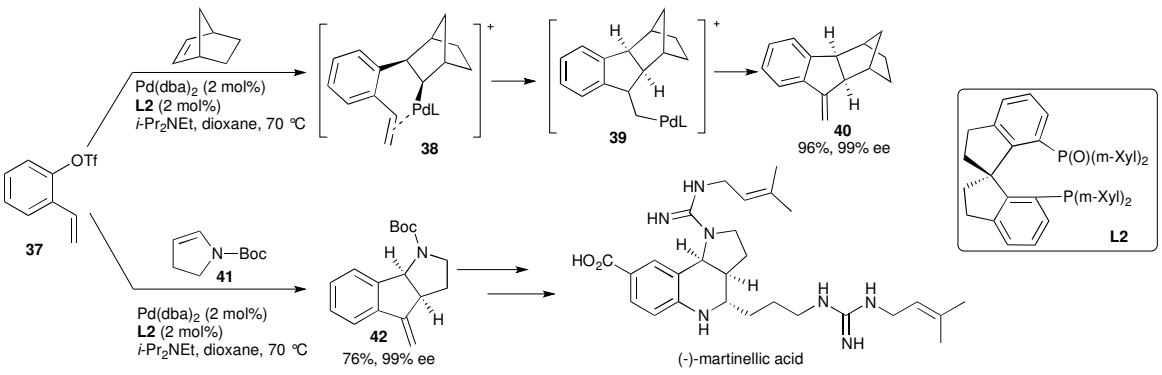

Scheme 11 Asymmetric synthesis of indanes via an organocatalyzed sequential Michael/Cycloaddition reactions

Another sequential organocatalytic Michael/cycloaddition reaction was likewise envisaged to construct the indanyl core.[40] Vinylbisphenyl sulfone was used as the Michael acceptor for the intermolecular addition of chiral enamine **33** to afford, under enantiocontrol, the adduct **34** (Scheme 11). Sequential addition of *N*-hydroxylamine gave the nitrone **35** as a dipole, which involved [3+2] cycloaddition with the pendant dipolarophile enoate and therefore delivered the *cis*-indane **36** in 98% yield and 98% ee as a single diastereomer. It is possible to isolate the Michael product and based on this experiment the authors assumed that the first stereocenter provides diastereoselectivity control in the isooxazoline formation.

### 2.2. Construction of indanes through a transition-metal catalyzed cyclization

#### 2.2.1. Intramolecular cross-coupling reactions

In many synthetic operations, it had become evident that the construction of multiple bonds from easily accessible substrates is highly desirable. Thus, the practical importance of the asymmetric Mizoroki-Heck transformation and their relevance in the construction of complex carbo- and heterocycles is evident. Zhou demonstrated that this kind of reaction could be involved in asymmetric domino cyclization to construct fused indanes of type **40** and **42** (Scheme 12).[41] Different chiral ligands including mono phosphineoxide BINAP(O) have been tested with varying success. The SPINOL derived ligand **L2** was selected to conduct this study and revealed high chemo-, regio- and stereoselectivity. This high selectivity was attributed to a rapid insertion of the strained olefin into the palladium-aryl bond. The resulting *cis*-palladium species would not engage *syn*-hydride elimination and therefore will be involved in a second Heck reaction. As a result of this discovery, the authors have explored this methodology to design a new route of formal synthesis of (-)-martinellic acid, a natural product utilized to treat eye infections.




Scheme 12 Asymmetric domino cyclizations via Mizoroki/Heck reactions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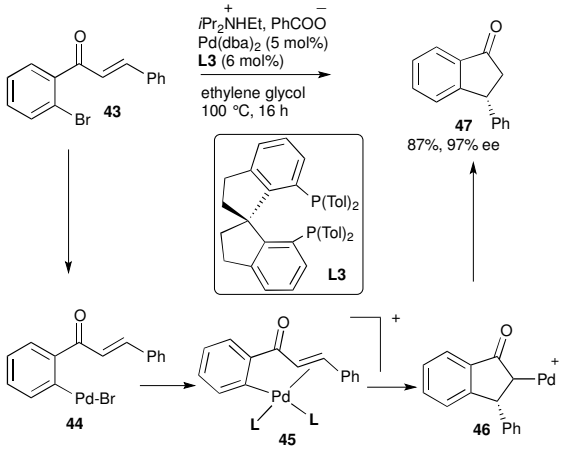



Scheme 13 Palladium-catalyzed asymmetric reductive cyclization of aryl halide

More recently, Calder and Sutherland disclosed an enantioselective synthesis of 3-methylindanols *via* one-pot allylboration/Mizoroki-Heck reaction of 2-bromobenzaldehyde.[42]

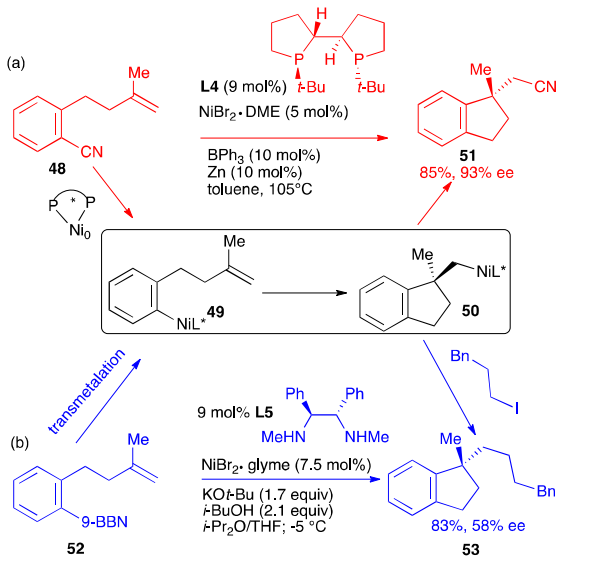
Enantioselective formation of vinylindane through palladium-catalyzed allyl-aryl cross-coupling was also successfully applied.[43]

Spirocyclic indanes have emerged as increasingly powerful ligands for enantioselective reactions.[6] Again, SPINOL derived chiral ligand **L3** demonstrated its power in palladium-catalyzed Mizoroki-Heck cyclization of enone **43** (Scheme 13).[44] This asymmetric reductive intramolecular insertion into the conjugated ketone was elegantly designed using alkylammonium salts and glycol to allow halide dissociation. Enantiomeric excess of 97 % was thereby achieved in the formation of indanone **47**.

It is important to mention that Buchwald had pioneered this type of reaction in 2007 with moderate to good ee's.[45]

Owing to the ability of nickel complexes to activate C–CN bonds demonstrated by Nakao and Hiyama,[46] Jacobsen disclosed the arylcyanation of unactivated olefin **48** to provide indane **51** with all-carbon quaternary stereocenter.[47] Tangphos (**L4**) was used as the chiral ligand to guarantee high enantioselectivity (Scheme 14a). In order to avoid the competing olefin isomerization, zinc was used to *in-situ* reduce the nickel(II) to the active catalyst nickel(0).

A related strategy was utilized by Fu to generate, through a transmetalation-insertion sequence, nickel indane intermediate **50** from arylboron substrate **52** (Scheme 14b).[48] This species was then trapped in a cross-coupling process by iodoalkane. Chiral diamine ligand afforded the cross-coupling product **53** with decent ee (58%).




Scheme 14 Indane synthesis through asymmetric nickel insertion sequence

### 2.2.2. Cyclizations involving C–H functionalization

As in the Mizoroki-Heck reaction, palladium catalyzed C–H functionalization led different research groups to develop broad strategies in the construction of carbocycles.[49,50] Efforts for understanding the mechanism set the stage for the synthesis of enantioenriched compounds thanks to the design of suitable ligands - particularly phosphines - for stereocontrol. Among them, TADDOL-based phosphoramidite ligand **L6** promoted enantioselective intramolecular arylation of alkenyl triflates in order to target indanes bearing all-carbon quaternary stereocenter **57** (Scheme 15).[51] The catalytic cycle proposed by different authors for this reaction starts with an oxidative addition of the alkenyl triflate substrate, followed by C–$H_{Ar}$ activation in which a carbonate (or carboxylate) acts as anchored base. This would initiate a concerted deprotonation and metalation of the aryl group.[52,53] The thus-formed chiral palladium species **55** should act as a chiral source to discriminate the two-enantiotopic aromatic *o*-hydrogens. It has been found that polar solvents, such as dimethylacetamide (DMAc), have a beneficial influence on both enantioselectivity and catalytic activity, under exceedingly mild reaction conditions at ambient temperature. *Ortho*, *meta*- or *para* aromatic substitution pattern was not detrimental for the reaction. Interestingly, a chlorinate substitution in *para*



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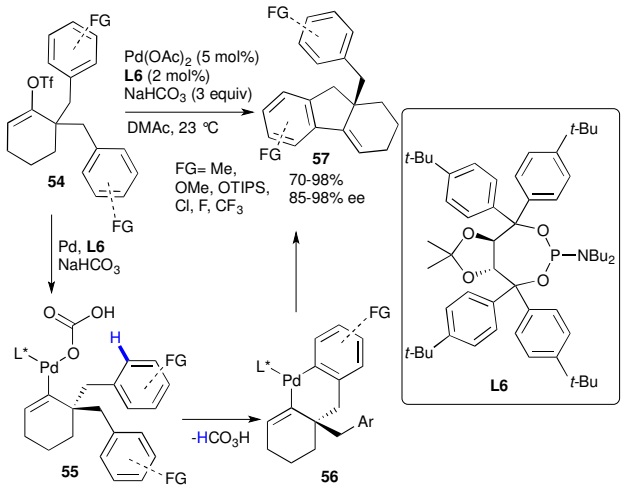
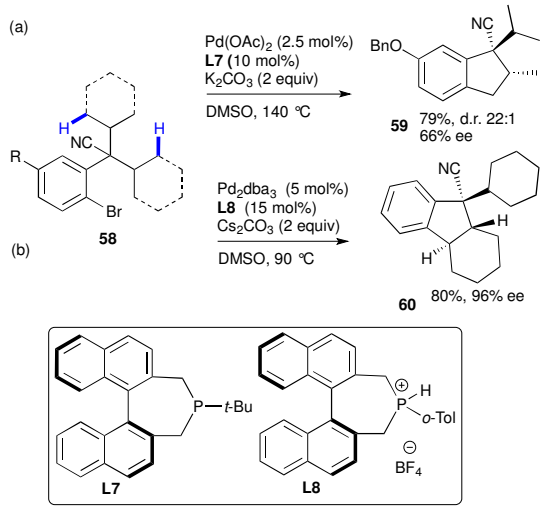
remains unreactive toward palladium and no proto-dehalogenation product was observed.




Scheme 15 Palladium C–H functionalization in the construction of chiral indanes

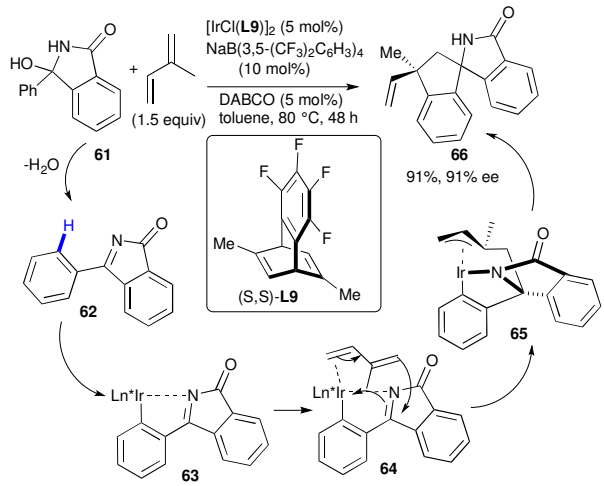
An intramolecular palladium-catalyzed enantioselective C($sp^3$)–H arylation was disclosed by Baudoin's team.[54] In this case, the substrate **58** bears diastereo- and enantiotopic C-H bonds.[55] In the presence of a chiral phosphine ligand, the desired indane **59** was obtained in high diastereomeric ratio (22:1) and acceptable enantiomeric excess (66%) (Scheme 16a). The scope of this reaction revealed that heterocylic analogues could be reached with higher enantioselectivity (90% ee).

An extension of this methodology to fused indanes **60** bearing three stereocenters has been recently reported (Scheme 16b).[56]




Scheme 16 Intramolecular Pd-Catalyzed C–H arylation

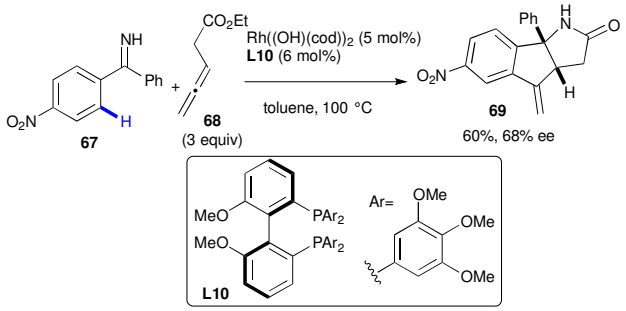
In 2013, the Nishimura group reported that iridium catalyst was involved in C($sp^3$)–H bond activation of ketimine **62** (Scheme 17).[57] The resulting chiral aryliridium(I) species **63** would then set the stage for an oxidative cyclization with 1,3-diene to afford **65** with most probably the control of the stereochemistry of the spiranic carbon. Reductive elimination of the iridium catalyst would generate spiroaminoindane **66** in high yield and enantioselectivity.




Scheme 17 Iridium C–H activation of ketimines in the asymmetric synthesis of spiranic indanes

In 2010, Cramer reported the elegant synthesis of indane based on direct C–H activation of ketimine **67** and allene **68** (Scheme 18). The presence of the nitrogen atom played a crucial role to enable the functionalization of the C($sp^2$)–H. However in this study, only a preliminary example was devised with enantiomeric excess of 68% in the formation of product **69**.[58]

In a work that followed this report, the use of racemic allene revealed that a dynamic kinetic asymmetric transformation (DYKAT) strategy was operable providing a high ee. [59]




Scheme 18 Enantioselective synthesis of indanes based on C–H functionalization

The rhodium-catalyzed cyclization of alkynes was the strategy of choice employed by Matsuda and co-workers. In this case, phenyl rhodium species - generated from a rhodium precursor and $PhB(OH)_2$ - was involved in the regioselective *syn*-addition to 1,4-enyne generating (*Z*)-alkenylrhodium intermediate **71** (Scheme 19).[60] This geometry is suited for C($sp^2$)–H bond activation producing 1,4-Rh migration, the resulted arylrhodium **72** is then undergoing intramolecular addition to



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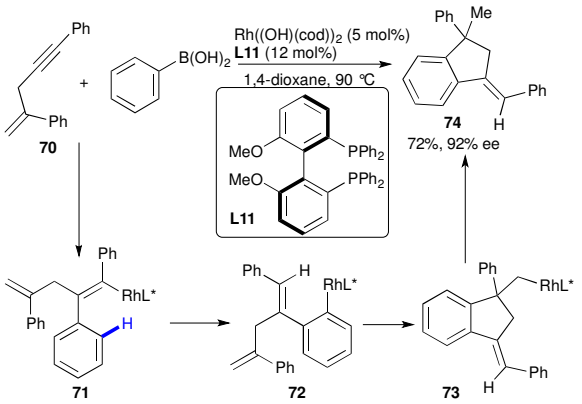
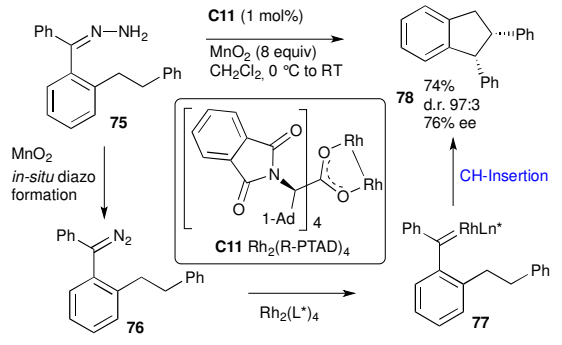
the tethered alkene moiety to release the indane methylene rhodium species **73**. Protonation of the latter is the last step to afford the desired product **74** bearing all-carbon quaternary stereocenter. Testing a series of axially chiral bisphosphine ligands revealed **L11** as the best choice giving 92% ee.




Scheme 19 Rhodium-catalyzed annulations of 1,4-enynes with aryl boronic acids

In recent years, rhodium complexes have been identified as very useful catalysts for C–H alkyl insertion reactions.[61] The selectivity challenge has been tackled notably through the development of elaborated catalytic systems. Among them rhodium-carbenoids obtained from the reaction of rhodium catalysts and diazoesters have proven to be extraordinarily useful in this regard. [62,63] These reactive metal carbenes are generated *in situ* after the extrusion of nitrogen from the diazoester.

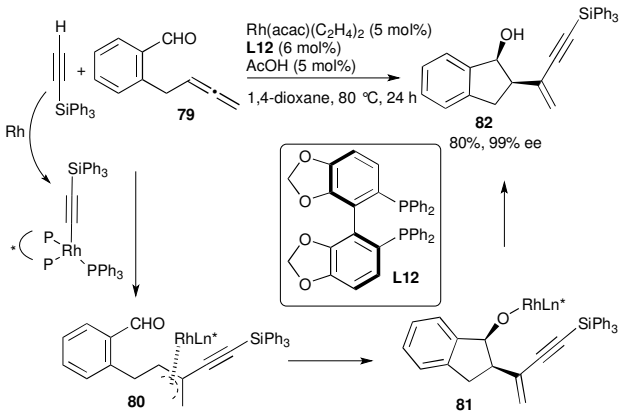
A recent study has demonstrated that efficient one-pot diazo formation and intramolecular C–H insertion of donor-donor metal carbenoid could be achieved with good enantioselectivities.[64] The use of hydrazone **75** was found to be beneficial for the *in situ* diphenydiazo formation upon $MnO_2$ oxidation (Scheme 20). These reaction conditions were compatible with the asymmetric C–H insertion, which allowed a one pot process for the indane framework construction. Compound **78** was obtained in *syn* form with high diastereoselectivity and 76% ee.




Scheme 20 Rhodium catalyzed C–H alkyl insertion in the access to chiral indanes

### 2.2.3. Transition-metal catalyzed addition reactions

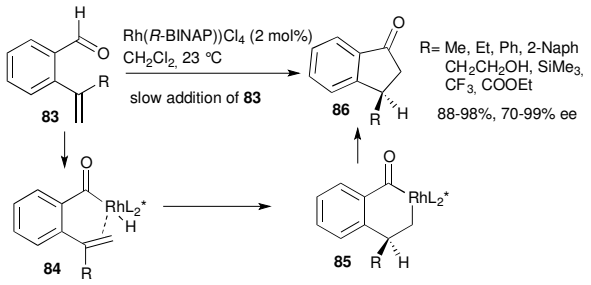
The development of axially chiral phosphine ligands is one of the cornerstones for the development of rhodium-catalyzed asymmetric transformations, such as C–H activation, addition, cycloisomerization, among others. The rhodium-catalyzed asymmetric addition of terminal alkynes to allenyl aldehyde **79** resulted in the formation of indanol **82** in good yields and excellent enantioselectivity.[65] The stereoinduction was accomplished by the use of (*S*)-Segphos ligand **L12** in the *cis*-cyclization of the $\pi$-allyl rhodium intermediate **80** (Scheme 21).




Scheme 21 Rhodium-catalyzed asymmetric additions of terminal alkynes to allenyl aldehydes

We have highlighted the NHC-catalyzed hydroacylation of unactivated olefins (Scheme 6). Rhodium catalyzed analogous reactions are also known. Morehead Jr. and co-workers reported hydroacylations of 2-vinyl benzaldehyde **83** to synthesize the indanone system (Scheme 22).[66] This reaction likely proceeds *via* initial oxidative addition to the aldehyde followed by 1,2-migratory insertion to lead to metallocycle **85**. Reductive elimination of the latter affords the desired product **86** with ee's ranging from 70% to 99% and yields of up to 98%.

The cobalt-catalyzed analogous reaction was reported more recently by Yoshikai.[67]




Scheme 22 Enantioselective rhodium-catalyzed hydroacylations of 2-vinyl benzaldehydes

The major problem that could arise from the use of diazoesters (like in Scheme 20 and Scheme 41) is their hazardous nature. The *in situ* generation of $\alpha$-oxo Au-carbene through oxidation of alkyne is an elegant strategy to address this problem.[68] This



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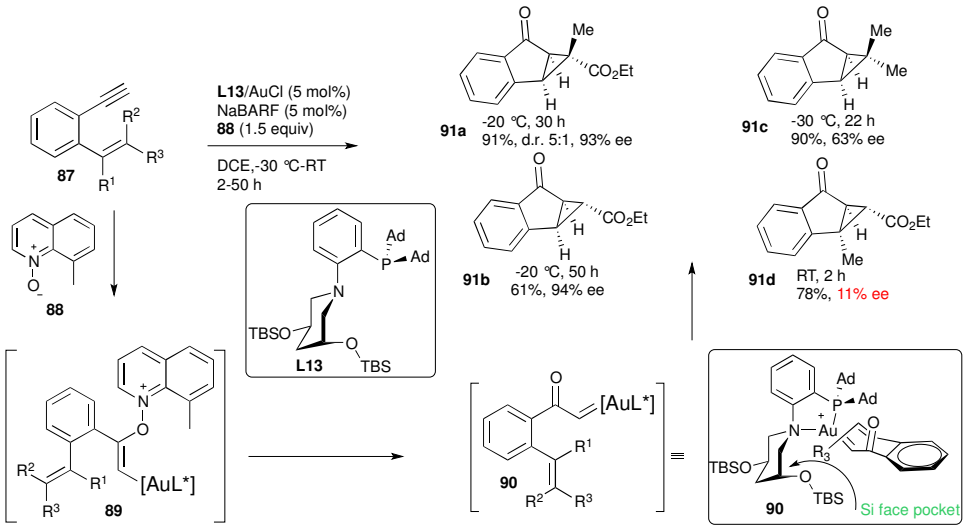
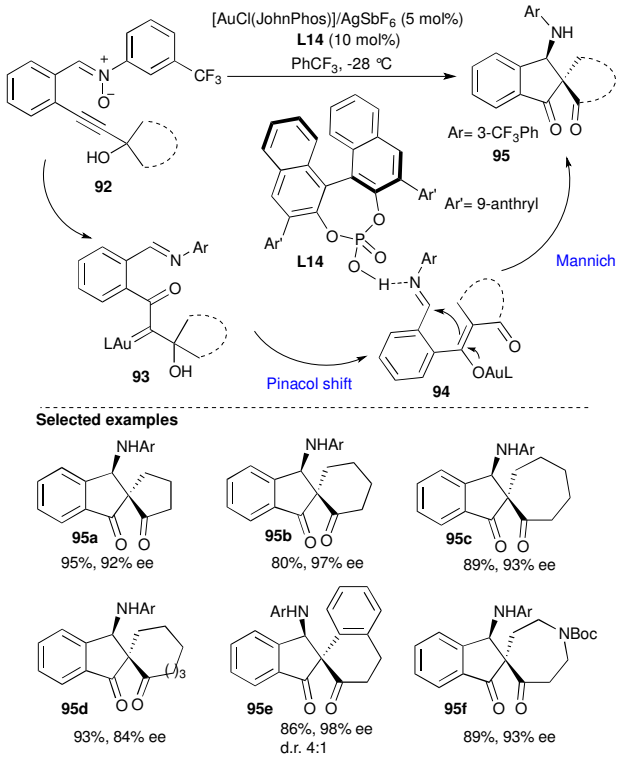
methodology was applied to the cylopropanation of 1,5-enynes to furnish cyclopropylindane in racemic form.[69]

In 2015, Zhang developed new chiral *P*,*N*-bidentate ligand **L13** that enabled enantioselective cyclopropanation of **87** (Scheme 23).[70] Conventional ligands, such as Segphos or a spiroketal bisphosphine, were unsuccessful in catalyzing the intramolecular process. However, the $C_2$-symmetric piperidine bidentate ligand allowed for the generation of efficient chiral α-oxo gold carbene intermediate **90** that triggered the asymmetric cyclopropanation of the pendant alkene in a high enantio- and diastereoselective fashion.




Scheme 23 Gold-catalyzed oxidative asymmetric intramolecular cyclopropanation




Scheme 24 Enantioselective synthesis of spiro-indanes through a cascade involving α-oxo gold-carbene formation/pinacol rearrangement/Mannich addition

Electron-poor and electron-rich olefins as well as α- and β-Me-substitutions were tolerated. Interestingly, when β-Me ($R^1$=H, $R^2$=Me, $R^3$=$CO_2$Et) was used as 5:1 *E*/*Z*-mixture, it afforded the desired product **91a** as a mixture of 5:1 of two diastereomers possessing 93% and 87% ee's. This result demonstrated the stereospecificity of the cyclization. In contrast, the α-methyl-substituted substrate ($R^1$=Me, $R^2$=H, $R^3$=$CO_2$Et) revealed a detrimental impact on the enantioselectivity of **91d** (11% ee only). The Absolute configuration assignments were established on the basis of X-Ray analysis data and helped the authors to rationalize the mode of chiral induction. The explanation for the stereochemistry observed is assumption that the axial OTBS on the piperidine shields the *Re* face and allows an opened pocket for the *Si* face attack. This hypothesis is supported by the experiment with axial OH catalyst instead of OTBS that afforded considerably lower ee (73 *vs* 94%).

A cascade reaction based on intramolecular *N*-oxide-mediated α-oxo gold-carbene formation, pinacol rearrangement followed by Mannich addition of the enolate was first developed by Shin in racemic version.[71] In 2013, Zhang has further developed this approach in its enantioselective version by using Brønsted acid **L14** as a chiral relay catalyst (Scheme 24).[72] The enantiodetermining step is clearly the Mannich addition. The rate of the catalyzed addition by the chiral Brønsted acid is faster than the non-catalyzed one, which is reflected by the high ee observed in the formation of product **95**.



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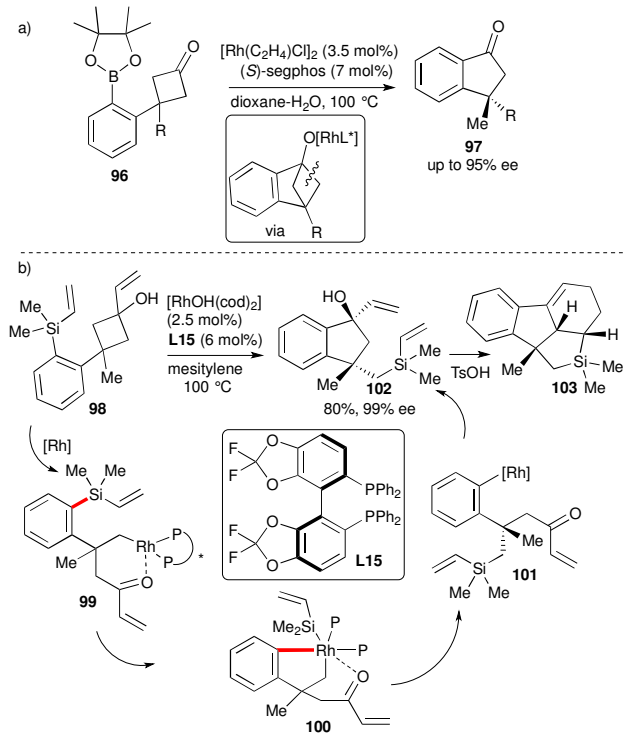
#### 2.2.4. Enantioselective C–C bond cleavage

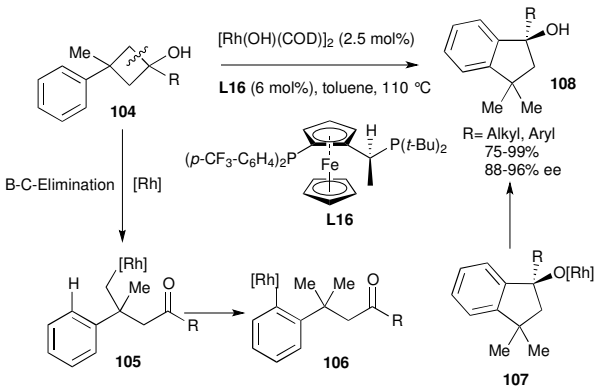
Compared to C–H bond functionalizations, asymmetric activations of C–C bonds are rather scarce, the reason being the inert nature of the C–C bond and the usually facile reverse pathway reaction.[73] To address this challenging task, metal-assisted oxidative β-cleavage ability of the cyclobutanols is a successful concept because the opening of this strained ring is thermodynamically favorable.[74,75] In 2006, Murakami and co-workers disclosed the first synthesis of enantioenriched indanone **97** catalyzed by chiral rhodium based on this strategy (Scheme 25a).[76]




Scheme 25 Enantioselective synthesis of indanol derivatives via Rh-catalyzed C–C activation

The rhodium-catalyzed activation of the C–Si bond was the key feature exploited by Cramer to induce a step-economical reaction (Scheme 25b).[77] The first elementary step starts with the enantioselective desymmetrizative β-C-elimination from cyclobutanol **98** that should give primary alkyl rhodium intermediate **99**. 1,4-Rhodium migration would afford the more stable aryl rhodium species **100**. The latter complex could then evolve through reductive elimination and addition of the resulting intermediate **101** to the tethered ketone which affords the indanol **102**. This bis vinyl product is further transformed to the tetracylic compound **103** after dehydration of the alcohol function followed by Diels-Alder reaction.

The same group developed a C–C/C–H activation sequence to indane analogues of **102**. Chiral Ferrocenyl ligand combined with rhodium catalyst gave access to enantiopure indanols **108** (Scheme 26).[78]

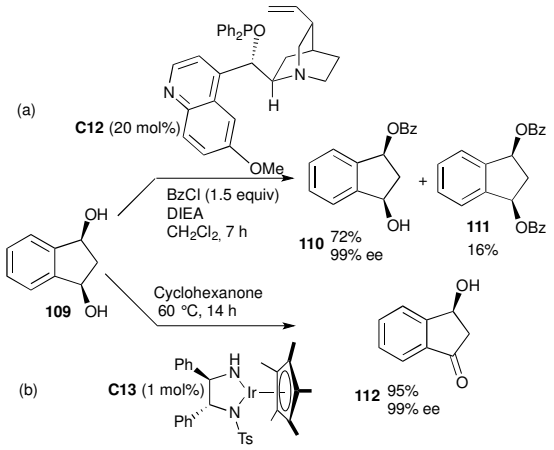



Scheme 26 C–C activation of cyclobutanols followed by C–H arylation in the enantioselective synthesis of indanols

## 3. Asymmetric catalysis involving an existing indanyl scaffold

### 3.1. Desymmetrization of prochiral indanes

The desymmetrization of *meso* diols was achieved in two manners, either by preserving the integrity of both prochiral stereocenters or through a stereoablative process, that is the destruction of one stereogenic center.[79,80] For instance, the enantioselective monobenzoylation of *cis* indane 1,3-diol **109** catalyzed by phosphinite-derived quinine **C12** was reported in 2005 (Scheme 27a).[81] The homochiral diol **110** was obtained in 72% yield and 99% ee, in addition to 16% yield of the dibenzoylated product **111**. Control experiment of kinetic resolution of racemic monobenzoylated **110** with the catalyst failed, suggesting that the initial acylation is responsible for the high enantioselectivity.

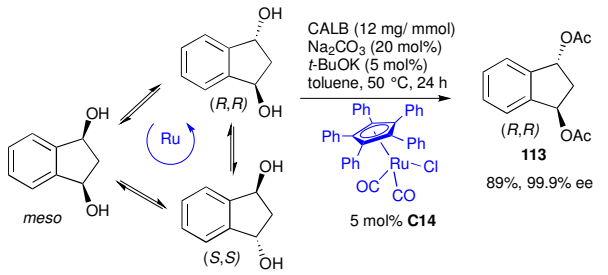



Scheme 27 Desymmetrization of meso diols

The enantioselective oxidation of the *meso* substrate is also a desymmetrizative process. Suzuki exploited this idea with chiral iridium catalyst **C13** in order to access the hydroxyl ketone **112** in 95% yield and 99% ee (Scheme 27b).[82] Cyclohexanone served as the solvent as well as the hydrogen

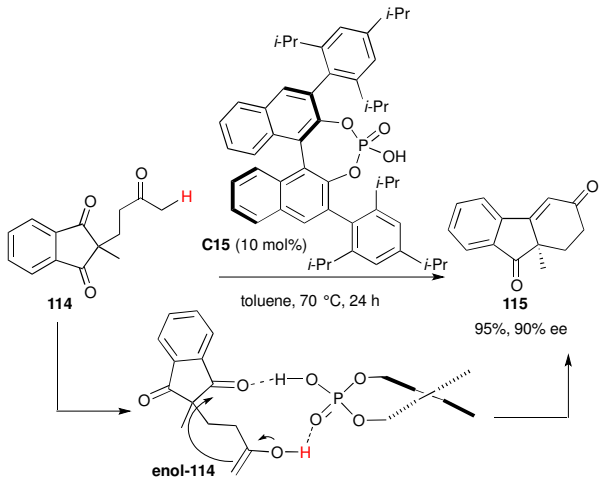
acceptor.[83] The oxidative strategy was also applied to racemic indanol and a high selectivity factor was viable in this efficient kinetic resolution.

In the two examples illustrated in Scheme 27, a pure *meso* starting material was used. The latter needs to be preliminarily separated from its *trans* isomer before submitting it to reaction conditions of the desymmetrization. This difficulty has been overcome by Bäckvall thanks to a DYKAT strategy (Scheme 28).[84,85] Indeed, coupled kinetic resolution (KR) and epimerization of a (±)/*meso* mixture of 1,3-diol **109** occurred efficiently by the combination of an enzyme and ruthenium catalyst **C14**. CAL-B lipase is known to ensure a high enantioselectivity in the acylation of alcohols and amines. In addition, the ruthenium catalyst is very efficient in the racemization of alcohols. The synergy of both processes constitutes an effective route toward the *trans* di-protected diol **113** obtained in 89% yield and 99.9 % ee.




Scheme 28 DYKAT desymmetrizative strategy in the access to enantiopure indane diacetate

A one-pot reaction combining hydrogenation of 1,2-indanedione and chemoenzymatic dynamic kinetic resolution of the resulting racemic 2-hydroxy-1-indanone was recently reported by Leino.[86]



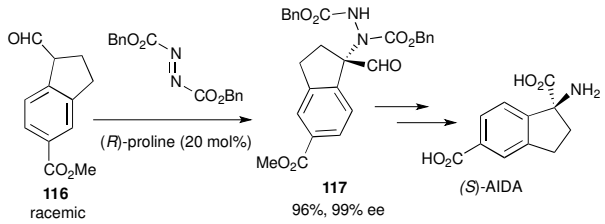

Scheme 29 Chiral phosphoric acid catalyzed aldol condensation

The asymmetric synthesis of fused indanone **115** *via* the desymmetrization of prochiral triketone **114** was investigated by Akiyama (Scheme 29).[87] Chiral phosphoric acid **C15** involved hydrogen bonding with **enol-114** and the resulting aldol product **115** was then released under enantiocontrol. Theoretical studies showed that the *Si* face attack was 1.3 kcal/mol preferred over the opposite face attack due to steric reasons.

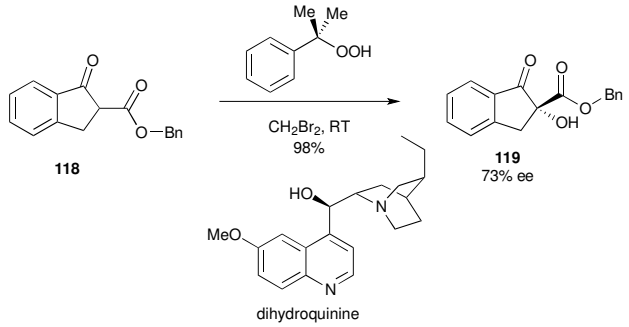
### 3.2. Organocatalyzed transformation of indanyl core

The last two decades have witnessed a wide use of proline as an efficient organocatalyst for asymmetric synthesis.[88,89] The ability of this catalyst to induce stereoselectivity was thus demonstrated in the enantioselective synthesis of indane **117** (Scheme 30).[90] The synthetic power of the strategy was demonstrated by targeting the metabotropic glutamate receptor ligand (*S*)-AIDA, known as antagonist in neurodegenerative diseases.[91] Enamine catalysis allowed high enantiocontrol in the elaboration of the indane bearing amino-acid.

The enantioselective palladium-catalyzed allylation of aldehyde **116** was furthermore reported by List, creating all-carbon stereogenic center.[92]




Scheme 30 Proline-catalyzed amination of indane carboxaldehydes




Scheme 31 Quinine-catalyzed asymmetric hydroxylation of indane ketoesters

Jørgensen reported metal-free organocatalytic asymmetric hydroxylation of β-ketoester **118** (Scheme 31).[93] In this reaction, the hydroquinine was used as organocatalyst and the cumyl peroxide as the stoichiometric oxidant.

Palladium-catalyzed enantioselective hydroxylation of β-ketoester with dioxirane has also been studied by Hii.[94]

Closely related work has been recently published by Zou *et. al*. using tartaric acid derived catalyst.[95]

α-Halogenation[96] and Michael addition[97,98] of β-keto esters **118** as well as α-protonation[99] and allylation[100] of TMS enolate could also furnish analogous products in an enantiomerically-enriched form.



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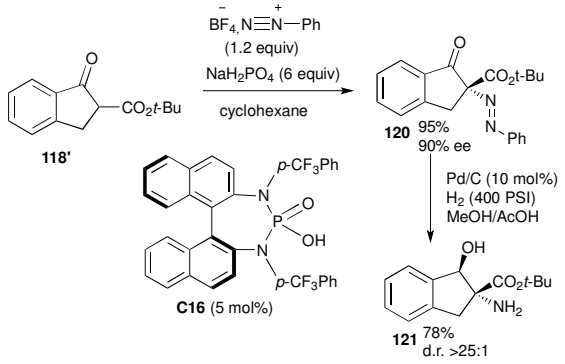
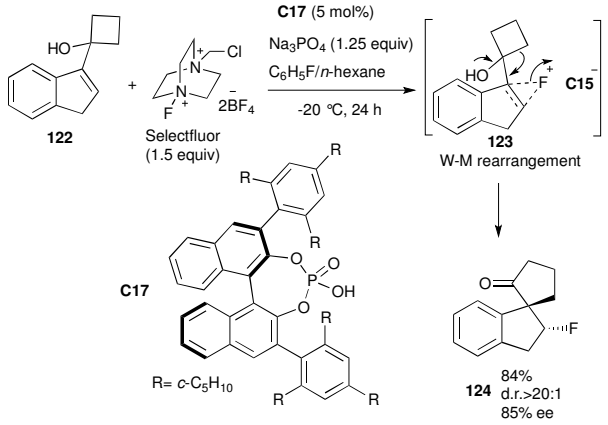
Lewis acid-catalyzed asymmetric hydroxylation of β-ketoester analogue of **118** in the presence of racemic oxaziridine as stoechiometric oxidant afforded product analogue of **119**.[101]

Very recently, Toste and co-workers have exploited chiral anion phase transfer catalysis as source of stereo-induction. Thus, aryldiazonium cations were used as the electrophilic partner and the resulting chiral pair reacted with nucleophilic enol of **118'** to deliver enantioenriched diazenated indanone **120** (Scheme 32).[102] Commonly used catalysts were found to provide only modest results. Therefore, novel chiral phosphate catalyst **C16** was designed to ensure high enantioselectivity of up to 90% ee. Hydrogenation of the diazene provided the amino acid derivative **121**. The strategy was also applied to access 5-hydroxy-2-aminoindan-2-carboxylic acid, a conformationally constrained tyrosine analogue.

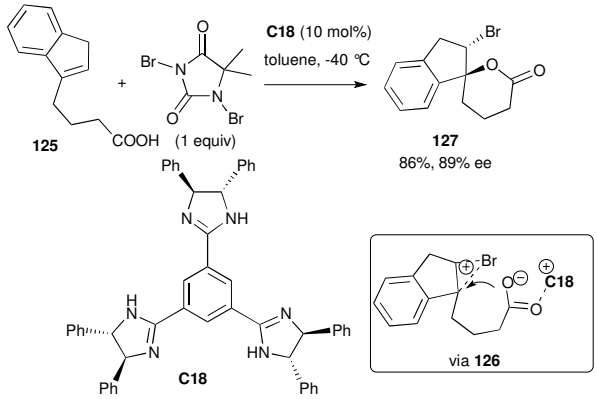



Scheme 32 Chiral anion phase transfer catalysis in the enantioselective diazenation of enolate



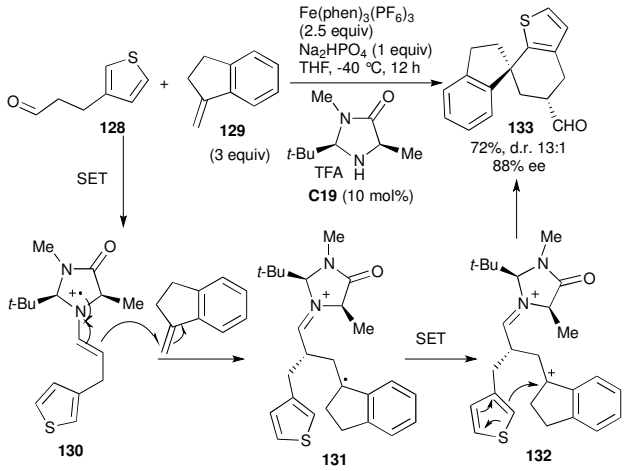

Scheme 33 Enantioselective fluorocylisation through chiral phase transfer strategy

In the previous examples we have highlighted the power of the chiral couterion strategy to induce high enantioselectivities. Alexakis and co-workers inspired by the fluorocyclization reactions reported by Toste,[103] endeavored to develop an elegant organocatalytic fluorination of allylic alcohol **122** followed by Wagner-Meerwein (W-M) rearrangement of **123** (Scheme 33).[104] The reaction obeyed to phase transfer catalysis (PTC) principles, where a lipophilic chiral anion (the active catalyst) extracts Selectfluor into the organic phase (hexane), affording thus a chiral electrophile. The latter is then engaged in electrophilic addition to the olefin. The Wagner-Meerwein (W-M) rearrangement would proceed with chiral induction since ion pairing still guarantees a chiral environment. The good enantioselectivity obtained for product **124** served as a proof for this assumption. Additionally, this information is supported by the d.r. of 1:1 obtained in the absence of the chiral catalyst whereas nearly total diastereoselectivity was reached in its presence. The same group has also reported the corresponding electrophilic iodination.[105]




Scheme 34 Enantioselective bromolactonization with $C_3$-symmetric catalyst

Enantioselective halocyclization was also achieved by Fujioka using $C_3$-symmetric trisimidazoline catalyst **C18**.[106] 1,3-Dibromo- hydantoin was used as a brominating agent in order to trigger the bromolactonization of the internal alkenoic acid **125** (Scheme 34). The origin of this asymmetric induction relies again on the chiral couterion strategy through the formation of chiral ammonium salt **126** between the carboxylic acid and the catalyst. The *anti*-selective bromonium ring opening was accomplished to afford compound **127** with high levels of enantiomeric excess.




Scheme 35 Organo-SOMO catalysis in the formation of spiro-indane **133**



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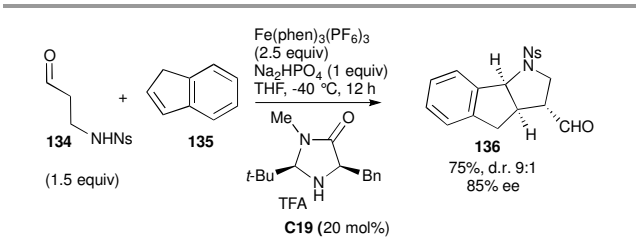
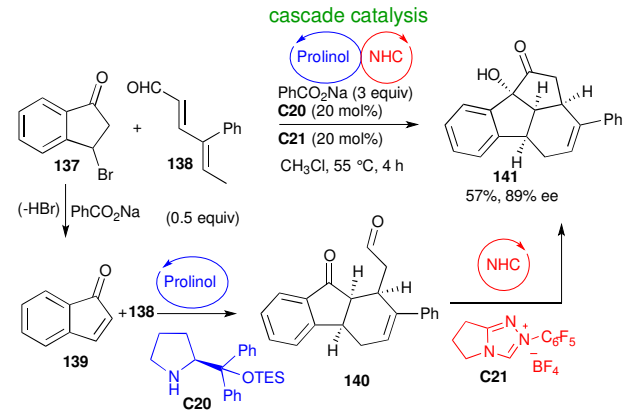
The enantioselective synthesis of carbocycles *via* radical/polar cascade reactions has gained exponential momentum in recent years.[107] For instance, MacMillan and Sibi independently developed the concept of "Organo-SOMO" catalysis.[108,109] As exemplified in Scheme 35, this strategy is based on aldehyde **128** activation with stoichiometric amounts of oxidant [$Fe(phen)_3(SbF_6)_3$] and chiral imidazolidone catalyst **C19** to form radical cation **130**.[110] Radical addition of the latter to the indene **129** gives rise to radical **131**. Stereocontrol is undoubtedly originating in this step through orientation opposite to the methyl group. A second oxidation of the resulting radical would liberate the benzylic cation **132**. Trapping this intermediate by the thiophene moiety through intramolecular Friedel-Crafts cyclization provides spiro indane **133** with high levels of dia- and enantioselectivities.

When the tethered thiophene nucleophilic part was replaced by a protected amine group, such as in substrate **134**, along with the radical acceptor was indene **135**, fused heterocycle **136** could then be obtained with the control of three contiguous stereocenters (Scheme 36).[111]




Scheme 36 Organo-SOMO-catalyzed formal cycloaddition of indenes



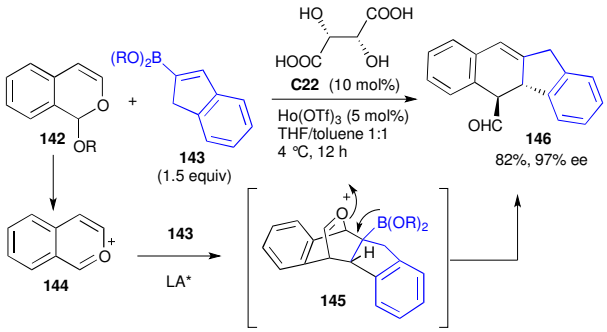

Scheme 37 Prolinol/NHC-catalyzed cascade Cycloaddition/benzoin condensation

Chen and co-workers reported a cascade catalysis involving prolinol organocatalyst **C20** to induce enantioselective Diels-Alder reactions followed by NHC-catalyzed **C21** intramolecular benzoin condensation (Scheme 37).[112] The stereodetermining step is constituted by the intermolecular cycloaddition of the trienamine (formed from prolinol and 2,4-dienal **138**) and *in situ* generated 1-indenone **139**. This process would release the fused indanone **140** with the control of three contiguous stereocenters. Subsequent diastereoselective intramolecular enol addition will establish the last created stereocenter in **141**. In addition to 15-examples of complex scaffolds, the authors were able to obtain tetrahydropyridine-fused indane after domino reductive amination of the DA adduct.

Very recently, Schaus and co-workers disclosed an asymmetric Diels-Alder reaction between isochromene acetal **142** and indenyl boronate **143** catalyzed by chiral Lewis acid (Scheme 38).[113] The acetal was used as precursor of the oxocarbenium ion **144** to undergo cycloaddition with the boronate dienophile **143**. Excellent asymmetric induction was achieved in this reaction with tartaric acid as the chiral source.

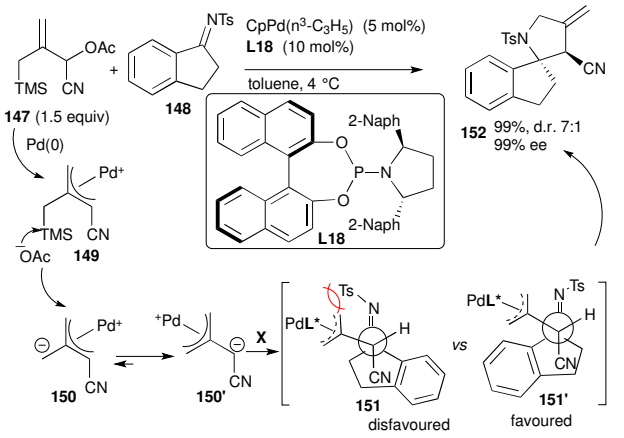
It is important to highlight that the fate of the reaction was altered when chromen acetal was used instead of isochromen. In this case, direct addition of boronate produces a chromen rather than the cycloadduct.[114]

A related reaction was reported by Qian *et. al*. in which the oxocarbenium ion was *in situ* formed by chiral Brønsted acid. However, no indane product has been targeted in this article.[115]




Scheme 38 Tartaric acid-catalyzed cycloaddition of acetals and boronates

### 3.3. Metal-catalyzed transformation of the indanyl core




Scheme 39 TMM-Pd mediated asymmetric [3+2] cycloaddition with ketimines

Trost introduced the trimethymethylene-palladium (TMM-Pd) mediated cycloaddition strategy in 1979.[116] Twenty years were necessary to realize the development of an enantioselective version by Hayashi with acceptable dia- and enantioselectivities.[117] The tremendous achievement in the design of chiral ligands has enabled the Trost group to disclose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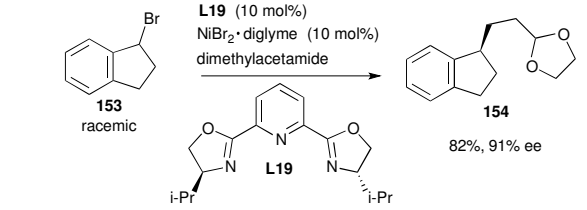
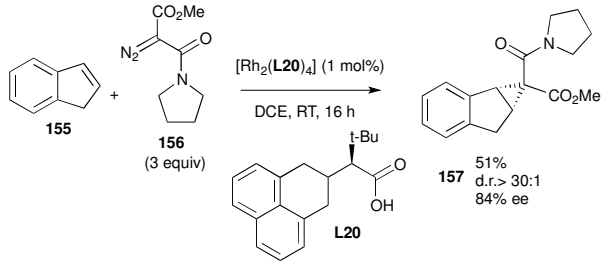
highly enantioselective [3+2] cycloaddition of ketimine **148** to furnish the spiro-indane **152** (Scheme 39).[118] Treatment of allyl acetate **147** with palladium(0) allows the formation of TMM-Pd **149** upon TMS loss. Cycloaddition of the more stable TMM complex through the stabilization of the negative charge by the cyano group occurs through two possible conformers. Steric repulsions explain the formation of the major diastereomer **152** with 99% ee. The minor isomer was also obtained highly enantioenriched (96% ee).

In Scheme 14, we have discussed a transmetalation-insertion sequence of aryl boron substrate with modest enantioselectivity described by Fu.[48] The same group has achieved success in the stereo-convergent Negishi cross-coupling of racemic 1-bromoindane **153** and organozinc reagents catalyzed by Ni/(*i*-Pr)-Pybox (Scheme 40).[119]

1-Chloroindane and vinylbromide[120] - or acid chloride -[121] also served as substrates in analogous reactions mediated by a chiral nickel catalysts, as was described by Reisman.




Scheme 40 Enantioselective Negishi cross-coupling of bromoindane and organozinc reagent

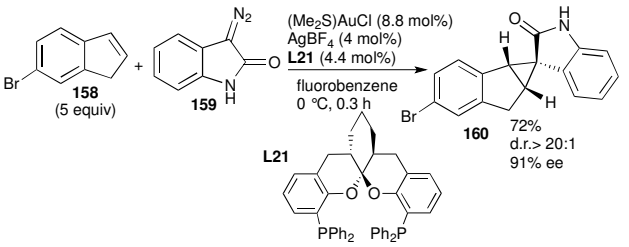



Scheme 41 Enantio- and diastereoselective synthesis of cyclopropylindanes

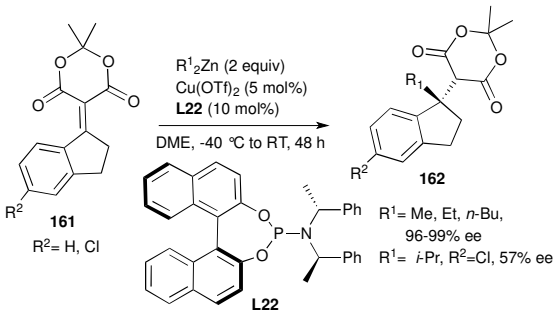
The dual electrophilic and nucleophilic character of metal carbenoids generated from diazoesters has allowed asymmetric cyclopropanations. For instance, they have been proven amenable to induce cyclopropanation of indene **155** in an enantio- and diastereoselective fashion (Scheme 41).[122] Rhodium catalyst, modified by the acid **L20** and diazoester **156** gave rise to chiral metal carbenoid that was involved as electrophile with the electron-rich olefin (the indene in this case). The authors assumed that in-out conformation of the carbenoid is responsible for the diastereoselectivity observed. The use of dissymmetric diazoester in this strategy is the key point to offer a high enantioselectivity.

Katsuki also successfully reported enantioselective iridium-catalyzed cyclopropanation of indenes with diazoesters.[123]

Gold-catalyzed cyclopropanation of indenes **158** with diazooxindole has been also used to provide access to indane **160** with high stereocontrol (Scheme 42).[124] A novel $C_2$-symmetric spiroketal bisphosphines ligand **L21** was successfully tested as a chiral source.

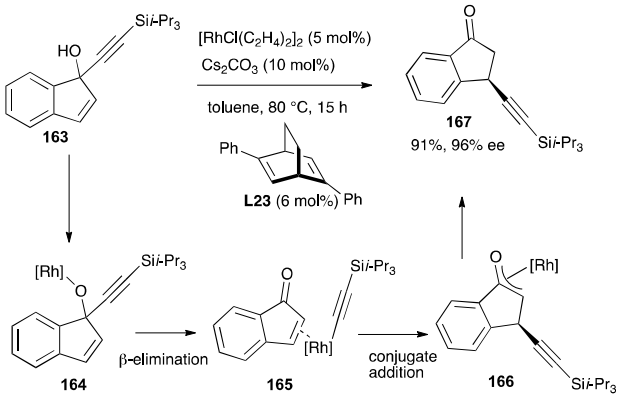



Scheme 42 C2-symmetric spiroketal bisphosphines ligand for the enantioselective gold-catalyzed cyclopropanation of indenes




Scheme 43 Asymmetric copper-catalyzed conjugate additions of organozinc reagents

The copper-catalyzed conjugate addition of dialkylzinc reagents to 5-(1-arylalkylidene) Meldrum's acids **161** investigated by Fillion,[125] allowed the preparation of 1,1-disubstituted indanes **162** with excellent enantioselectivities (96-99 % ee's) except for the addition of *i*-$Pr_2Zn$ that afforded 57% ee (Scheme 43).

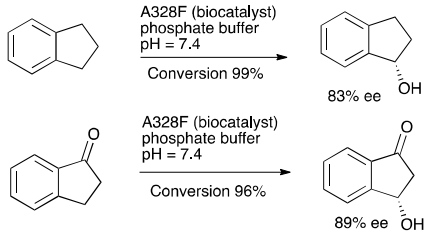



Scheme 44 Rhodium-catalyzed asymmetric 1,3-migration of alkynyl group

A synthetic equivalent of an asymmetric conjugate addition of terminal alkyne to β-substituted enone **165** after β-alkynyl elimination from racemic alkynyl indanol **163** was reported by Nishimura *et. al.* (Scheme 44).[126] The 1,3-rearrangement took place in a stereoselective fashion through the use of chiral diene ligand **L23**.

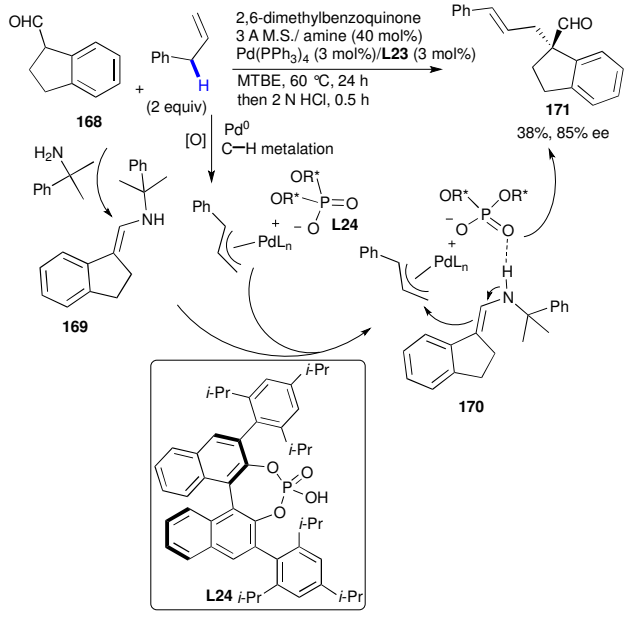
### 3.4. C-H Functionalization

The enzymatic C–H bond oxidation is well known and their benefits are recognized.[127] These processes are popular in pharmaceutical industry. Biocatalysis with cytochrome P450 monoxygenase is attractive, since it offers a high level of regio- and stereoselectivity.[128]




Scheme 45 Enzymatic C–H bond oxidation of indane and indanone

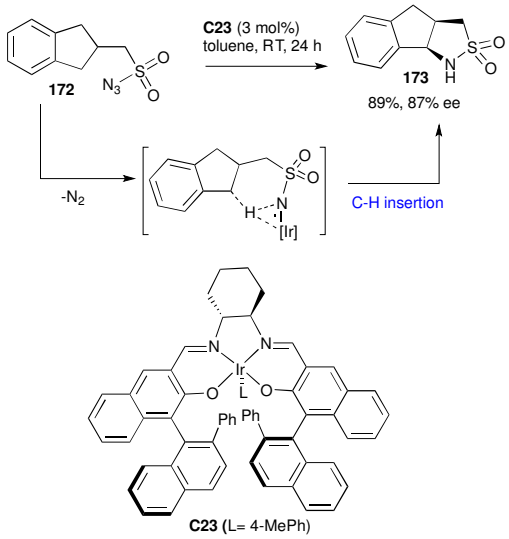
Recently Reetz and co-workers demonstrated that mutants of P450-BM3 (*Bacillus megaterium*) are highly efficient biocatalysts for the oxidative hydroxylation of indane and indanone to produce (*S*)-indanol and (*S*)-3-hydroxy-indanone, respectively (Scheme 45).[129] Docking experiments with a tetralone analogue revealed that the substrate is well placed to be involved in pro-*S* H-atom abstraction by the heme-Fe=O active site.




Scheme 46 Asymmetric oxidative C(sp3)–H/C(sp3)–H couplings of allylic compounds and indane carboxaldehyde

Challenging asymmetric oxidative C($sp^3$)–H/C($sp^3$)–H couplings have been realized by Gong and co-workers. [130] A chiral counterion strategy has been used to induce enantioselective α-allylation of enamine **169** obtained from aldehyde **168** (Scheme 46). The C–H activation with olefin bearing allylic hydrogen generates π-allyl palladium cation. Chiral phosphate served as chiral catalyst through secondary interactions with the cation and hydrogen bonding with the enamine. This optically active complex then collapses, after hydrolysis of the resulting imine, delivering the enantioenriched indane **171** bearing a quaternary stereocenter.

Katsuki is recognized for his pioneering contributions in metal-salen complexes-catalyzed enantioselective transformations. Among others, he demonstrated the efficiency of iridium-salen complexes in the enantio- and diastereoselective intramolecular benzylic C–H bond amination using sulfonyl azide.[131,132] Catalyst **C23** offered high stereoselectivity in the desymmetrization of indane **172** to deliver the sultame indane derivative **173** with excellent yield (Scheme 47).




Scheme 47 Iridium Salen-catalyzed C–H bond amination

### 3.5. Asymmetric synthesis of indanes using chiral reagents

The central challenge of preparing chiral indanes is to construct C-C bonds through the use of transition metal catalysts. However, some metals are expensive and toxic, therefore the use of inexpensive and non-toxic lithium reagents could be considered as an alternative in some cases.

Aggarwal targeted indanes bearing tertiary alcohols **177** *via* enantiodivergent nucleophilic attack addition to boronic ester or borane (Scheme 48).[133] The deprotonation of enantiopure alcohol **174** with *s*-BuLi afforded the lithiated indanyl intermediate **175** that is configurationally stable at -78 °C. Addition, with retention of configuration, at this temperature to boronic ester will generate the "ate" complex **176**. The presence of oxygen atom in the boronic ester allows its participation to the lithium complexation. Therefore, the boron attack happens on the same face as the metal. Allowing the reaction mixture to warm up induced 1,2-alkyl (R) migration. High chirality transfer was observed in the whole process.

Addition to borane implicates inversion of configuration. In this case absence of anchoring atom from the borane orientates the attack to the opposite face (less hindered). Even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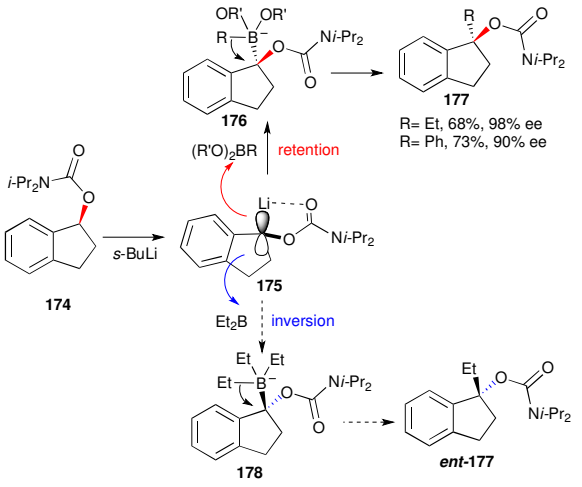
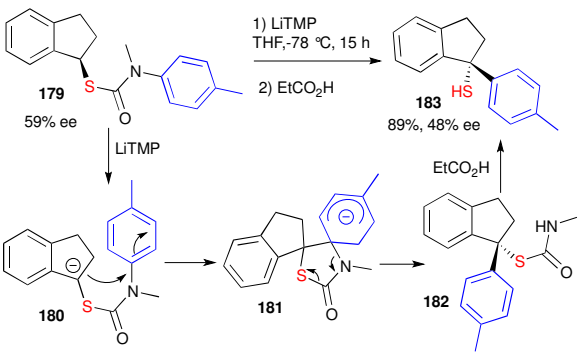
though this observation was made only on analogous substrates such as tetralinol derivative, one could expect a similar 1,2-R migration that would afford the optically opposite tertiary indanol ***ent*-177**.




Scheme 48 Enantiodivergent nucleophilic attack addition of lithiated indane to boronic ester or borane

Clayden reported the aryl migration from thiocarbamate **179** to indanyl core **183** generating tertiary thiol (Scheme 49).[134] Transfer of chirality of 81% is involved in this process. The preservation of stereochemistry integrity is certainly maintained through a transient axial chirality.[135]

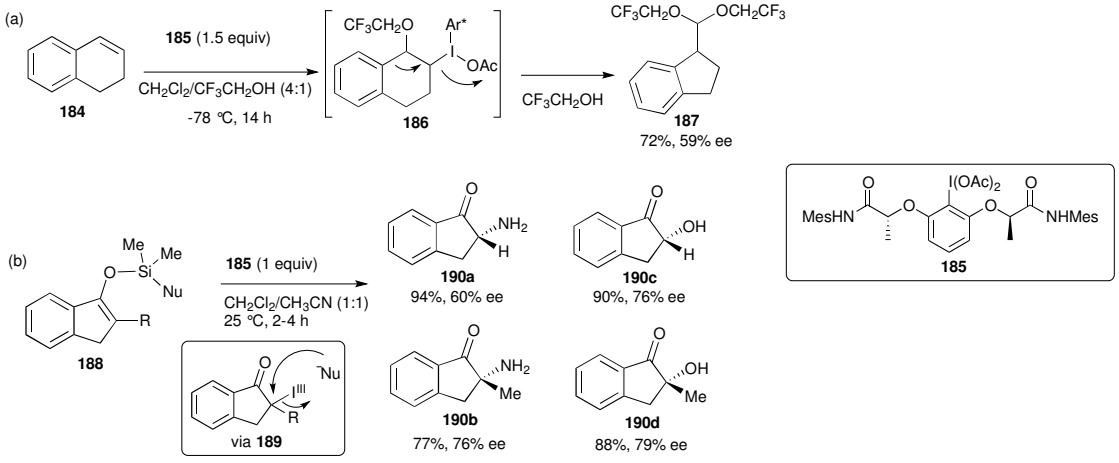
The transfer of chirality strategy was also exploited to synthesize benzofulvenes,[136] indenes and indanes.[137]




Scheme 49 Intramolecular aryl migration of lithiated thiocarbamate with transfer of chirality

Hypervalent iodine reagents have been considered as environmentally benign reagents and their use is increasingly popular.[138] The utilization of chiral reagents is particularly attractive.[139,140]

The Wirth group has recently demonstrated the utility of hypervalent iodine reagents in the control of stereochemistry in the synthesis of indanes **187** (Scheme 50a).[141] The authors developed the ring contraction of tetralinol **186** generated from oxidative addition of chiral hypervalent reagent **185** to tetralone **184**. Modest enantioselectivity (59%) was observed in this reaction. They met with more success with the same reagent in the functionalization of enol **188** through reverse polarity addition. Thus, the nucleophilic silyl enol ether turns out to be electrophilic upon addition of the chiral lactate hyperiodine derivative. Nucleophilic displacement of the resulting electrophile **189** afforded the functionalized indane **190a-d** bearing tetrasubstituted stereocenter with ee's ranging from 60 to 79% (Scheme 50b).[142]




Scheme 50 Oxidative additions of chiral hypervalent iodine reagents



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Review

## 4. Conclusions

The use of chiral indanes in bioactive compounds and as catalysts in asymmetric synthesis is a growing area of topical interest. The increasing demand for such molecular architectures led to the development of many successful routes, providing rapid access to this scaffold in an enantiomerically-enriched form. This success has been enabled by the tremendous input of chiral catalysts among them organocatalysts and metal catalysts played a pivotal role.

Further advances could be expected from the advent of novel synthetic strategies discovered recently and disclosed in racemic version. For instance, Ackermann and co-workers applied manganese-catalyzed C–H activation for diastereo-selective indane syntheses, which offers great potential for challenging enantioselective transformations.[143] Moreover, Nevado very recently designed an elegant radical cascade synthesis of highly functionalized indanes.[144] The enantioselective radical addition in this stimulating reaction sequence would be feasible through the impressive achievements in asymmetric radical transformations accomplished in the last decade. These two examples indicate research areas that thus far continue to be relatively underexplored. More-over, the improving of understanding factors governing stereoselectivity and the impact of DFT calculations as well as the development of new tools for determination of absolute configurations will certainly stimulate new curiosities. In connection to these studies and thanks to the considerable progress in the design of chiral ligands, one would expect new horizon in the field of asymmetric catalysis.

## Notes and references

1 I. Gallou and C. H. Senanayake, *Chem. Rev.*, 2006, **106**, 2843–2874.
2 Y. Gao, Q. Ren, H. Wu, M. Li and J. Wang, *Chem. Commun.*, 2010, **46**, 9232–9234.
3 M. S. Kerr and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 8876–8877.
4 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692–12693.
5 T. Hashimoto, Y. Kawamata and K. Maruoka, *Nat. Chem.*, 2014, **6,** 702–705.
6 S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res.*, 2012, **45**, 1365–1377.
7 R. Ćwiek, P. Niedziejko and Z. Kałuża, *J. Org. Chem.*, 2014, **79**, 1222–1234.
8 a) R. Noyori, *Asymmetric catalysis in organic synthesis*, Wiley, New York, 1994. b) For a special issue on asymmetric hydrogenation see *Acc. Chem. Res*. 2007, **40**, 1237–1419.
9 W. J. Choi and C. Y. Choi, *Biotechnol. Bioprocess Eng.*, 2005, **10**, 167–179.
10 J.-N. Desrosiers and A. B. Charette, *Angew. Chem. Int. Ed.*, 2007, **46**, 5955–5957.
11 T. Bleith, H. Wadepohl and L. H. Gade, *J. Am. Chem. Soc.*, 2015, **137**, 2456–2459.
12 M. Hayashi, M. Iwanaga, N. Shiomi, D. Nakane, H. Masuda and S. Nakamura, *Angew. Chem. Int. Ed.*, 2014, **53**, 8411–8415.
13 M. Nechab, L. El Blidi, N. Vanthuyne, S. Gastaldi, M. P. Bertrand and G. Gil, *Org. Biomol. Chem.*, 2008, **6**, 3917–3920.
14 M. Nechab, N. Azzi, N. Vanthuyne, M. Bertrand, S. Gastaldi and G. Gil, *J. Org. Chem.*, 2007, **72**, 6918–6923.
15 U. H. Dolling, P. Davis and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446–447.
16 B.-C. Hong and S. Sarshar, *Org. Prep. Proced. Int.*, 1999, **31**, 1–86.
17 For additional examples those are not detailed in this review, see Electronic supplementary information (ESI): (a) A. Biswas, S. D. Sarkar, R. Fröhlich and A. Studer, *Org. Lett.*, 2011, **13**, 4966–4969. (b) X. Yu and X. Lu, *Org. Lett.*, 2009, **11**, 4366-4369. (c) X.-H. Li, B.-H. Zheng, C.-H. Ding and X.-L. Hou, *Org. Lett.*, 2013, **15**, 6086-6089. (d) K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang and W. Tang, *Angew. Chem. Int. Ed.*, 2015, **54**, 3033 –3037. (e) Y.-N. Yu and M.-H. Xu, *J. Org. Chem.*, 2013, **78**, 2736−2741. (f) Y. Natori, M. Anada, S. Nakamura, H. Nambu and S. Hashimoto, *Heterocycles*, 2006, **70**, 635-646. (g) R. Shintani and T. Hayashi, *Org. Lett.*, 2011, **13**, 350-352. (h) J. Nie, H.-W. Zhu, H.-F. Cui, M.-Q. Hua, and J.-A. Ma, *Org. Lett.*, 2007, **9**, 3053-3056. (i) W. Zi and F. D. Toste, *J. Am. Chem. Soc.*, 2013, **135**, 12600−12603. (j) S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco and F.

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Marini, *Angew. Chem. Int. Ed.*, 2011, **50**, 9382 –9385. (k) M. W. Paixão, N. Holub, C. Vila, M. Nielsen and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2009, **48**, 7338 –7342. (l) Y.-P. Chang, R. Gurubrahamam and K. Chen, *Org. Lett.*, 2015, **17**, 2908–2911. (m) J. Zhao and D. A. Clark, *Org. Lett.*, 2012, **14**, 1668–1671. For application in total synthesis see: (n) B. Hong, C. Li, Z. Wang, J. Chen, H. Li and X. Lei, *J. Am. Chem. Soc.*, 2015, **137**, 11946-11949. (o) S. Chen, C. Rong, P. Feng, S. Li and Y. Shi, *Org. Biomol. Chem.*, 2012, **10**, 5518–5520.

18 N. Kumagai and M. Shibasaki, *Isr. J. Chem.*, 2012, **52**, 604–612.

19 Y. Suzuki, R. Yazaki, N. Kumagai and M. Shibasaki, *Chem. Eur. J.*, 2011, **17**, 11998–12001.

20 C. L. Oswald, J. A. Peterson and H. W. Lam, *Org. Lett.*, 2009, **11**, 4504–4507.

21 D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899–1902.

22 T. Rovis and C. Filloux, in *Comprehensive Chirality*, Elsevier, 2012, pp. 318–344.

23 D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387.

24 E. M. Phillips, M. Wadamoto, A. Chan and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 3107–3110.

25 V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691–2698.

26 R. S. Menon, A. T. Biju and V. Nair, *Chem. Soc. Rev.*, 2015, **44**, 5040–5052.

27 Y. Li, X.-Q. Wang, C. Zheng and S.-L. You, *Chem. Commun.*, 2009, 5823–5825.

28 A. Biswas, S. D. Sarkar, R. Fröhlich and A. Studer, *Org. Lett.*, 2011, **13**, 4966–4969.

29 D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2011, **133**, 2714–2720.

30 D. Janssen-Müller, M. Schedler, M. Fleige, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed.*, 2015, **54**, 12492–12496

31 I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme and F. Glorius, *Angew. Chem. Int. Ed.*, 2011, **50**, 4983–4987.

32 J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036–15037.

33 J.-F. Brière, S. Oudeyer, V. Dalla and V. Levacher, *Chem. Soc. Rev.*, 2012, **41**, 1696–1707.

34 J. Lacour and D. Moraleda, *Chem. Commun.*, 2009, 7073–7089.

35 C. P. Johnston, A. Kothari, T. Sergeieva, S. I. Okovytyy, K. E. Jackson, R. S. Paton and M. D. Smith, *Nat. Chem.*, 2015, **7**, 171–177.

36 K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191.

37 I. V. Alabugin and K. Gilmore, *Chem. Commun.*, 2013, **49**, 11246–11250.

38 C. C. J. Loh, I. Atodiresei and D. Enders, *Chem. Eur. J.*, 2013, **19**, 10822–10826.

39 C. C. J. Loh, D. Hack and D. Enders, *Chem. Commun.*, 2013, **49**, 10230–10232.

40 P. J. Chua, B. Tan, L. Yang, X. Zeng, D. Zhu and G. Zhong, *Chem. Commun.*, 2010, **46**, 7611–7613.

41 J. Hu, H. Hirao, Y. Li and J. S. Zhou, *Angew. Chem. Int. Ed.*, 2013, **52**, 8676–8680.

42 E. D. D. Calder and A. Sutherland, *Org. Lett.*, 2015, **17**, 2514–2517.

43 C. H. Schuster, J. R. Coombs, Z. A. Kasun and J. P. Morken, *Org. Lett.*, 2014, **16**, 4420–4423.

44 G. Yue, K. Lei, H. Hirao and J. S. Zhou, *Angew. Chem. Int. Ed.*, 2015, **54**, 6531–6535.

45 A. Minatti, X. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 9253–9258.

46 Y. Nakao, S. Oda and T. Hiyama, *J. Am. Chem. Soc.*, 2004, **126**, 13904–13905.

47 M. P. Watson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2008, **130**, 12594–12595.

48 H. Cong and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 3788–3791.

49 L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792–9826.

50 R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272.

51 M. Albicker and N. Cramer, *Angew. Chem. Int. Ed.*, 2009, **48**, 9139–9142.

52 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345.

53 D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118–1126.

54 S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou and O. Baudoin, *J. Am. Chem. Soc.*, 2010, **132**, 10706–10716.

55 N. Martin, C. Pierre, M. Davi, R. Jazzar and O. Baudoin, *Chem. Eur. J.*, 2012, **18**, 4480–4484.

56 P. M. Holstein, M. Vogler, P. Larini, G. Pilet, E. Clot and O. Baudoin, *ACS Catal.*, 2015, **5**, 4300–4308.

57 T. Nishimura, M. Nagamoto, Y. Ebe and T. Hayashi, *Chem. Sci.*, 2013, **4**, 4499–4504.

58 D. N. Tran and N. Cramer, *Angew. Chem. Int. Ed.*, 2010, **49**, 8181–8184.

59 D. N. Tran and N. Cramer, *Angew. Chem. Int. Ed.*, 2013, **52**, 10630–10634.

60 T. Matsuda and S. Watanuki, *Org Biomol Chem*, 2015, **13**, 702–705.

61 M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724.

62 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev*. 2003, **103**, 2861-2904.

63 D. Gillingham and N. Fei, *Chem. Soc. Rev.*, 2013, **42**, 4918.

64 C. Soldi, K. N. Lamb, R. A. Squitieri, M. González-López, M. J. Di Maso and J. T. Shaw, *J. Am. Chem. Soc.*, 2014, **136**, 15142–15145.

65 X.-X. Guo, T. Sawano, T. Nishimura and T. Hayashi, *Tetrahedron Asymmetry*, 2010, **21**, 1730–1736.

66 K. Kundu, J. V. McCullagh and A. T. Morehead Jr., *J. Am. Chem. Soc.*, 2005, **127**, 16042–16043.

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67 J. Yang and N. Yoshikai, *J. Am. Chem. Soc.*, 2014, **136**, 16748–16751.
68 L. Ye, L. Cui, G. Zhang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 3258–3259.
69 D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das and R.-S. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 6911–6914.
70 K. Ji, Z. Zheng, Z. Wang and L. Zhang, *Angew. Chem. Int. Ed.*, 2015, **54**, 1245–1249.
71 H.-S. Yeom, Y. Lee, J. Jeong, E. So, S. Hwang, J.-E. Lee, S. S. Lee and S. Shin, *Angew. Chem. Int. Ed.*, 2010, **49**, 1611–1614.
72 D. Qian and J. Zhang, *Chem. Eur. J.*, 2013, **19**, 6984–6988.
73 L Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410–9464.
74 T. Nishimura, S. Matsumura, Y. Maeda and S. Uemura, *Chem. Commun.*, 2002, 50–51.
75 S. Matsumura, Y. Maeda, T. Nishimura and S. Uemura, *J. Am. Chem. Soc.*, 2003, **125**, 8862–8869.
76 T. Matsuda, M. Shigeno, M. Makino and M. Murakami, *Org. Lett.*, 2006, **8**, 3379–3381.
77 T. Seiser and N. Cramer, *Angew. Chem. Int. Ed.*, 2010, **49**, 10163–10167.
78 T. Seiser, O. A. Roth and N. Cramer, *Angew. Chem. Int. Ed.*, 2009, **48**, 6320–6323.
79 Á. Enríquez-García and E. P. Kündig, *Chem. Soc. Rev.*, 2012, **41**, 7803–7831.
80 J. T. Mohr, D. C. Ebner and B. M. Stoltz, *Org. Biomol. Chem.*, 2007, **5**, 3571–3576.
81 S. Mizuta, T. Tsuzuki, T. Fujimoto and I. Yamamoto, *Org. Lett.*, 2005, **7**, 3633–3635.
82 T. Suzuki, K. Ghozati, T. Katoh and H. Sasai, *Org. Lett.*, 2009, **11**, 4286–4288.
83 T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825–1845.
84 P. Krumlinde, K. Bogár and J.-E. Bäckvall, *Chem. Eur. J.*, 2010, **16**, 4031–4036.
85 J. Steinreiber, K. Faber and H. Griengl, *Chem. Eur. J.*, 2008, **14**, 8060–8072.
86 O. Långvik, T. Sandberg, J. Wärnå, D. Y. Murzin and R. Leino, *Catal Sci Technol*, 2015, **5**, 150–160.
87 K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka and T. Akiyama, *Angew. Chem. Int. Ed.*, 2009, **48**, 9652–9654.
88 P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2001, **40**, 3726–3748.
89 S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471–5569.
90 J. T. Suri, D. D. Steiner and C. F. Barbas, *Org. Lett.*, 2005, **7**, 3885–3888.
91 D. D. Schoepp, D. E. Jane and J. A. Monn, *Neuropharmacology*, 1999, **38**, 1431–1476.
92 S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336–11337.
93 M. R. Acocella, O. G. Mancheño, M. Bella and K. A. Jørgensen, *J. Org. Chem.*, 2004, **69**, 8165–8167.
94 A. M. R. Smith, D. Billen and K. K. (Mimi) Hii, *Chem. Commun.*, 2009, 3925–3927.
95 L. Zou, B. Wang, H. Mu, H. Zhang, Y. Song and J. Qu, *Org. Lett.*, 2013, **15**, 3106–3109.
96 G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre and L. Sambri, *Angew. Chem. Int. Ed.*, 2005, **44**, 6219–6222.
97 C. L. Rigby and D. J. Dixon, *Chem. Commun.*, 2008, 3798–3800.
98 P. Elsner, L. Bernardi, G. D. Salla, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2008, **130**, 4897–4905.
99 T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer and V. Levacher, *Angew. Chem. Int. Ed.*, 2007, **46**, 7090–7093.
100 É. Bélanger, K. Cantin, O. Messe, M. Tremblay and J.-F. Paquin, *J. Am. Chem. Soc.*, 2007, **129**, 1034–1035.
101 T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *J. Am. Chem. Soc.*, 2006, **128**, 16488–16489.
102 H. M. Nelson, J. S. Patel, H. P. Shunatona and F. D. Toste, *Chem. Sci.*, 2015, **6**, 170–173.
103 V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, *Science*, 2011, **334**, 1681–1684.
104 F. Romanov-Michailidis, L. Guénée and A. Alexakis, *Angew. Chem. Int. Ed.*, 2013, **52**, 9266–9270.
105 F. Romanov-Michailidis, M. Romanova-Michaelides, M. Pupier and A. Alexakis, *Chem. Eur. J.*, 2015, **21**, 5561–5583.
106 K. Murai, A. Nakamura, T. Matsushita, M. Shimura and H. Fujioka, *Chem. Eur. J.*, 2012, **18**, 8448–8453.
107 S. Mondal, M. P. Bertrand and M. Nechab, *Angew. Chem. Int. Ed.*, 2013, **52**, 809–811.
108 M. P. Sibi and S. Nad, *Angew. Chem. Int. Ed.*, 2007, **46**, 9231–9234.
109 T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton and D. W. C. MacMillan, *Science*, 2007, **316**, 582–585.
110 N. T. Jui, E. C. Y. Lee and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 10015–10017.
111 N. T. Jui, J. A. O. Garber, F. G. Finelli and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2012, **134**, 11400–11403.
112 Z.-J. Jia, K. Jiang, Q.-Q. Zhou, L. Dong and Y.-C. Chen, *Chem. Commun.*, 2013, **49**, 5892–5894.
113 Y. Luan, K. S. Barbato, P. N. Moquist, T. Kodama and S. E. Schaus, *J. Am. Chem. Soc.*, 2015, **137**, 3233–3236.
114 P. N. Moquist, T. Kodama and S. E. Schaus, *Angew. Chem. Int. Ed.*, 2010, **49**, 7096–7100.
115 H. Qian, W. Zhao, Z. Wang and J. Sun, *J. Am. Chem. Soc.*, 2015, **137**, 560–563.
116 B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 1979, **101**, 6432–6433.
117 A. Yamamoto, Y. Ito and T. Hayashi, *Tetrahedron Lett.*, 1989, **30**, 375–378.
118 B. M. Trost and S. M. Silverman, *J. Am. Chem. Soc.*, 2010, **132**, 8238–8240.
119 F. O. Arp and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 10482–10483.
120 A. H. Cherney and S. E. Reisman, *J. Am. Chem. Soc.*, 2014, **136**, 14365–14368.
121 A. H. Cherney, N. T. Kadunce and S. E. Reisman, *J. Am. Chem. Soc.*, 2013, **135**, 7442–7445.



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122 D. Marcoux and A. B. Charette, *Angew. Chem. Int. Ed.*, 2008, **47**, 10155–10158.
123 H. Suematsu, S. Kanchiku, T. Uchida and T. Katsuki, *J. Am. Chem. Soc.* 2008, **130**, 10327–10337.
124 Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou and K. Ding, *J. Am. Chem. Soc.*, 2013, **135**, 8197–8200.
125 E. Fillion and A. Wilsily, *J. Am. Chem. Soc.*, 2006, **128**, 2774–2775.
126 T. Nishimura, T. Katoh, K. Takatsu, R. Shintani and T. Hayashi, *J. Am. Chem. Soc*. 2007, **129**, 14158–14159.
127 J. C. Lewis, P. S. Coelho and F. H. Arnold, *Chem. Soc. Rev.*, 2011, **40**, 2003–2021.
128 G.-D. Roiban and M. T. Reetz, *Chem. Commun.*, 2015, **51**, 2208–2224.
129 G.-D. Roiban, R. Agudo, A. Ilie, R. Lonsdale and M. T. Reetz, *Chem Commun*, 2014, **50**, 14310–14313.
130 P.-S. Wang, H.-C. Lin, Y.-J. Zhai, Z.-Y. Han and L.-Z. Gong, *Angew. Chem. Int. Ed.*, 2014, **53**, 12218–12221.
131 M. Ichinose, H. Suematsu, Y. Yasutomi, Y. Nishioka, T. Uchida and T. Katsuki, *Angew*. *Chem. Int. Ed.*, 2011, **50**, 9884–9887.
132 A. G. Schafer and S. B. Blakey, *Chem. Soc. Rev*., 2015, **44**, 5969–5980.
133 J. L. Stymiest, V. Bagutski, R. M. French and V. K. Aggarwal, *Nature*, 2008, **456**, 778–782.
134 P. MacLellan and J. Clayden, *Chem. Commun.*, 2011, **47**, 3395–3397.
135 D. Campolo, S. Gastaldi, C. Roussel, M. P. Bertrand and M. Nechab, *Chem. Soc. Rev*., 2013, **42**, 8434–8466.
136 D. Campolo, T. Arif, C. Borie, D. Mouysset, N. Vanthuyne, J.-V. Naubron, M. P. Bertrand and M. Nechab, *Angew. Chem. Int. Ed.*, 2014, **53**, 3227–3231.
137 T. Arif, C. Borie, A. Tintaru, J.-V. Naubron, N. Vanthuyne, M. P. Bertrand and M. Nechab, *Adv. Synth. Catal.*, 2015, 356, 3611–3616.
138 E. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052–9070.
139 H. Liang and M. A. Ciufolini, *Angew. Chem. Int. Ed*., 2011, **50**, 11849–11851.
140 U. Farid and T. Wirth, in *Asymmetric Synthesis II*, eds. M. Christmann and S. Bräse, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2013, pp. 197–203.
141 U. Farid, F. Malmedy, R. Claveau, L. Albers and T. Wirth, *Angew. Chem. Int. Ed.*, 2013, **52**, 7018–7022.
142 P. Mizar and T. Wirth, *Angew. Chem. Int. Ed.*, 2014, **53**, 5993–5997.
143 W. Liu, D. Zell, M. John and L. Ackermann, *Angew. Chem. Int. Ed.*, 2015, **54**, 4092–4096.
144 W. Kong, N. Fuentes, A. García-Domínguez, E. Merino and C. Nevado, *Angew. Chem. Int. Ed.*, 2015, **54**, 2487–2491.