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Indenylmetal Catalysis in Organic Synthesis

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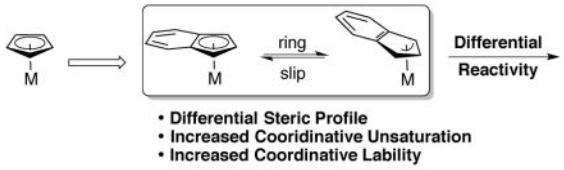
Abstract

Synthetic organic chemists have a long-standing appreciation for transition metal cyclopentadienyl complexes, of which many have been used as catalysts for organic transformations. Much less well known are the contributions of the benzo-fuzed relative of the cyclopentadienyl ligand, the indenyl ligand, whose unique properties have in many cases imparted differential reactivity in catalytic processes toward the synthesis of small molecules. In this review, we will present examples of indenylmetal complexes in catalysis and compare their reactivity to their cyclopentadienyl analogues, wherever possible.

Graphical Abstract



Keywords

organic synthesis; organometallic chemistry; cyclopentadienyl; indenyl; coordination chemistry

1. Introduction

Ever since Wilkinson, Woodward, and Fischer elucidated the bonding structure of ferrocene in 1952,[1] the cyclopentadienyl (Cp) ligand has been seen as a cornerstone of modern organometallic chemistry. While this ligand exhibits unique electronic properties and a fascinating bonding motif[2] that has been implemented in many scaffolds for catalysis,[3] it often behaves as a three-coordinate spectator ligand that does not directly participate in reactions. However, when an additional benzo ring is fused to the Cp ring to form a metal indenyl (Ind) complex, a noticeable acceleration of fundamental organometallic reactions and catalysis is observed.

This effect was first seen by Hart-Davis and Mawby while they were studying the rate of ligand-induced migratory insertion reactions of coordinatively saturated 18-electron molybdenum carbonyl complexes (Scheme 1).[4] An increase in rate of around an order of

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magnitude was observed when comparing the indenyl complex to the analogous cyclopentadienyl complex. The origin for this increase was independent of the identity of the phosphine ligand used to trigger migratory insertion and could not be explained by the difference in electronic structure of the indenyl moiety, as the Ind complex exhibited nearly identical carbonyl stretching frequencies as the Cp complex. A negative entropy of activation ($\Delta S^{\ddagger} = -24.2$ cal/mol*K in *n*-hexane with P(*n*Bu)$_3$ as ligand) implies an associative mechanism for this reaction. Coordination by an exogenous ligand *via* an associative mechanism would necessitate the intermediacy of a high-energy 20-electron coordination complex. Therefore, the authors proposed a mechanism whereby the η^5-indenyl ligand slips into an η^3-allyl coordination mode to accommodate the additional ligand necessary to induce migratory insertion. X-ray crystal structures of indenyl complexes have provided direct evidence of ring slippage by correlation to the degree of folding of the indenyl ligand.[5] The additional stabilization of the fused benzo ring on the indenide facilitates this ring slippage, and therefore accelerates the rate of the reaction.

Similar effects in rate acceleration have also been observed for CO[6] and ethylene[7] ligand substitution reactions. In one such study by Basolo and coworkers,[8] the observed rate of carbonyl substitution by triphenylphosphine on a coordinatively saturated indenylrhodium(I) complex was observed to be 10^8 times faster than with the analogous cyclopentadienylrhodium complex [Eq. (1)]. Again, the increase in rate is attributed to the ease in which the metal is able to

$$(\eta^5\text{- Ind})\mathrm{Rh(CO)_2} + \mathrm{PPh_3} \xrightarrow[20\,^\circ\mathrm{C}]{\text{toluence}} (\eta^5\text{- Ind})\mathrm{Rh(CO)PPh_3} \quad (1)$$

adopt an η^3 coordination geometry in an associative substitution mechanism.

Many chemists have noted the special properties the indenyl ligand imbues a coordination complex and have used these compounds to increase the rates of catalytic reactions. The purpose of this review is to present these cases where these indenylmetal complexes have been used in the context of catalysis, particularly for the synthesis of small, organic molecules. The use of indenylmetal complexes for polymerization reactions, including the work of Brintzinger,[9] is outside the scope of this review, and has been reviewed elsewhere.[3],[10]

2. Titanium, Zirconium, and Rare Earth Metals

Due to the success of chiral indenyltitanium and -zirconium complexes in the context of stereoselective olefin polymerization, it is unsurprising that researchers would utilize similar complexes for the catalytic transformation of small molecules. In 1992, Halterman and coworkers disclosed an asymmetric olefin migration reaction of cyclohexane **1** using chiral bis(indenyl) titanium complex **2** (Scheme 2).[11] One of the disadvantages of using planar chiral Ziegler-Natta olefin polymerization catalyst **3** is that it must be resolved from a racemic mixture of complexes. On the other hand, the synthesis of catalyst **2** is completely diastereoselective due to the chirality already present on its backbone. The bulky indenyl

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moieties prefer to orient themselves away from the isopropyl groups on the cyclohexane ring, which results in the complex seen in Scheme 2. When substrate **1** is subjected to 2 mol % of catalyst **2** along with 8 mol% of lithium aluminum hydride, quantitative conversion and a 74% *ee* of alkene **4** could be obtained. A strong temperature dependence was observed; higher temperatures led to significant erosion of enantioselectivity. Although a direct comparison of reactivity to a cyclopentadienyl complex was not made in this publication, previous studies[12] have indicated that terminal olefins that contain α-branching similar to **1** have been problematic olefin isomerization substrates for achiral Cp_2TiCl_2. The Halterman group have synthesized other bis(indenyl)titanium and zirconium complexes with chiral backbones, including binapththyl-based complex **5** (Figure 1).[13] This complex was used to study the catalytic asymmetric epoxidation of electronically unbiased olefins, though low turnovers and *ee*'s were observed with this system.

Menthyl-derived indenylzirconium complexes like **6** have been shown to be an excellent catalyst for the stereoregular polymerization of polypropylene (Scheme 3).[14] Realizing that these complexes would be a readily available source of chiral information for zirconium-catalyzed asymmetric carboalumination (ZACA) reaction, Negishi *et al.* observed good enantioselectivities of **8** for the addition of Me_3Al to terminal alkenes **7**.[15–17] A subsequent publication noted that carboalumination of longer chain organometallics such as Et_3Al and n-Pr_3Al proceed to even higher enantioselectivities (>90% *ee*).[18] The proposed rationale for the stereochemical outcome of this reaction is that the zirconium complex enforces the preferential coordination of the olefin face seen in intermediate **9** by placing the olefin substituent away from its bulky indenyl ligands. Interestingly, attempted methylalumination of 1-octene with Cp_2ZrCl_2 resulted solely in products related to β-hydride elimination. The authors speculate that the bulky indenyl ligands prevent this side reaction from occurring. In addition to simple olefins, the Negishi group has also extended their studies of the ZACA reaction toward allyl alcohols,[19] 1,4-dienes,[20] and 1,4-pentenynes.[21]

Wipf and Ribe noted a significant increase in rate as well as a slight increase in enantioselectivity of ZACA reactions when 1 equivalent of water was added to the reaction.[22] The origin of this rate increase was attributed to the *in situ* partial hydrolysis of trimethylaluminum reagent. Using methylaluminoxane (MAO) instead of trimethylaluminum was also observed to increase reaction rate, albeit to a lesser extent.

The ZACA process can be used to stereoselectively construct cyclic products when α,ω-dienes are used as substrates (Scheme 4). Waymouth and coworkers subjected 1,5-hexadiene **10** to modified ZACA conditions, resulting in a 62% yield of cyclopentane **11** as a 2:1 ratio of *trans:cis* diastereomers and in a 79% *ee* for the major diastereomer.[23] Tris(pentafluorophenyl)borane[24] was added as a co-catalyst to abstract a methyl group from catalyst precursor **12**.[25] Mechanistically, after the first intermolecular migratory insertion reaction, alkylzirconium intermediate **13** is primed to perform a second intramolecular carbometallation reaction, furnishing the observed product. A reversal in diastereoselectivity (3:7 *trans:cis*) is observed when $Cp^*_2ZrCl_2$ (Cp^*=1,2,3,4,5-pentamethylcyclopentadienyl) is used as a catalyst in the same reaction.

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Waymouth *et al.* have also used ZACA catalysts for desymmetrizing ring-opening reactions of oxanorbornene derivatives **14** (Scheme 5).[26] They discovered that the nature of the zirconocene derivative was crucial to both the absolute configuration and enantioselectivity of the overall process. bis(Neoisomenthylindenyl) **16** catalyzed the ring opening of **14** in a 64% yield and an excellent 96% *ee*. Catalyst diastereomer bis(neomenthylindenyl) **6** delivered the antipode of **15** in a −52% *ee*. In comparison, catalysis with achiral titanocene Cp_2TiCl_2 required higher reaction temperatures and provided **15** in a low 16% yield. Whether the improved reactivity of catalysts **16** and **6** is due to the indenyl effect or due to the difference in reactivity between a first and second row transition metal is unclear.

Negishi broadened the scope of alkylaluminum species that can be used by reporting the tandem hydroalumination/ZACA of terminal olefins (Scheme 6).[27] After hydroalumination of a terminal olefin by diisobutylaluminum hydride (DIBAL-H), the less sterically encumbered alkyl chain transmetallates to zirconium in preference to the sterically bulky isopropyl groups on aluminum. While this reaction displays good yields and excellent enantioselectivities, the drawbacks include long reaction times necessary to generate the diisobutylalkylaluminum reagent and the requirement that only terminal olefins can be used for hydroalumination. Nevertheless, this method was used to synthesize the vitamin E side chain **17**[28] in four steps and 45% overall yield from 4-methyl-1-pentene.

In addition to oxidation to primary alcohols and protonolysis, alkylaluminum intermediates obtained from ZACA processes can be used for one-pot Pd- and Cu-catalyzed cross-coupling reactions.[29] The ability to append on olefins *via* cross-coupling enables an iterative ZACA/cross-coupling approach to the synthesis of complex molecules. An impressive example of this strategy was the utilization of multiple, consecutive ZACA/cross-coupling reactions for the enantioselective synthesis of phthioceranic acid **18**, which contains seven deoxypropionate subunits (Scheme 7).[30] ZACA with *ent*-**6** on 1-octadecene **19** resulted in alkylaluminum intermediate **20**, which could be directly cross-coupled with vinyl bromide after transmetallation to zinc. A second ZACA reaction followed by oxidation constructed the second tertiary stereocenter in **22** in a 44% yield over two steps. Primary alcohol **22** was isolated in a greater than 50:1 d.r. and 97% *ee*. Bromination of **22** to **23** completed the first key fragment of the synthesis of **18**.

The second key fragment was constructed in a similar fashion (Scheme 8). ZACA with **6** and Negishi cross-coupling furnished **24**. This alkene was then subjected to another carboalumination reaction, followed by *in situ* oxidation to alcohol **25**. This alcohol was isolated in a 34% overall yield over two steps and in >30:1 d.r.. Iodination of **25**, lithium-halogen exchange, and Negishi cross-coupling of vinyl bromide introduces the terminal alkene necessary for the final carboalumination reaction of **26**. ZACA of **26** and bromination of the resulting alcohol results in the construction and isolation of the second key intermediate **27** towards the synthesis of phthioceranic acid. Bromide **27** could be isolated in greater than 50:1 d.r. and greater than 99% *ee*.

The two fragments were then brought together using stereospecific copper-catalyzed S_N2 substitution reactions (Scheme 9). Fragment **28**, which can be synthesized in three steps from acetylacetone, undergoes sp^3-sp^3 cross-coupling of its tosylate with the *in* situ-formed

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Grignard reagent of **23** with complete inversion of configuration. After functional group interconversion to tosylate **30**, a second copper-catalyzed coupling using the alkylmagnesium of **27** was performed with complete stereospecificity. Oxidation of the phenyl group to a carboxylic acid completes this highly convergent synthesis of phthioceranic acid **18** in a 45% yield over two steps. The Negishi group and others have also used the strategies described in this synthesis for the total and partial synthesis of other natural products with deoxypropionate subunits.[31]

Zirconocene complex **31** (Figure 2) was found by Lipshutz *et al.* to be a highly active and regioselective catalyst for the methylalumination of terminal alkynes.[32] Carbon-carbon bond formation occurs selectively on the internal position of a terminal alkyne so that steric interactions between substrate and catalyst are minimized. Though not explicitly measured, the authors noted a significant faster rate of reaction when using **31** compared to bis(tetrahydroindenyl)zirconocene **3**.

The Doye research group has shown that $(Ind)_2TiMe_2$ is a particularly active and selective general catalyst for the intermolecular hydroamination of alkynes.[33],[34] They were able to demonstrate a broad substrate scope for this reaction; both symmetrical and unsymmetrical alkynes reacted efficiently and with high regioselectivity (Scheme 10). The imine/enamine mixture formed from hydroamination was immediately reduced with sodium cyanoborohydride to simplify reaction analysis. In general, sterically hindered primary alkylamines tended to react the most efficiently, giving the highest yields in the shortest reaction times (Scheme 10a). Anilines were also effective nucleophiles, despite their sluggish reaction times. Unhindered primary alkylamines proved to be the poorest substrates for hydroamination. For example, hydroamination of tolane with benzyl amine only proceeded to about 30% conversion after 48 hours. The authors were able to cut down the reaction times and improve the yields of hydroaminations with sterically unhindered amines by performing a slow addition of the amine over four hours. By performing this adjustment, the yield of tolane hydroamination by benzylamine increased to 67%. Hydroamination of unsymmetrical 1-phenyl-1-propyne proceeded with good (3:1) to excellent (>99:1) anti-Markovnikov regioselectivity for a variety of amine nucleophiles (Scheme 10b). In contrast, lower selectivities are observed for primary alkylamine additions to 1-phenyl-1-propyne with $Cp^*_2TiMe_2$ as a catalyst (Scheme 11).[35] Furthermore, Cp^*TiMe_2 is completely unsuitable for the hydroamination of terminal alkynes, a reaction the indenyl complex can catalyze in high yields (Scheme 10c). The dominant regioisomer obtained was highly dependent on the nature of the nucleophile. High anti-Markovnikov hydroamination of terminal alkynes was observed with sterically bulky *tert*-butyl amine whereas Markovnikov addition dominated with anilines. However, phenylacetylene acceptors favored anti-Markovnikov addition regardless of the amine employed.

Buil *et al.* have demonstrated that indenyltitanium half-sandwich complexes containing tethered ethers **32** (Figure 2) are incredibly active alkyne hydroamination catalysts (5 mol% of complex, full conversion after 15 minutes with some substrates).[36]

The Doye group was also able to show that alkyne hydroamination can also be performed intramolecularly to form dihydro-[37] and tetrahydroisoquinolines[38] (Scheme 12).

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Following ring closure to the dihydroisoquinoline, 1-benzoyldihydroisoquinoline **33** can be isolated after oxidation by palladium on carbon. Alternatively, the dihydroisoquinoline can be reduced under standard sodium cyanoborohydride conditions to afford the tetrahydroisoquinoline **34**.

Using aryl cyclopropyl alkynes, the Doye group performed a one-pot intermolecular hydroamination/cyclopropylimine rearrangement reaction to synthesize pyrrolidines after reduction (Scheme 13).[39] The regioselectivity of addition to these unsymmetrical alkenes is excellent, >98:2 favoring the anti-Markovnikov product. Heating the imine with a catalytic amount of Brønsted acid promotes the cyclopropylimine rearrangement. After reduction, the pyrrolidine products can be isolated in modest to excellent yields.

$(Ind)_2TiMe_2$ has also been shown to be an efficient catalyst for intramolecular alkene hydroamination (Scheme 14).[40] Using primary amine **35** as a test substrate, the Doye group showed that $(Ind)_2TiMe_2$ is a much more active catalyst when compared to Cp_2TiMe_2, but less active than known hydroamination catalyst $Ti(NMe_2)_4$.[41] The diphenylmethyl backbone of **35** was necessary for successful pyrrolidine formation; this moiety provides an essential Thorpe-Ingold effect to affect ring closure and without it, only recovered starting material is observed. Six-membered piperidine rings can also be constructed using this methodology, and $(Ind)_2TiMe_2$ proved to be more active for the 6-*exo*-*trig* cyclization than either Cp_2TiMe_2 or $Ti(NMe_2)_4$.

In addition to titanium, indenyl complexes of rare earth metals have been used for intramolecular hydroamination of alkenes. Taking inspiration from the seminal report on cyclopentadienyllanthanide hydroamination by Marks,[42] researchers have prepared and tested a number of indenyl complexes of ytterbium,[43] yttrium,[43b,44] lutetium,[44a,45] and dysprosium.[44a] Although direct comparisons between cyclopentadienyl and indenyl complexes are limited, Vitanova and coworkers reported a substantial increase in rate of hydroamination using chiral indenylyttrium complex 38 when compared to complex 37 (Scheme 15).[44a] Unfortunately, the diastereo- and enantioselectivity for this desymmetrative hydroamination reaction was modest.

$(Ind)_2TiMe_2$ is also a catalyst for the regioselective hydroaminomethylation of alkenes under comparatively mild conditions (Scheme 16).[46] Heating a mixture of N-methylaniline **39** and 1-octene **40** in toluene with a desired titanium catalyst, a mixture of branched **41** and linear **42** is obtained. Whereas $Ti(NMe_2)_4$ provides a low yield of **41/42**, $(Ind)_2TiMe_2$ efficiently delivers the hydroaminomethylated product in high yield and high regioselectivity for the branched product. Furthermore, the catalyst can perform hydroaminomethylation at a lower temperature. Styrene-based substrates tended to give lower regioselectivities (~85:15 branched:linear). The mechanism for this reaction is postulated to be similar to the mechanism proposed for tantalum-catalyzed hydroaminomethylation.[47] C-H activation of the *N*-methyl group of **37** results in titanaaziridine intermediate **43**, which then undergoes regioselective olefin insertion to form titanacycle **44**. *N*-Alkyl substrates other than methyl failed to react, presumably due to their more sterically demanding nature.

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3. Iron and Ruthenium

In 1993, the Trost group reported the ruthenium-catalyzed redox isomerization of allylic alcohols.[48] The scope of this reaction was originally explored with $CpRu(PPh_3)_2Cl$, and while the authors noted the exquisite chemoselectivity of this complex, they also observed sluggish reactivity of 1,2-disubstituted allylic alcohols. As seen in entry 1 of Scheme 17, ketone **45** could only be isolated in 23% yield after 9 hours using $CpRu(PPh_3)_2Cl$, with the remainder of the mass balance being 1-phenyl-1,3-heptadiene resulting from acid-catalyzed elimination. When the authors switched their catalyst to $(Ind)Ru(PPh_3)_2Cl$, full conversion of the allylic alcohol could be obtained in only two hours in 83% yield of **45**. A similar increase in rate was detected in the redox isomerization reaction resulting in ketone **46**. In this case, even after 24 hours, the CpRu catalyst could not catalyze the reaction to complete conversion, and starting material was recovered from the reaction mixture. On the other hand, catalysis utilizing $(Ind)Ru(PPh_3)_2Cl$ was complete in 3 hours, and ketone **46** was isolated in an 81% yield.

Rate acceleration with $(Ind)Ru(PPh_3)_2Cl$ was also observed in the case of cyclic allylic alcohol **47** (Scheme 18a). A reaction that would normally require 24 hours with the CpRu catalyst was complete in only 3 hours and in an improved isolated yield of ketone **48**. It is important to mention that while $(Ind)Ru(PPh_3)_2Cl$ does display an increased reactivity, sometimes this advantage is accompanied by decreased chemoselectivity for allylic alcohol isomerization. While the allylic alcohol in **49** was successfully isomerized to ketone **51**, significant isomerization of the terminal olefin to **50** was also observed (Scheme 18b). The isomerization of terminal olefins is not observed with $CpRu(PPh_3)_2Cl$. Therefore, it is important to be mindful of functional group reactivity trends when choosing an appropriate catalyst for the redox isomerization, as this factor can be crucial to the success of the reaction.

After the success of allylic alcohols, Trost and Livingston extended the ruthenium-catalyzed redox isomerization reaction to propargyl alcohols.[49] Again, $(Ind)Ru(PPh_3)_2Cl$ proved to be catalyst of choice for this transformation, isomerizing propargyl alcohol **52** to enal **53** to full conversion in 30 min (Scheme 19a). By comparison, $CpRu(PPh_3)_2Cl$ required a full 4 h to reach full conversion. The catalyst loading of $(Ind)Ru(PPh_3)_2Cl$ could be dropped to 1 mol% and 1 mol% $In(OTf)_3$ co-catalyst without affecting conversion; **53** was obtained in an 83% yield.

The mechanism of this reaction was probed using deuterium-labeled substrate **54** (Scheme 19b). Enal **55** was isolated with complete deuterium incorporation at the α-position of its aldehyde. Based on this evidence, the authors propose a mechanism where $(Ind)Ru(PPh_3)_2Cl$ is activated by the indium co-catalyst to form cationic ruthenium complex **56**. After phosphine dissociation and bidentate propargyl alcohol coordination, **57** undergoes a 1,2-hydride shift where one of the carbinol protons migrates to the alkyne. Protodemetallation of vinylruthenium intermediate **58** to the enal completes the catalytic cycle and regenerates the catalyst.

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To demonstrate the synthetic utility of the redox isomerization reaction, the Trost group applied this methodology to the total syntheses of leukotriene B_4 (Scheme 20a)[49b] and adociacetylene B (Scheme 20b).[50] With 5 mol% of ruthenium catalyst, 4-en-2-yn-1-ol **59** could be isomerized to dienal **60** in a 92% yield - an impressive display of catalyst chemoselectivity considering the functionality on the molecule. The synthesis of leukotriene B_4 could then be completed with an additional five steps. In the synthesis of adociacetylene B, the symmetric advanced intermediate **61** underwent two redox isomerizations with 10 mol% of catalyst to provide dialdehyde **62** in good yield. Using (*S,S*)-Prophenol **63**, an asymmetric alkynylation of both aldehydes was performed in excellent diastereo- and enantioselectivity. After desilylation, adociacetylene B was synthesized in only four steps (longest linear sequence).

Redox isomerization can also be combined in tandem with Michael addition reactions in order to increase molecular complexity and simplify multistep processes. For example, substituted indoles and furans can be included in the reaction mixture to synthesize β-substituted ketones (Scheme 21a).[51] An asymmetric intermolecular conjugate addition of methylene bis(sulfones) can also be executed in one pot following the ruthenium step (Scheme 21b).[52] Bidentate 1,3- bis(diphenylphosphino)propane(dppp) is added in order to prevent interference of the organocatalytic step by the ruthenium catalyst. Using these conditions, carbocycles with enantioselectivities up to 97% *ee* can be obtained.

(Ind)$Ru(PPh_3)_2Cl$ is an efficient catalyst for the ring expansion of alkynylcyclopropanols **64** (Scheme 22).[53] Depending on the functional group attached to the alkyne, either cyclobutanone **65** or cyclopentenone **66** is observed as the major product. The authors attribute this mechanistic dichotomy to the degree in which the substrate can stabilize the buildup of positive charge at the alkynyl carbon adjacent to the cyclopropane.

(Ind)$Ru(PPh_3)_2Cl$ has also been used as an effective catalyst for the dynamic kinetic resolution of secondary alcohols in conjunction with *Pseudomonas cepacia* lipase (PCL; Scheme 23).[54]

Related indenyl complex (Ind)$Ru(C{\equiv}CPh)(PPh_3)_2$ can perform head-to-head dimerization of terminal alkynes to form enynes in modest *E* to *Z* ratios (Scheme 24).[55]

Itoh and coworkers have noted an interesting trend in the product distributions of ruthenium-catalyzed reactions of 1,6-heptadiynes with strained bicyclic alkenes (Scheme 25). [56] When dimethyl dipropargylmalonate **67** is reacted with an excess of norbornene and chloro(η^5-indenyl)ruthenium(1,5-cycloocatdiene) **70**, polycyclic **68** is formed as the primary reaction product, with minor amounts of diene **69**. However, when indenyl complex **70** is exchanged for its cyclopentadienyl analogue **71**, more of the diene is formed in proportion to **68**. A reversal in selectivity is seen with the more electron-donating ligand Cp^* (η^5-pentamethylcyclopentadienyl). With complex **72**, diene **69** is favored in roughly a 3:1 ratio. The difference in product distributions can be explained by the degree in which a given ruthenium complex can stabilize a ruthenacyclopentatriene intermediate like **73**. Such intermediates have been proposed for other ruthenium-mediated transformations.[57] Ruthenacyclopentatrienes are a resonance form of a ruthenacyclopentadiene, and an increase

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in the number of vacant orbitals around a transition metal complex increases its ability to π-bond with a coordinated ligand. Therefore, an increase in the degree of cyclopentatriene character is observed in more coordinatively unsaturated intermediates such as η^3-indenyl complex **73**. Intermediate **73** can be seen to be a bis(carbene) complex that can perform two successive cyclopropanation reactions *via* a metathesis-like [2+2] cycloaddition with the strained norbornene. Reductive elimination generates the observed cyclopropane. Because the Cp^* ligand has less of a propensity to slip into a η^3 coordination mode, more cyclopentadiene character is observed in intermediate **74**, and therefore the olefin insertion product (i.e. **69**) dominates as the major reaction product.

Indenyl complex **70** has also been studied by Alvarez *et al.* for [2+2] and [4+2] cycloaddition reactions of alkynes (Scheme 26).[58] For the indenylruthenium-catalyzed [4+2] cycloaddition reaction, the authors noted a stronger dependence of the electronics and steric properties of the alkyne on product yield. In previous work, Trost and coworkers have shown that CpRu(COD)Cl **71** provides much higher yields of the [4+2] cycloaddition products across a diverse range of alkynes.[59]

Kündig and coworkers have reported that ruthenium catalysts **75** containing bidentate C_2-symmetric chiral phosphinite ligands are excellent catalysts for asymmetric Diels-Alder cycloaddition reactions (Scheme 27).[60] In their studies, they observed an interesting reversal of selectivity of the reaction between cyclopentadiene and acrolein that depended on whether a Cp or indenyl ligand was incorporated on the catalyst scaffold. Using (*S,S*)-Cp-**75**, the *endo* diastereomer **78** was favored in a 70:30 ratio over the exo diastereomer **77**. On the other hand, (*R,R*)-Ind-**75** reversed the diastereoselectivity of the process, favoring the *exo* isomer in a 71:29 ratio and in 85% *ee*. The authors attribute this reversal in selectivity to the increased steric demands of the indenyl ligand. Ind-**75** also proved to be a more reactive complex, catalyzing the Diels-Alder reaction between cyclopentadiene and methacrolein to completion within 3 hours. By comparison, Cp-**75** only reached 60% conversion after 5 hours. Related complexes Cp- and Ind-**76** are excellent catalysts for asymmetric intramolecular Diels-Alder reactions. [61] In some of the intramolecular cases, Ind-**76** delivered higher enantioselectivities than Cp-**76**, albeit with comparable catalytic rates (Scheme 27).

Although indenyl variants of complex **75** and **76** have been shown to be effective catalysts for cycloaddition reactions, the bidentate nature of their phosphinite ligands limits their use to reactions requiring single-point coordination to a Lewis acidic metal center. Recently, the Trost group introduced a novel class of chiral catalyst **79** that contains a chiral sulfoxide bound to its indenyl ring *via* a *peri*-naphthalene tether (Scheme 28).[62] The fact that this catalyst has a maximum of three possible sites around ruthenium for substrate coordination opens up a broader range of synthetic possibilities for chiral ruthenium catalysis. Therefore, when enyne **80** is subjected to 10 mol% of **79** and one equivalent of water, a 1:10 ratio of diene **81** to alcohol **82** is obtained. Alcohol **82**, a product which hadn't been observed under CpRu catalysis, could be isolated in an 80% yield and 84:16 e.r.. Catalyst **79** could also perform an asymmetric redox isomerization/C-H insertion reaction of acrylate **83**. Though the reaction proceeds to 43% conversion in THF, carbocycle **84** was observed to have a promising 90:10 e.r..

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In 2012, the Nolan group reported that 1-phenylindenylruthenium complex **85**[63] was an exceptionally active catalyst for the transfer hydrogenation of aldehydes, ketones, and imines (Scheme 29).[64] Complex **85**, which can be synthesized in one high yielding step from commercially available $RuCl_2(PPh_3)_3$, outperformed $CpRu(PPh_3)_2Cl$, $(Ind)Ru(PPh_3)_2Cl$, and Shvo's catalyst **86** in the transfer hydrogenation of benzophenone. This increase in activity cannot be explained by the indenyl effect alone, as $(Ind)Ru(PPh_3)_2Cl$ actually performed *worse* than either $CpRu(PPh_3)_2Cl$ or **85** in the transfer hydrogenation reaction.

One example of an asymmetric transfer hydrogenation has been reported with an indenylruthenium complex **87** bearing a chiral bidentate PHOX ligand in 76% *ee* (Scheme 30),[65] though this complex was inferior in terms of activity and selectivity when compared to other complexes.

The phenyl substitution on complex **85** proved to be differential for the ruthenium-catalyzed redox isomerization of allylic alcohols at room temperature (Scheme 31).[66] $CpRu(PPh_3)_2Cl$ and $(Ind)Ru(PPh_3)_2Cl$ were completely inactive in isomerizing **88** at room temperature. Trost *et al.* showed that elevated temperatures are necessary for redox isomerizations with these complexes (see Scheme 17). On the other hand, **85** completely isomerized **88** to ketone **89** at room temperature in one hour. A range of terminal, 1,1-disubtituted, and 1,2-disubstituted secondary allylic alcohols were successfully isomerized to their corresponding ketones. Trisubstituted olefins failed to react for steric reasons. Mechanistic studies and DFT calculations point to the likelihood of a π-oxo-allyl complex **90** as the key intermediate of the reaction, which was originally proposed by Trost.[48] Related cationic complex **91** proved to be ideal for the isomerization of primary allylic alcohols under base-free conditions,[67] the stereoselective isomerization of terminal to internal alkenes,[67] and for the dynamic kinetic resolution of secondary alcohols.[68]

Complex **85** can also be used to perform chemoselective reductions of carboxylic acids.[69] Using 1 mol% of **85** with two equivalents of phenylsilane, excellent yields of primary alcohols **92–95** could be obtained without affecting any reducible functionalities (Scheme 32). Other silanes (PMHS, Ph_2SiH_2, Ph_2MeSiH, $PhMe_2SiH$, etc.) were ineffective reducing agents. A silyl ester was postulated to be an intermediate in the catalytic cycle. Similar complexes to a proposed catalytic intermediate of this transformation, **96**, has been synthesized independently and used for pyridine-directed catalytic C-H borylation of arenes[70] and for heteroarene-directed H-D exchange reactions.[71]

Bauer *et al.* investigated complex **97** for catalytic activity toward OH exchange with OR of terminal propargyl alcohols (Scheme 33).[72] Typically, good isolated yields could be obtained when primary aliphatic alcohols were used as the nucleophiles for propargylation. Using more sterically restricting secondary alcohols as nucleophiles resulted in lower yields. This reaction is proposed to proceed through a ruthenium allenylidene intermediate.

There is a single report of indenyliron catalysis in the literature, also published by the Bauer group.[73] In their studies on using Lewis acidic iron complexes for Mukaiyama aldol reactions to form β-siloxyester **98**, they observed a significant increase in catalytic rate

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going from Cp-phosphinoxazoline (PHOX) complex **99** to indenyl-PHOX complex **100** (Scheme 34). Unfortunately, no enantioinduction was observed with either **99** or **100**. It was also discovered that achiral **101** could serve as an efficient catalyst for this transformation. Using **100**, both aryl and alkyl aldehydes were effective substrates for the Mukaiyama aldol reaction.

4. Cobalt, Rhodium, and Iridium

The earliest examples of catalysis with group-9 indenyl transition metal complexes were reported while studying ligand effects for [2+2+2] cycloaddition reactions of alkynes. Abdulla and coworkers reported that (Ind)Rh(COD) **102** catalyzed the cyclotrimerization of dimethylacetylenedicarboxylate (DMAD) to hexacarbomethoxybenzene at an initial rate approximately ten times that of CpRh(COD) **103**.[74] Whereas cyclotrimerizations with CpRh complexes required 24 hour reaction times, reactions with **102** were complete within 2 hours and produced no polymeric byproducts. Rate studies by Borrini *et* al. measuring the reactivity of various Cp and indenylrhodium cyclotrimerization catalysts agree with Abdulla's observations.[75] These indenylrhodium complexes were shown to be active even at room temperature or below, albeit with significantly reduced turnover numbers. Again, increased catalytic activity was linked to the increased facility of slippage of the indenyl ligand. Computational studies by Orian on the effect of the indenyl ligand in cyclotrimerization reactions are in agreement with this line of reasoning.[76]

Despite exhibiting significant rate differences, **102** and **103** provide similar regiosisomeric mixtures when unsymmetrical alkynes are subject to [2+2+2] cycloaddition (Scheme 35).[74] For example, cyclotrimerization of ethyl propiolate with either **102** or **103** results in a 1:1 mixture of triesters **104** and **105** (Scheme 35a). Indenyl complex **102** can catalyze the cyclotrimerization of ethyl propiolate and propargyl alcohol **106** in an 83% yield of lactone **107**, which was observed to be the sole product (Scheme 35b). Based on the product distributions of Scheme 35a and b, rhodacyclopentadiene **108** is most likely catalyst intermediate for these reactions. Propargyl alcohol **106** was also tested for [2+2+2] cycloaddition with DMAD to ester **109** (Scheme 35c), although competitive formation of hexacarbomethoxybenzene **110** was also observed.

In 1995, the Heller group reported the cobalt-catalyzed [2+2+2] cycloaddition of acetylene and nitriles in water (Scheme 36).[77] Both (Ind)Co(COD) **111** and CpCo(COD) **112** were established to be competent catalysts for this reaction, with no apparent significant differences in reactivity or selectivity of 2-phenylpyridine **113** over benzene.

However, planar chiral 1-neomenthylindenylcobalt complexes reminiscent of the ZACA complexes developed by Negishi (*vide supra*) proved to be differential for an atroposelective variant of this reaction (Scheme 37).[78] Using nitrile **114**, a low 10% yield but promising 64% *ee* was obtained of **115** using indenylcobalt complex **119** as a catalyst for heterocyclotrimerization. Note that CpCo complexes **116** and **117** were less selective catalysts. The authors attribute the low yields of this reaction to the bulkiness of the complex; unsubstituted achiral CpCo(COD) **112** could catalyze this transformation in a 71% yield. Fortunately, by tethering the two alkynes together in the same substrate, as in naphthyl

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120, excellent yields and enantioselectivities of tetrahydroquinolines **121** were obtained with **118** (Scheme 38).

Cobalt complexes **118** and **119** deliver high enantioselectivities in the [2+2+2] cycloaddition of alkynylphosphine oxide **122** (Scheme 39).[79] Biaryl **123** can be recrystallized to >99% *ee*, and after reduction, phosphine **124** can be used as an effective ligand for palladium-catalyzed asymmetric hydrosilylation of alkenes. Chiral helicenes can also be constructed with this [2+2+2] reaction using catalyst **118**, though in low (20% *ee*) enantioselectivity.[80]

Chiral 1-menthylindenyl ligands were examined for rhodium-catalyzed asymmetric olefin hydrogenation of itaconic acid (Scheme 40).[81] Though both complex **125** and planar chiral **126** exhibited excellent reactivity, chiral succinic acid **128** was isolated in low *ee*. These two complexes can also be used for branched-selective hydroformylation of styrene to 2-phenylpropanal, but no enantioselectivity was observed.

(Ind)Co(COD) **111** has also been used for catalytic intermolecular Pauson-Khand reactions of norbornadiene (Scheme 41).[82] Both internal and terminal alkynes **129** are effective substrates for this reaction; cyclopentenones **130** can be isolated in good to excellent yields with complete *exo* selectivity. Neither CpCo(COD) **112** nor $CpCo(CO)_2$ provided any of the desired product under the standard reaction conditions, underscoring the necessity of the indenyl ligand for this transformation.

The Milstein group found that the indenyl ligand was also essential for observing catalytic activity in the intermolecular rhodium-catalyzed hydroacylation of olefins (Scheme 42).[83] With benzaldehyde as a substrate under 1000 psi of ethylene at 100 °C in benzene, turnover rates of up to ca. 4 h^{-1} were achieved with $(Ind)Rh(C_2H_4)_2$ as the catalyst. Propiophenone was the sole product detected by NMR; no decarbonylation of benzaldehyde by the catalyst was observed by ^{13}C NMR under these conditions. This complex could also catalyze the addition of methyl formate to ethylene, although the reaction was much slower (2–3 turnovers after 24 hours). $CpRh(C_2H_4)_2$, $(acac)Rh(C_2H_4)_2$, and $(Ph_3P)_2RuCl_2$ were all inactive catalysts under the above reaction conditions.

Indenylrhodium complex **131** displays increased reactivity and catalyst lifetimes for the tail-to-tail dimerization of methyl acrylate (Scheme 43).[84] The catalytic acid is added to generate the catalytically active Rh^{III} hydride complex. Turnover frequencies of 11 min^{-1} could be achieved with **131** under these conditions, nearly twice that of $Cp^*Rh(C_2H_4)_2$, with excellent selectivity for the linear product dimethyl (*E*)-hex-2-enedioate. Indenylrhodium complexes can also dimerize methyl vinyl ketone with excellent *trans* selectivity albeit at drastically reduced rates (0.1–3 min^{-1}), whereas $Cp^*Rh(C_2H_4)_2$ completely failed to produce dimers.

Indenylrhodium complexes have also displayed increased turnover frequencies for the photocatalytic acceptorless dehydrogenation of isopropanol, octane, and cyclooctane (Scheme 44).[85]

During their studies of substrate-directed hydroboration reactions, the Fu research group noted that rhodium complexes containing indenyl ligands tended to give higher ratios of *cis*

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isomers of **133** for the hydroboration of alkene **132** compared to their related Cp analogs (Scheme 45).[86] The amount of benzyl ether-directed *cis* hydroboration is directly correlated to the ability of a Cp or indenyl ring to slip, indicating that the additional open coordination site provided by ring slippage is required for substrate binding. Brinkman and coworkers have shown that even greater *cis* selectivities for this substrate can be obtained with CF_3-substituted indenyl ligands under either rhodium or iridium catalysis.[87] If the benzyl ether is exchanged for a TBS ether, or if a more Lewis basic solvent such as THF is used, the directing ability of the substrate is greatly reduced, even with (Ind)Rh$(C_2H_4)_2$.

While studying the stoichiometric borylation of metal arene complex $Cp^*(PMe_3)Ir(H)(Ph)$ with HBPin (Pin=pinacol), the Smith research group noted that the major metal-containing product of this reaction, $Cp^*(PMe_3)Ir(H)(BPin)$ **134**, could catalyze the C-H borylation of benzene to up to three turnovers.[88] Additionally, **134** was found to be more regioselective for *meta* borylation[89] than $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ originally developed by Hartwig for the C-H borylation of alkanes.[90] These two pieces of data led Smith *et al.* to pursue other iridium complexes for arene C-H borylation.[91] Mechanistic studies of the Ir-catalyzed reaction indicated that the Cp^* ligand was disassociating during the catalytic cycle. Indeed, when Cp^* was replaced with a more labile ligand, as in (η^6-mesitylene)$Ir(BPin)_3$, turnover numbers increased dramatically in comparison to **134** when used in conjunction with two catalyst equivalents of PMe_3. However, because the synthesis of (η^6-mesitylene)$Ir(BPin)_3$ was low yielding, the authors decided to look for an alternative pre-catalyst that can be readily synthesized in high yields and contains an equally labile ligand as an η^6-coordinated arene.

(Ind)Ir(COD) **135** can be synthesized in one step from indenyllithium and commercially-available $[IrCl(COD)]_2$ in a 86% yield.[92] Used in conjunction with bidentate phosphine 1,2-bis(diphenylphosphino)ethane (dppe), 2 mol% **135** can catalyze the C-H borylation of benzene in high yields and in only two hours (Scheme 46a). The catalyst loading for this transformation can be reduced to as little as 0.02 mol% of iridium when using 1,1-bis(dimethylphosphino)ethane (dmpe) as a ligand; this represents a turnover number of 4500, which is a 1000-fold increase over pre-catalyst **134**. Complete *meta* borylation of 1,3-dibromobenzene can be achieved (Scheme 46b) and **136** can be isolated in 92% yield. Notable is the fact that the reactive aryl bromide bonds are unaffected by the iridium catalyst under the reaction conditions. One-pot C-H borylation/oxidation with this catalyst system has been performed on multigram scale.[93] This *meta*-selective borylation reaction can also be used in conjunction with palladium-catalyzed amidation reactions in high yields (Scheme 46c).[94] The borylation and amidation steps can be performed in one pot, but filtration of the reaction mixture through silica prior to oxidation proved to be crucial in order to obtain high yields of phenol **137**. Although (Ind)Ir(COD) **135**/phosphine catalyst system has been largely supplanted by the Miyaura/Hartwig$[Ir(COD)(OMe)]_2$/4,4′-di-*tert*-butyl-2,2′-bipyridine catalyst system which can catalyze arene *meta* C-H borylations at room temperature,[95] there is a notable exception for particularly electron-rich heteroaromatics such as 2,5-dimethylthiophene (Scheme 46d).[96] Under the standard Miyaura/Hartwig reaction conditions, no borylation is observed after 20 hours. However, the **135**/dmpe system can successfully catalyze the borylation of 2,5-dimethylthiophene to **138** in a 97% yield.

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(Ind)Ir(COD) **135** has also been studied as a catalyst for hydrosilylation of terminal alkynes (Scheme 47).[97] Using **135** alone for the hydrosilylation of 1-octyne, a low 34% combined yield of hydrosilylated products was obtained, favoring β-(*Z*)-**140**. However, by adding biphosphinine **139**, the yield can be increased to 96% and a switch in selectivity for β-(*E*)-**140** is observed. The **135**/**139** catalyst system is complementary to $[Ir(COD)_2][BF_4]$, which delivers high yields of β-(*Z*)-**140**. A broad substrate scope of aryl, alkyl, alkenyl, and silyl terminal alkynes were explored for the hydrosilylation, with yields ranging from 44% to 96%.

5. Nickel and Palladium

Compared to other *d*-block transition metals, the catalytic properties of indenylnickel and –palladium complexes in the context of organic synthesis have been underexplored. (1-MeInd)Ni(PPh_3)Cl, which had previously been studied as a catalyst for dehydropolymerzation of phenylsilane,[98] can be used as a catalyst for the hydrosilylation of styrene with phenylsilane with 2 mol% catalyst loading.[99] Tethered amino complex **141** displays longer catalytic lifetimes and as little as 1 mol% of this complex can be used to give a quantitative yield of the α-silylated product **142** as the sole regioisomer (Scheme 48).[100] The tethered ligand prevents catalyst deactivation *via* decomposition to an unknown number of nickel complexes. Alternatively, bulky indenyl complexes [1,3-$(TMS)_2$Ind]Ni(PPh_3)Cl)[101] can be used instead of **141** to deliver **142** in an 82% yield.

(Ind)Pd(PPh_3)Cl can catalyze the hydrosilylation of styrene with trichlorosilane with 1 mol % catalyst loading to 92% conversion.[102] Like the nickel-catalyzed hydrosilylation described above, this reaction proceeds with complete α-regioselectivity. Phenylacetylene can also be hydrosilylated under these conditions, though a 1:1 mixture of regioisomers is observed.

There has been interest in using indenylpalladium complexes as pre-catalysts for cross-coupling reactions. (1-TMSInd)Pd(PPh_3)Cl can catalyze the Heck coupling of PhX (X=Br, I) to styrene in nearly quantitative conversion (9:1 ratio (*E*):(*Z*) of stillbene).[100] The same complex can be used for the Buchwald-Hartwig coupling of aniline to *o*- and *p*-chlorotoluene in quantitative conversion.

More recently, (η^3-1-*t*-Bu-Ind)LPdCl **143** (L=phosphine, NHC) has been shown to be exceptionally active catalysts for a wide range of cross-coupling reactions).[103] Hruszkewycz *et al*. noted that allylpalladium complexes **144**, originally developed by the Nolan research group,[104] tended to form inactive Pd^I dimers during catalysis (Scheme 49a).[105] This would occur *via* comproportionation of the Pd^{II} precatalyst **144** with catalytically-active Pd^0 generated under the reaction conditions. The sterically encumbering *t*-Butyl group of **143** prevents such dimers from forming, thus resulting in an especially active catalyst system. Scheme 49b shows a side-by-side comparison of IPr-**143** with IPr-**144** in room temperature Suzuki cross-coupling reactions (IPr=1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene). IPr-**143** outperformed IPr-**144** for all of the couplings tested, providing the desired biaryls in short reaction times and low catalyst loadings.

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XPhos-**143** can efficiently catalyze the Suzuki coupling of electron-rich heteroarylboronic acids and the α-arylation of aryl methyl ketones (Scheme 50a). RuPhos-**143** is an effective catalyst for Buchwald-Hartwig amination reactions (Scheme 50b). Thus, (η^3-1-*t*-Bu-Ind)LPdCl **143** complexes can be seen to be a versatile structural motif that can catalyze a diverse variety of reactions in high yield, mild reaction conditions, and low catalyst loadings.

6. Summary and Outlook

Since the discovery of the indenyl effect by Hart-Davis and Mawby in 1969, researchers have documented many cases in which the deliberate choice of an indenyl ligand had a consequence on catalysis. Indenylmetal complexes have been shown in many instances, but not all, to be superior catalysts to their cyclopentadienyl counterparts in terms of reactivity, selectivity, and stability. As can be seen from the examples presented in this review, it is difficult to predict *a priori* what impact an indenyl ligand will have on a catalytic reaction as this will be highly dependent on the metal, the reaction conditions, and the chemical transformation in question. For example, the positive effect of indenyl substitution in zirconium-catalyzed carboalumination appears to be purely steric in that it prevents substantial β-hydride elimination whereas in ruthenium-catalyzed redox isomerization, a true acceleration in reaction rate is observed.

Regardless, the indenyl ligand still remains an underexplored motif for transition metal catalysis, especially in the context of organic synthesis. The low usage of these indenyl complexes is likely due to their limited commercial availability. It is our hope that this review will inspire chemists to invent new and creative ways of designing and implementing these fascinating complexes.

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Biographies

Barry M. Trost was born in Philadelphia, PA in 1941 and studied at the University of Pennsylvania (BA, 1962). He obtained his PhD in 1965 at MIT. He moved to the University of Wisconsin where he was made Professor in 1969 and subsequently Vilas Research Professor in 1982. He moved to Stanford University in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition to holding Visiting Professorships at several universities worldwide, he has been awarded numerous prizes worldwide. His interests span the entire field of organic synthesis, particularly in the development of novel methodology and strategy for total synthesis of bioactive complex molecules.

Michael Ryan was born in Whitefish Bay, WI and studied chemistry and physics at Boston College (BS, 2010). He completed his doctoral studies in 2016 at Stanford University in the laboratory of Professor Barry M. Trost on catalytic asymmetric cyclization reactions of ruthenium complexes. He is currently a postdoctoral associate at the University of Wisconsin-Madison in the laboratory of Professor Shannon S. Stahl working on copper-catalyzed aerobic oxidation reactions.

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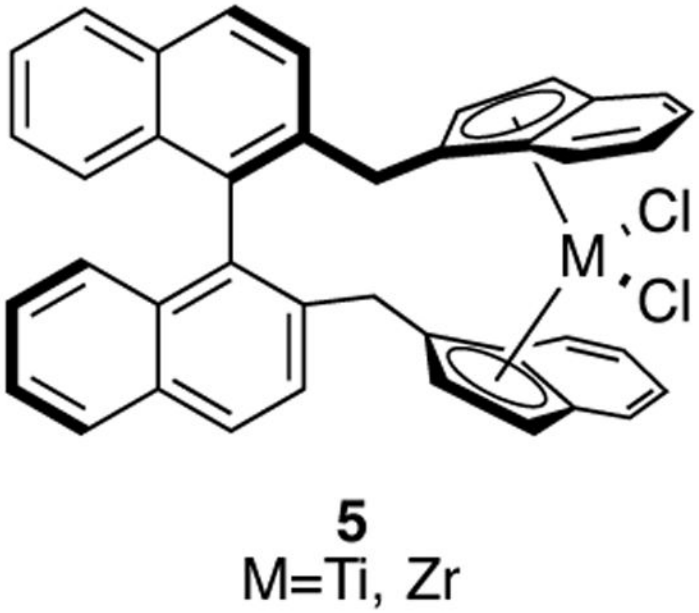

Figure 1.
Binaphthyl-based complex **5**.

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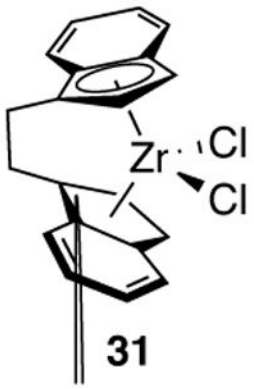

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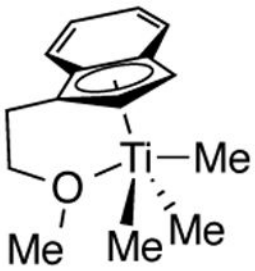

32

Figure 2.
Zirconium complex **31** and Titanium Complex **32**

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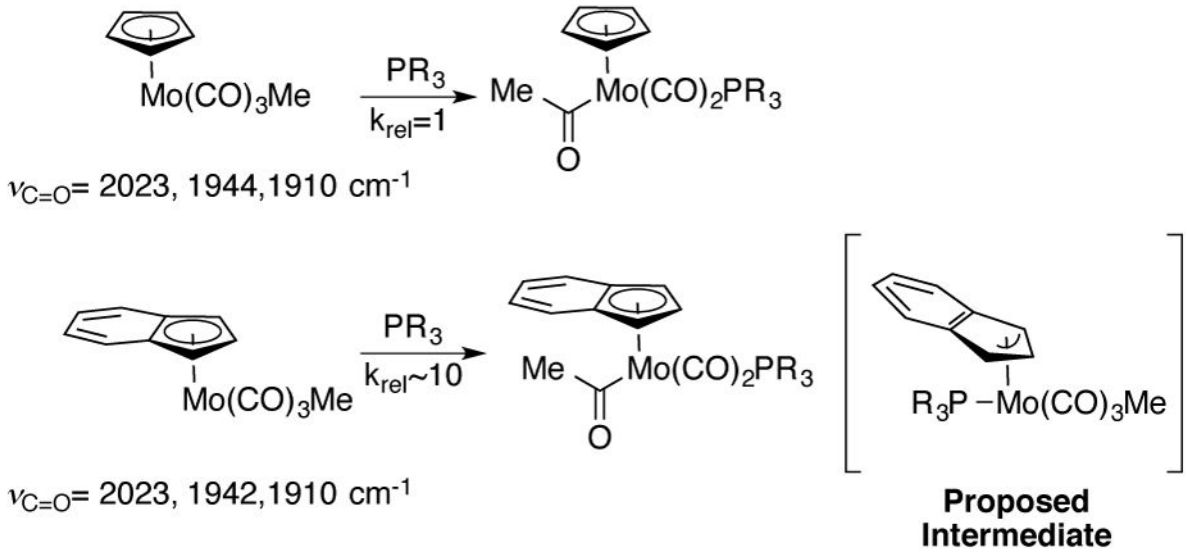

Scheme 1.

Rate acceleration of migratory insertion reactions observed with indenylmolybdenum carbonyl complexes

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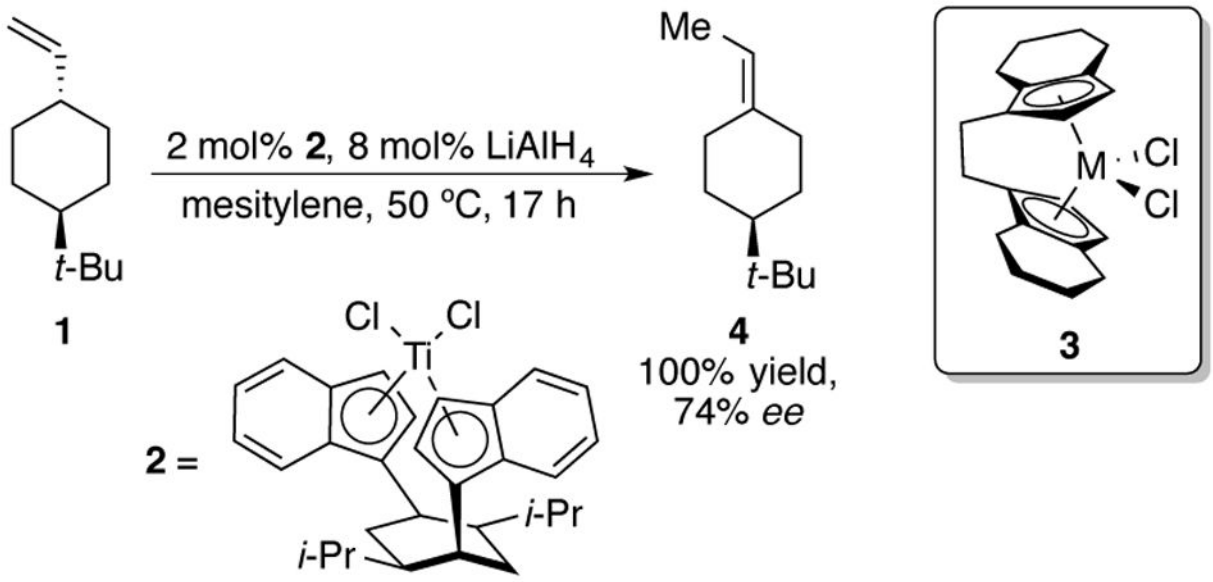

Scheme 2.

Asymmetric olefin isomerization with chiral bis(indenyl)titanium catalyst **2**

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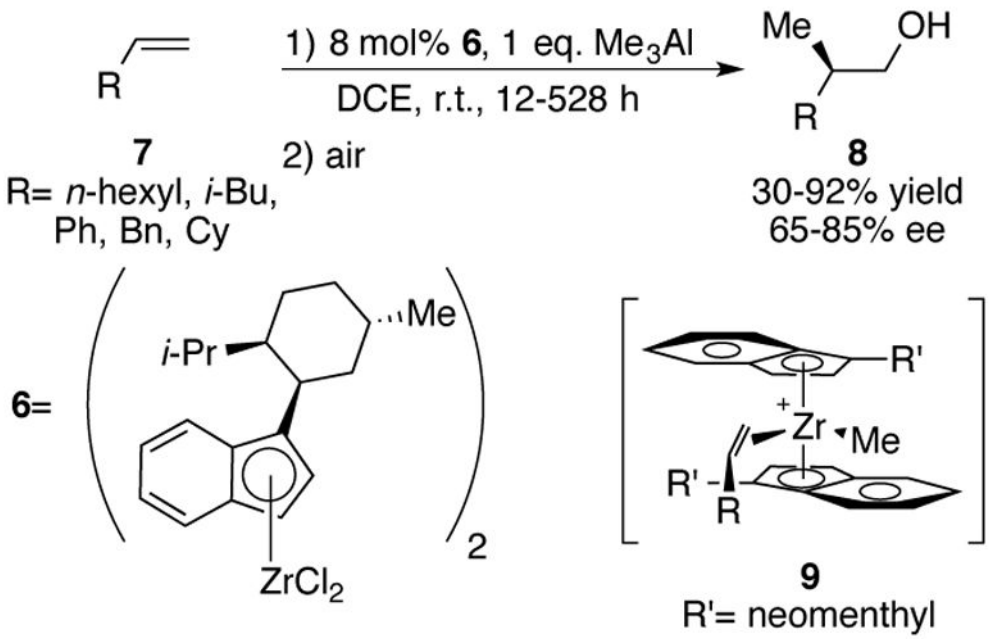

Scheme 3.
Negishi's Zr-catalyzed asymmetric carboalumination (ZACA)

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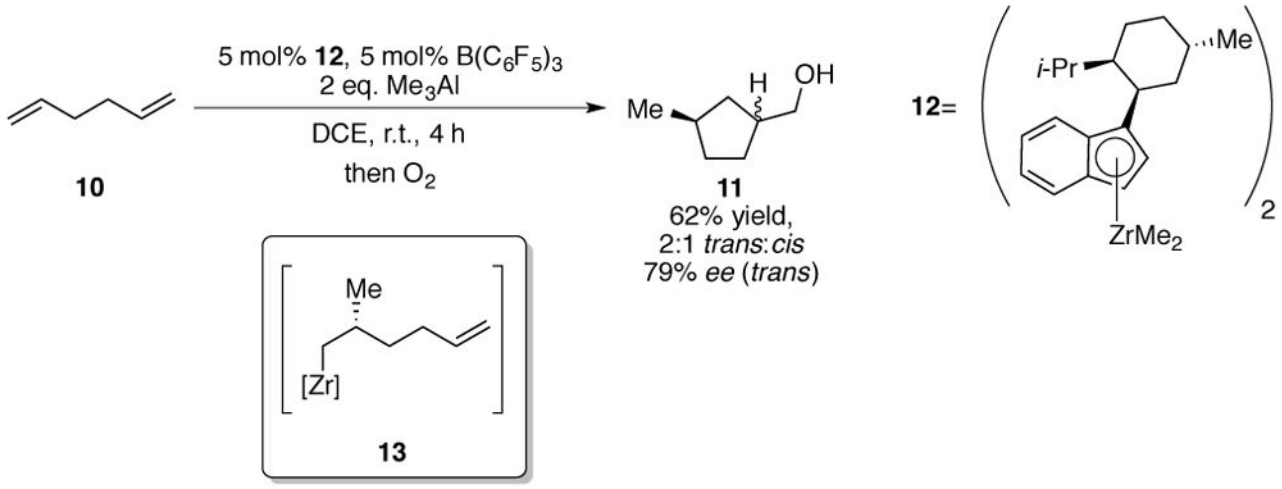

Scheme 4.

Zr-catalyzed asymmetric carboalumination (ZACA) of α,ω-dienes

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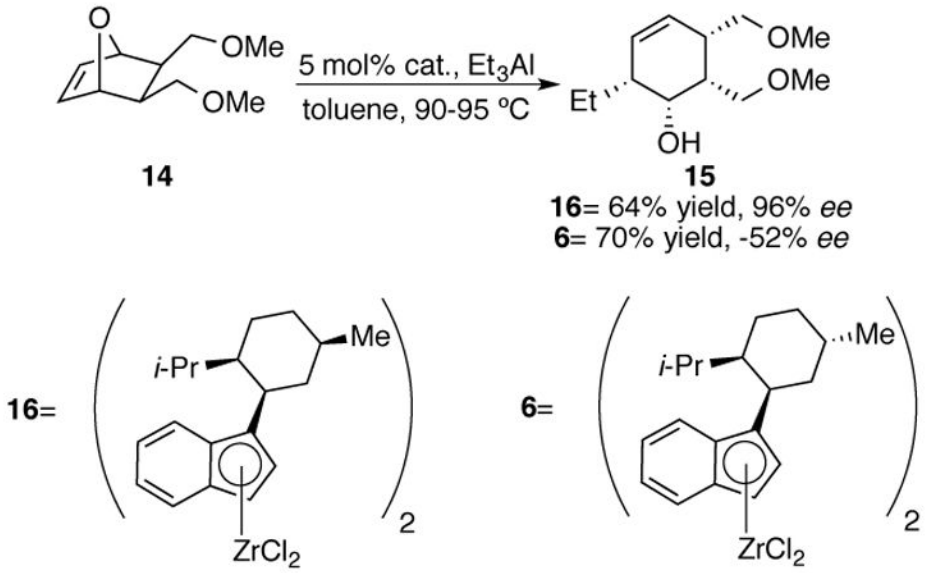
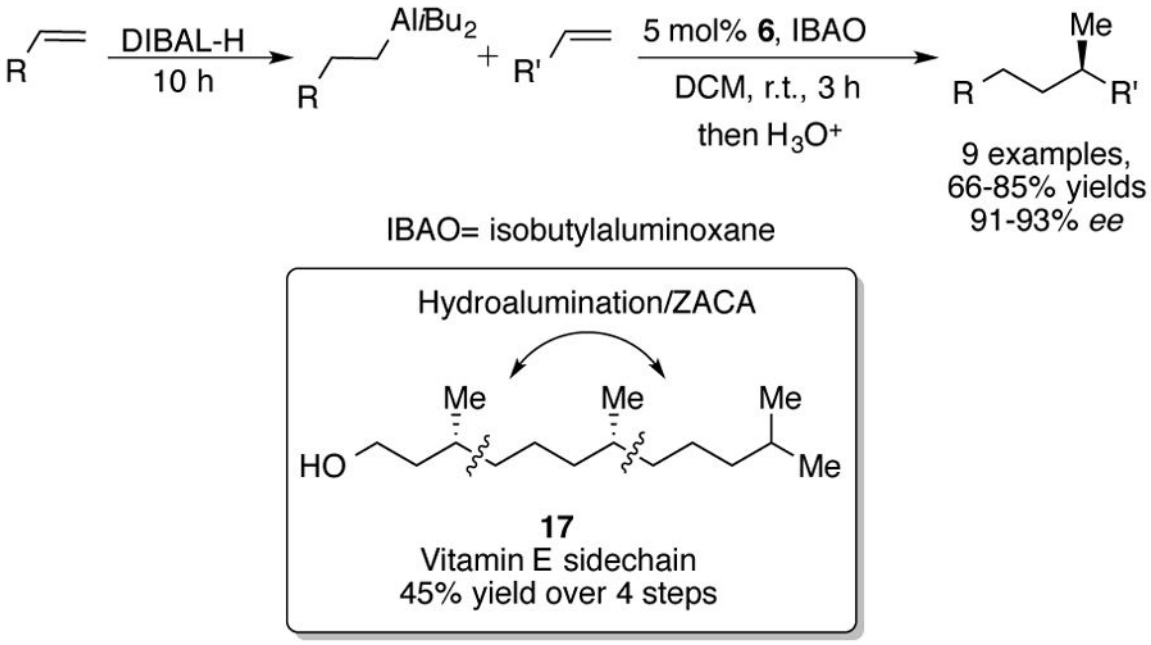


Scheme 5.
Asymmetric desymmetrization of oxanorbornenes



Scheme 6.
Tandem hydroalumination/ZACA reaction

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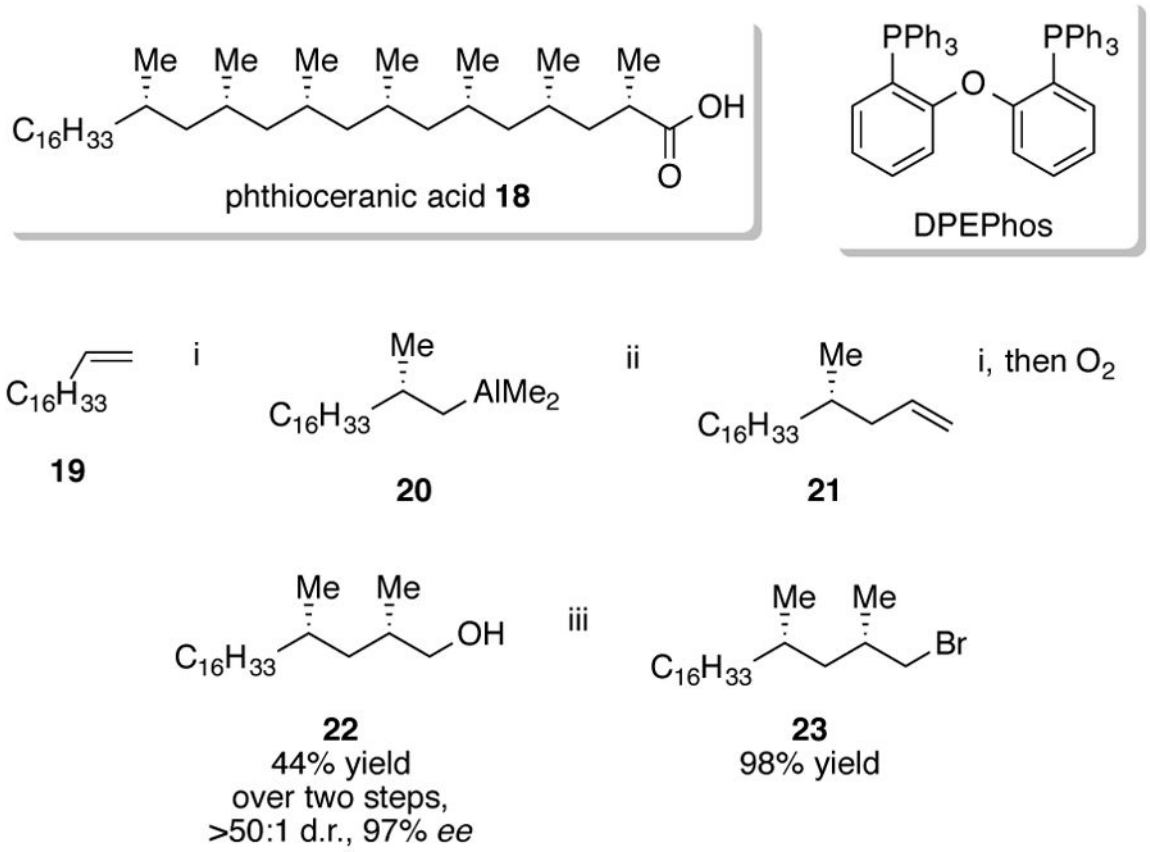

Scheme 7.

Iterative ZACA reactions for the total synthesis of phthioceranic acid **18**

Conditions: i. 1 mol% [(+)-$(NMI)_2ZrCl_2$] *ent*-**6**, 1.5 eq. $AlMe_3$, 1 eq. H_2O, DCM, 0 °C; ii. 1.2 eq. $Zn(OTf)_2$, 3 mol% [$PdCl_2$(DPEPhos),] 6 mol% DIBAL-H, 6 eq. vinyl bromide, DMF, r.t., iii. NBS, PPh_3, DCM, 0 °C.

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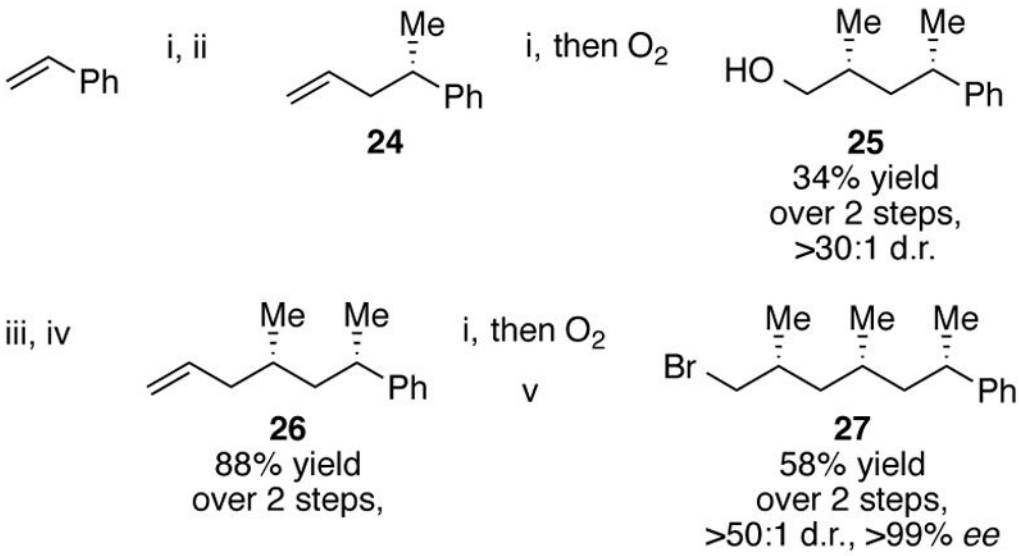
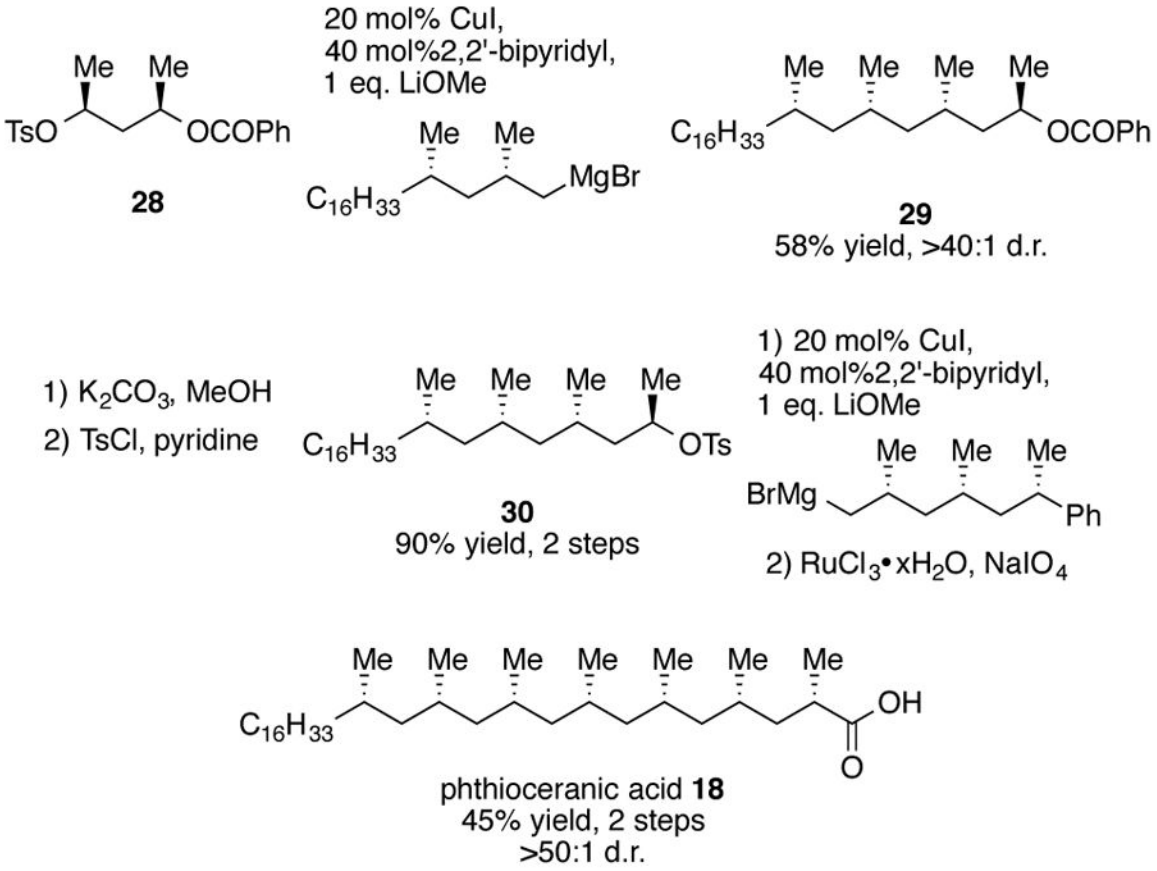


Scheme 8.

Second key fragment in the construction of phthioceranic acid **18**

Conditions: i. 2 mol% [(−)-$(NMI)_2ZrCl_2$] **6**, 2–3 eq. $AlMe_3$, 1 eq. H_2O, DCM, 0 °C; ii. 1.2 eq. $Zn(OTf)_2$, 3 mol% [$PdCl_2$(DPEPhos),] 6 mol% DIBAL-H, 6 eq. vinyl bromide, DMF, r.t., iii. PPh_3, I_2, imidazole, DCM; iv. *t*BuLi, Et_2O, −78°C then $ZnBr_2$, THF, −78 °C to 0 °C then 5 mol% [$PdCl_2$(DPEPhos),] 10 mol% DIBAL-H, 4 eq. vinyl bromide, 0 °C to r.t., v. NBS, PPh_3, DCM, 0 °C.



Scheme 9.

Endgame of Negishi's total synthesis of phthioceranic acid **18**

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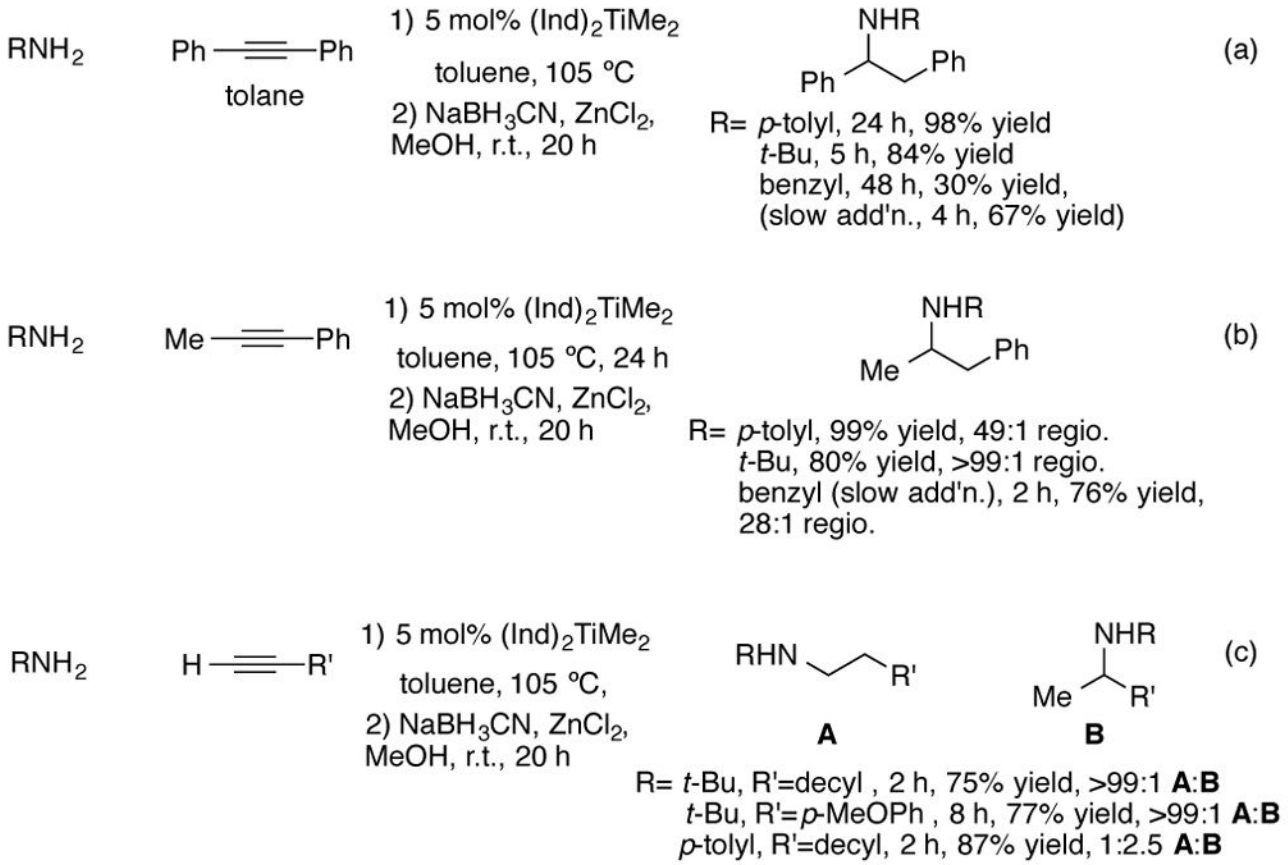
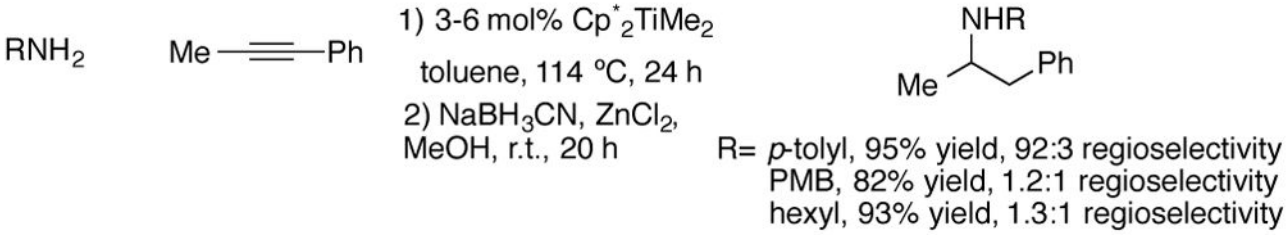


Scheme 10.
Catalytic intermolecular hydroamination of alkynes with $(Ind)_2TiMe$



Scheme 11.
Hydroamination of unsymmetrical alkynes with $Cp^*_2TiMe_2$

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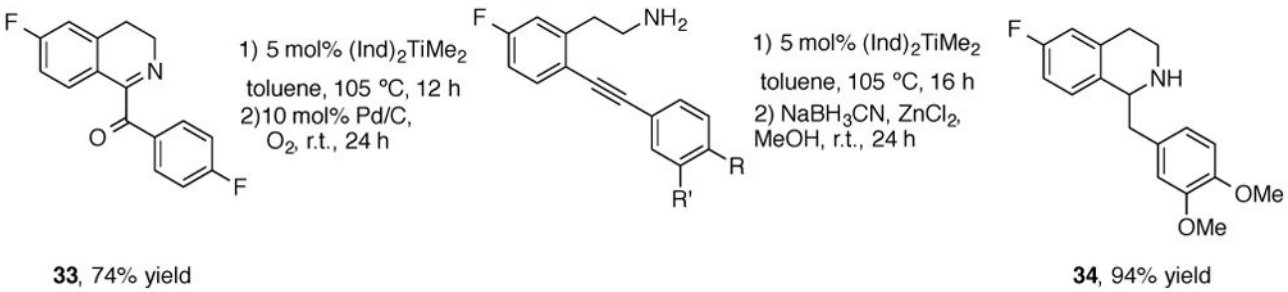

33, 74% yield

34, 94% yield

Scheme 12.
Catalytic intramolecular hydroamination for the synthesis of heterocycles

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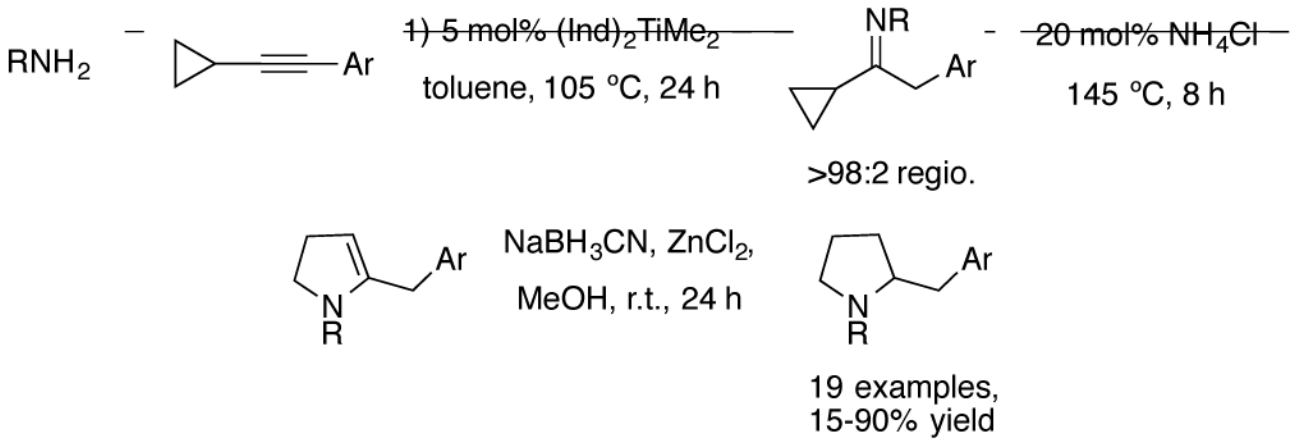

Scheme 13.

Catalytic intermolecular hydroamination/cyclopropylimine rearrangement for the construction of pyrrolidines

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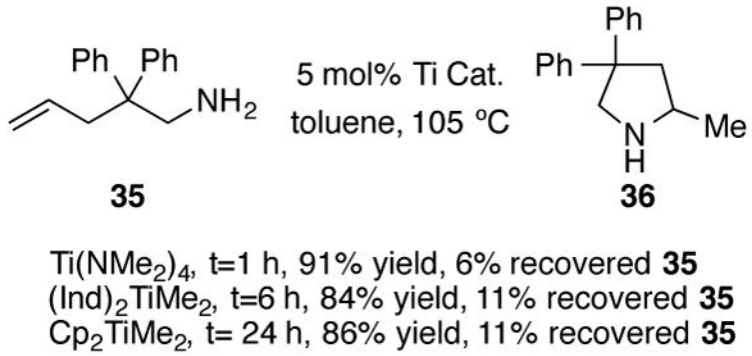

Scheme 14.
Catalytic intramolecular hydroamination of alkenes

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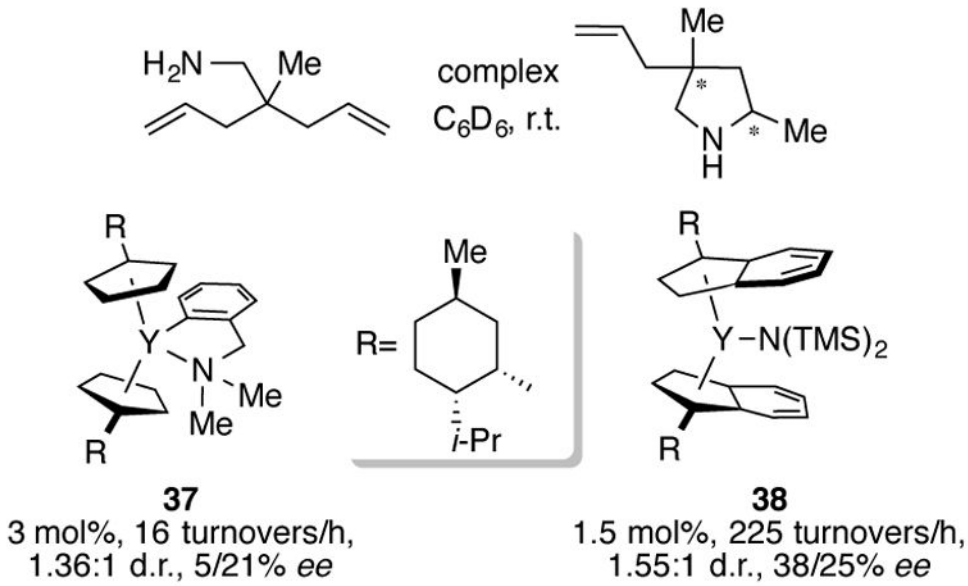
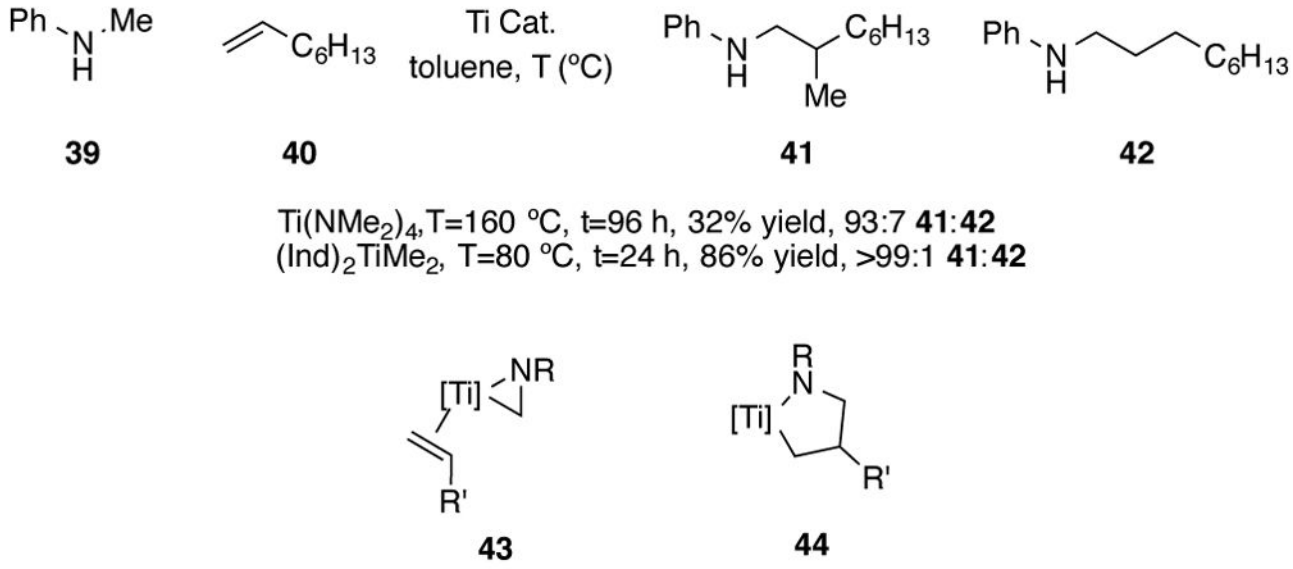


Scheme 15.
Desymmetrative hydroamination using chiral yttrium complexes



Scheme 16.
Catalytic intermolecular hydroaminomethylation of alkenes

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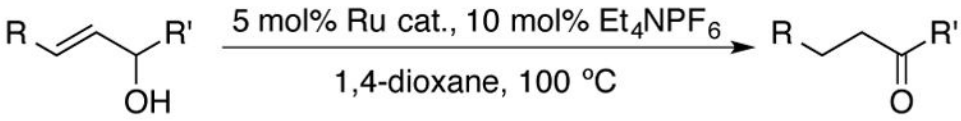

entry	R	R'	product	Ru cat	time	yield (%)
1	Ph–	*n*Bu–	**45**	$CpRu(PPh_3)_2Cl$	9 h	23
				$(Ind)Ru(PPh_3)_2Cl$	2 h	83
2	$Ph(CH_2)_2$–	$CH_3(CH_2)_8CH_2$–	**46**	$CpRu(PPh_3)_2Cl$	24 h	53 (64)[a]
				$(Ind)Ru(PPh_3)_2Cl$	3 h	81

[a] Yield in parenthesis based on recovered starting material.

Scheme 17.
Redox isomerization of 1,2-disubstituted allylic alcohols

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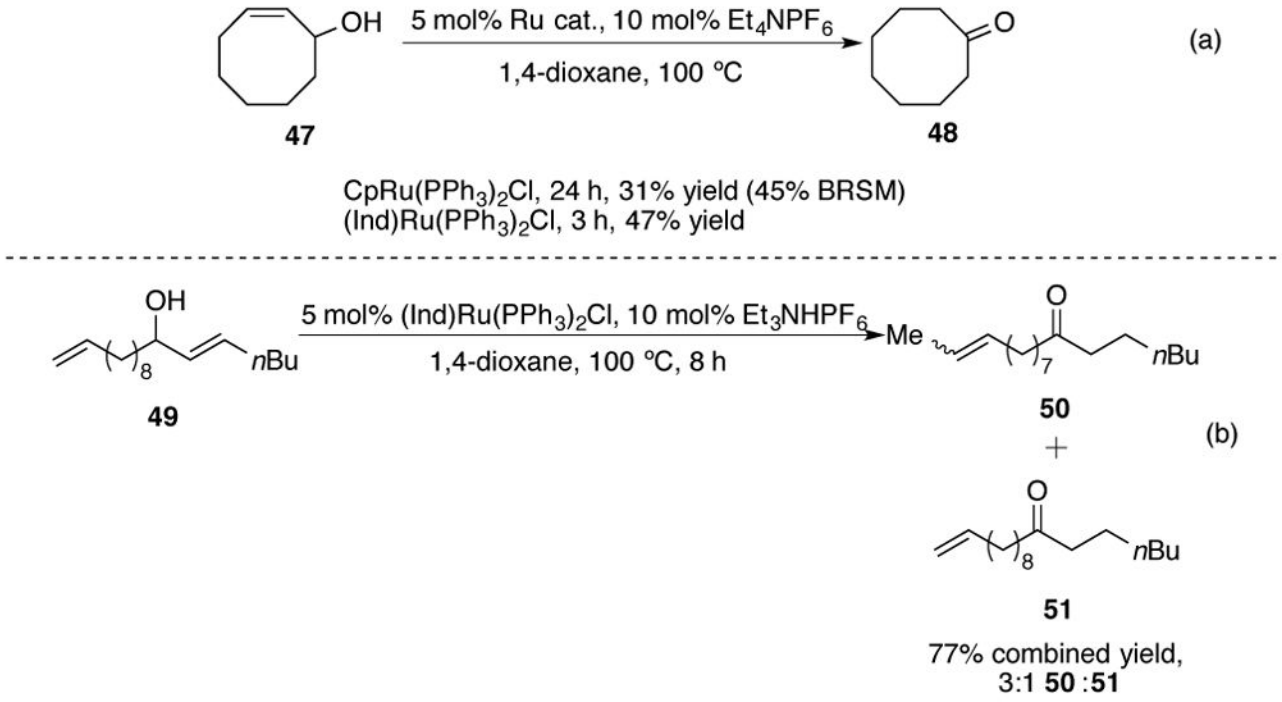

Scheme 18.

(a) Redox isomerization of a cyclic allylic alcohol (b) chemoselectivity of (Ind)Ru(PPh_3)$_2$Cl

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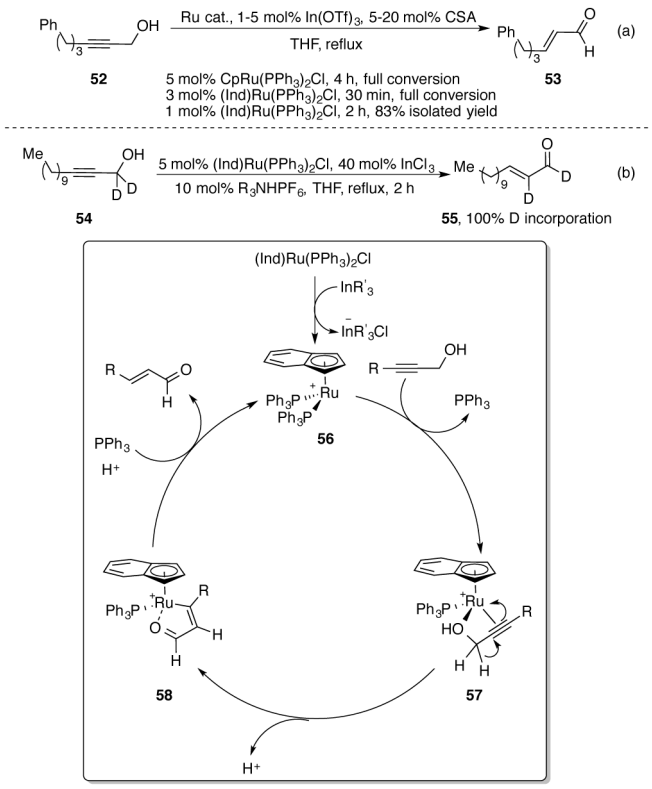

Scheme 19.

(a) Redox isomerization of propargyl alcohol **52** (b) Deuterium labeling study and proposed mechanism of ruthenium-catalyzed redox isomerization of propargyl alcohols

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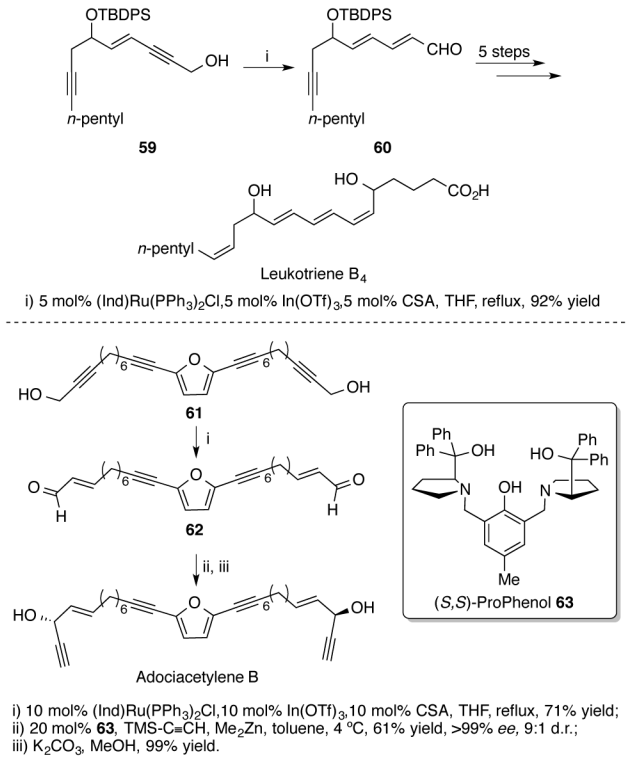

Scheme 20.

(a) Using redox isomerization in the total synthesis of leukotriene B_4 (b) Concise total synthesis of adociacetylene B via double redox isomerization/Prophenol-catalyzed zinc alkynylation

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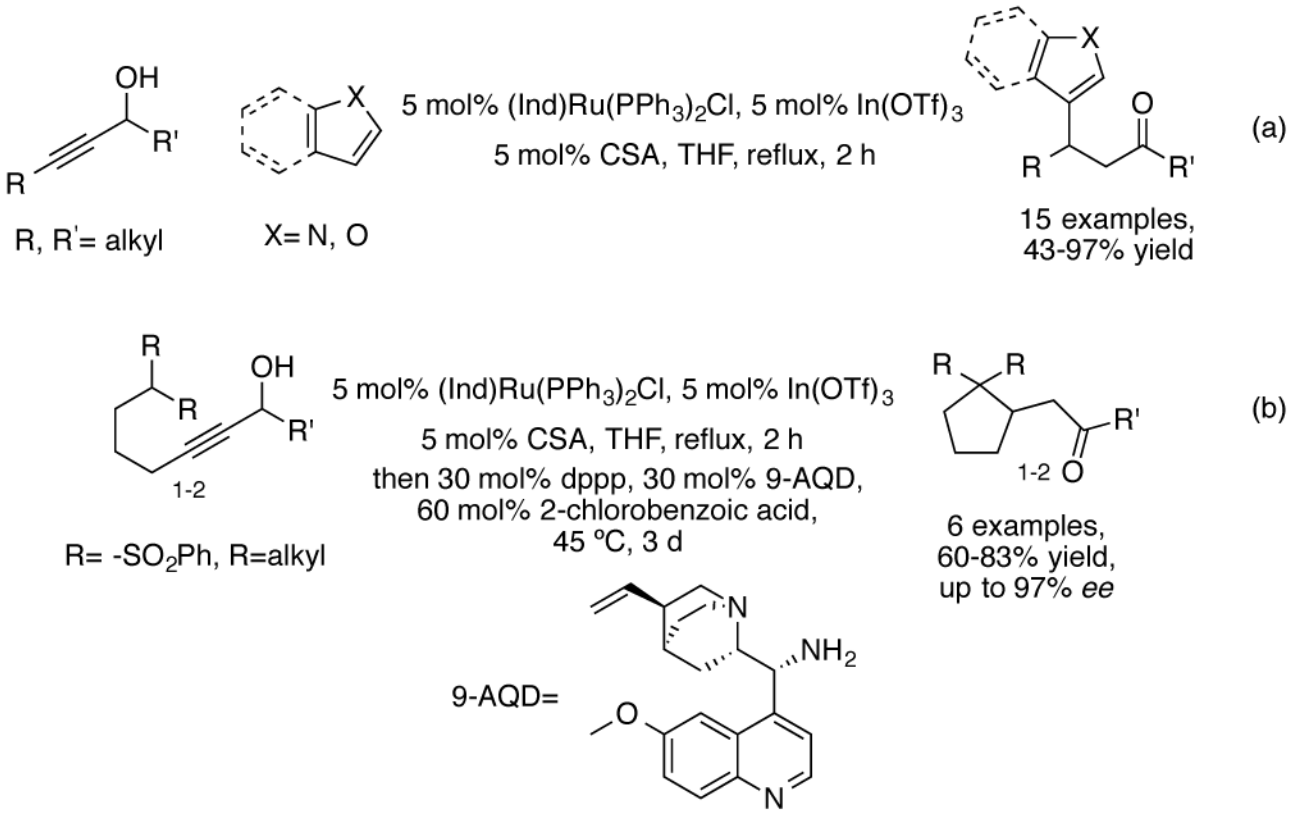
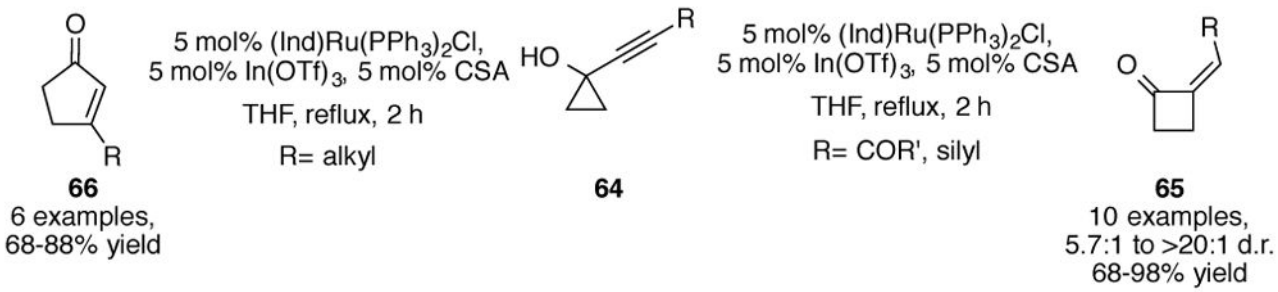


Scheme 21.

(a) Redox isomerization/conjugate addition of heteroarenes (b) Redox isomerization/ Asymmetric intramolecular conjugate addition



Scheme 22.
Ruthenium-catalyzed ring expansion of alkynylcyclopropanols

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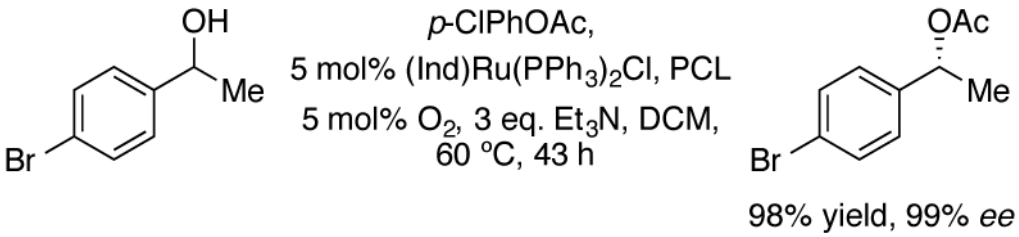

Scheme 23.
Dynamic kinetic resolution of secondary alcohols with (Ind)Ru(PPh_3)$_2$Cl and PCL

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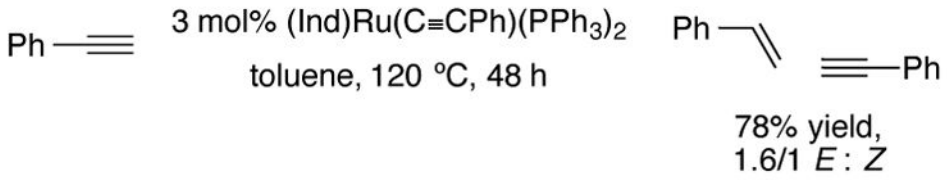

Scheme 24.
Head-to-head dimerization of phenylacetylene

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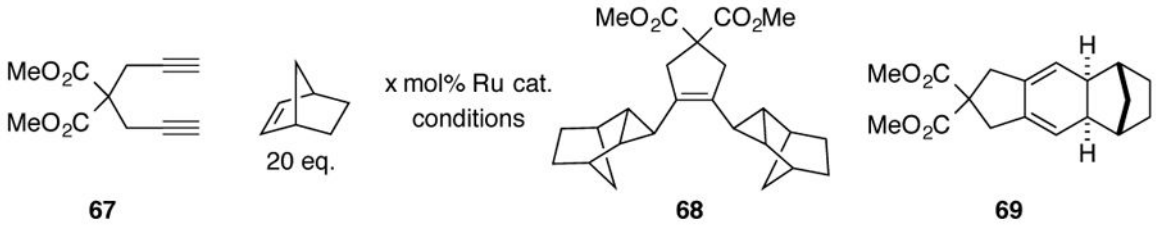
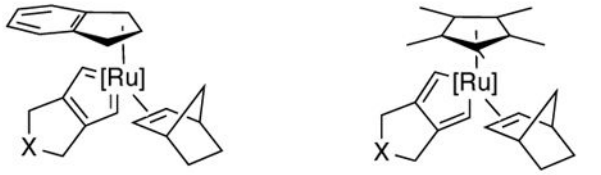


67 68 69

entry	catalyst	mol%	conditions	time (h)	yield **68** (%)	yield **69** (%)
1	(Ind)Ru(COD)Cl **70**	5	DCE, 40 °C	24	77	12
2	CpRu(COD)Cl **71**	10	DCM, reflux	7	45	20
3	Cp*Ru(COD)Cl **72**	10	DCM, reflux	17	15	47

COD= 1,5-cyclooctadiene



73 (η^3-indenyl) **74** (η^5-cyclopentadienyl)

cyclo-propanation olefin insertion

68 **69**

Scheme 25.
Ruthenium-catalyzed reactions of 1,6-heptadiynes with norbornene

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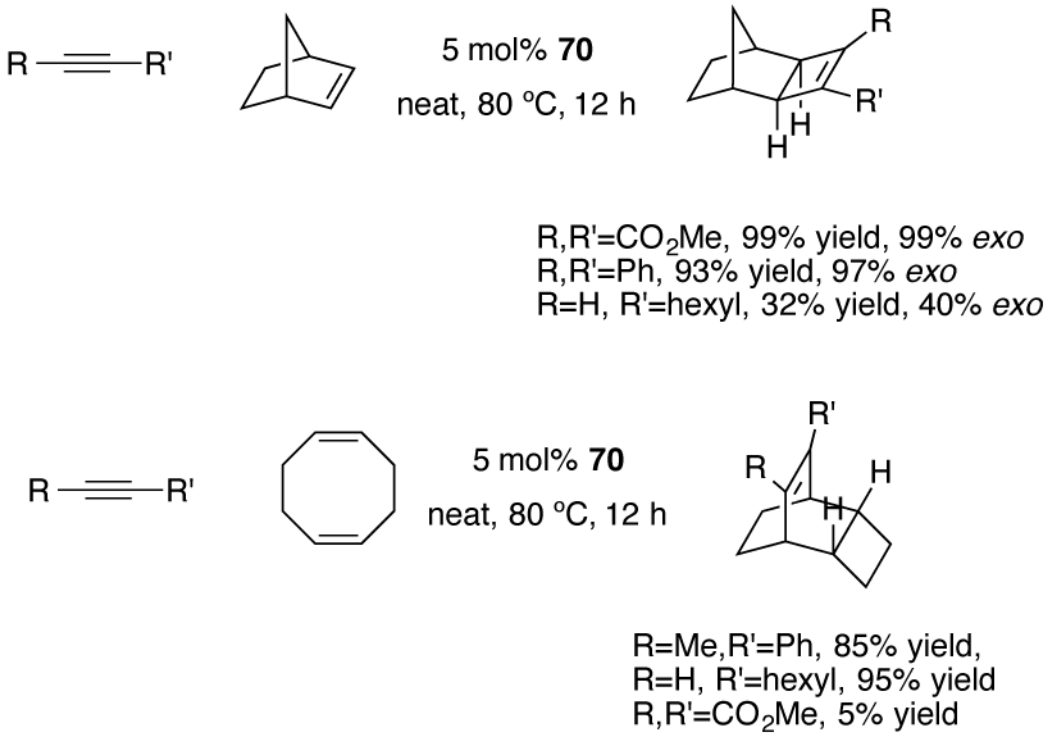

Scheme 26.
Indenylruthenium-catalyzed [2+2] and [4+2] reactions

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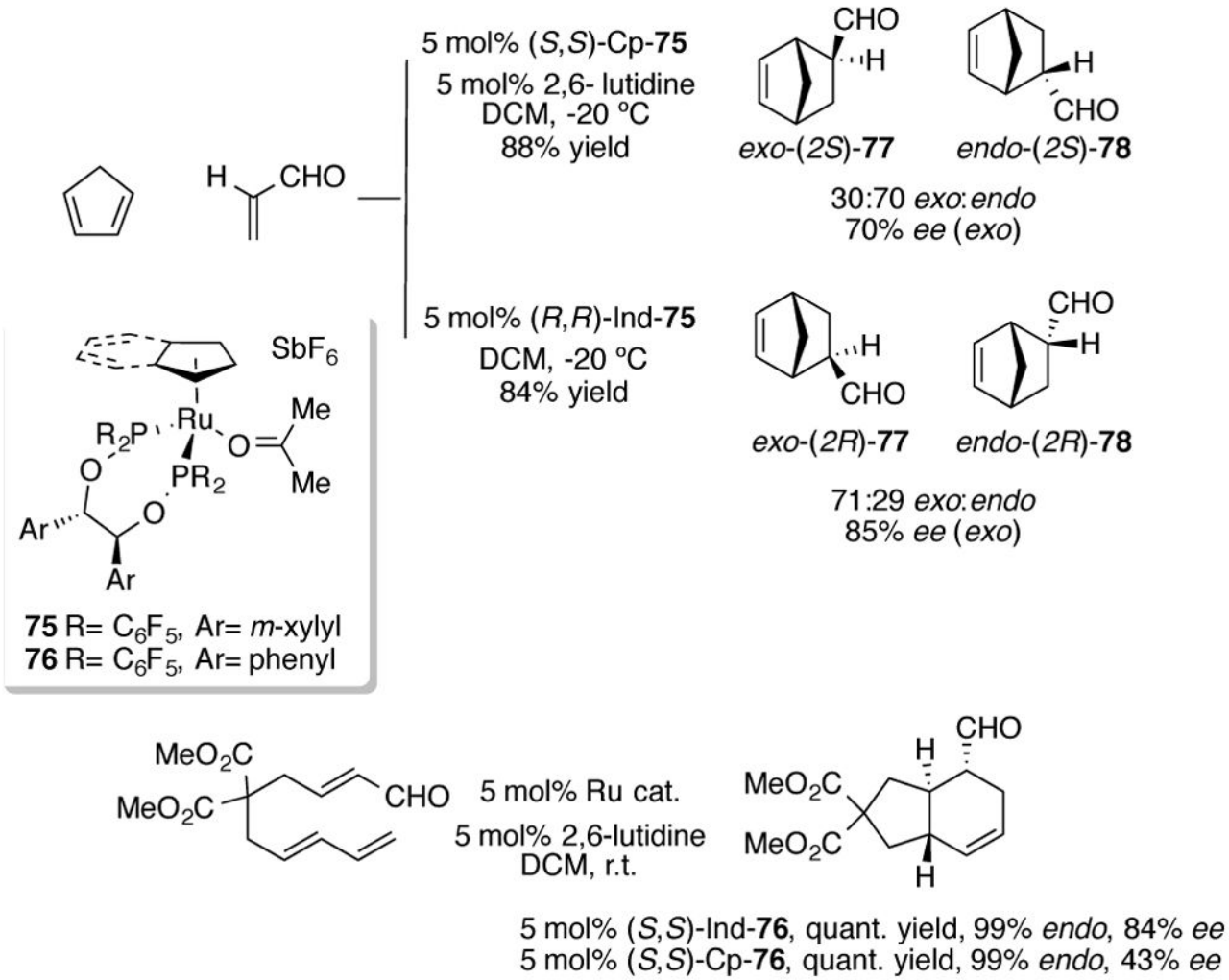
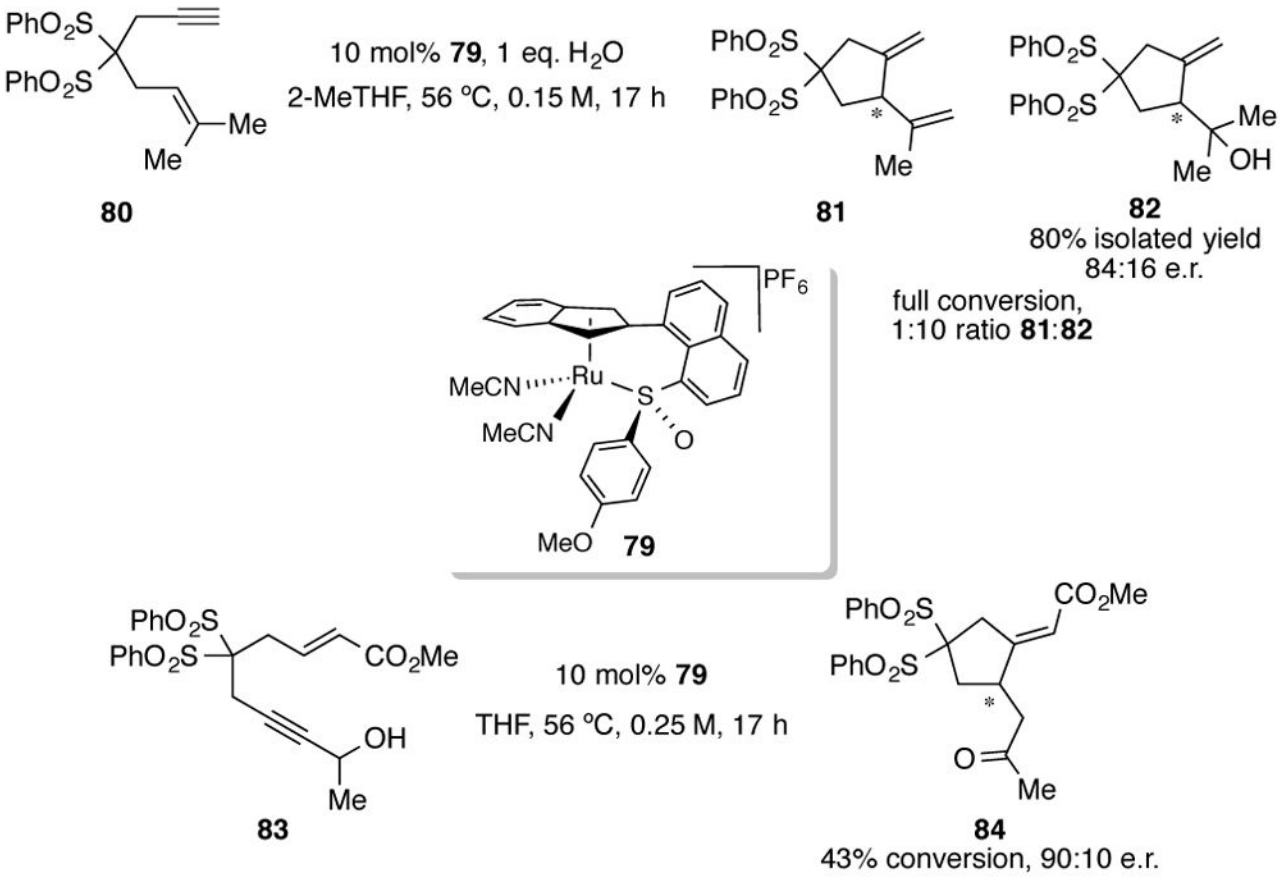


Scheme 27.

Ruthenium-catalyzed asymmetric Diels-Alder reaction between cyclopentadiene and acrolein



Scheme 28.

Indenylruthenium complex **79** with a tethered chiral sulfoxide developed by Trost

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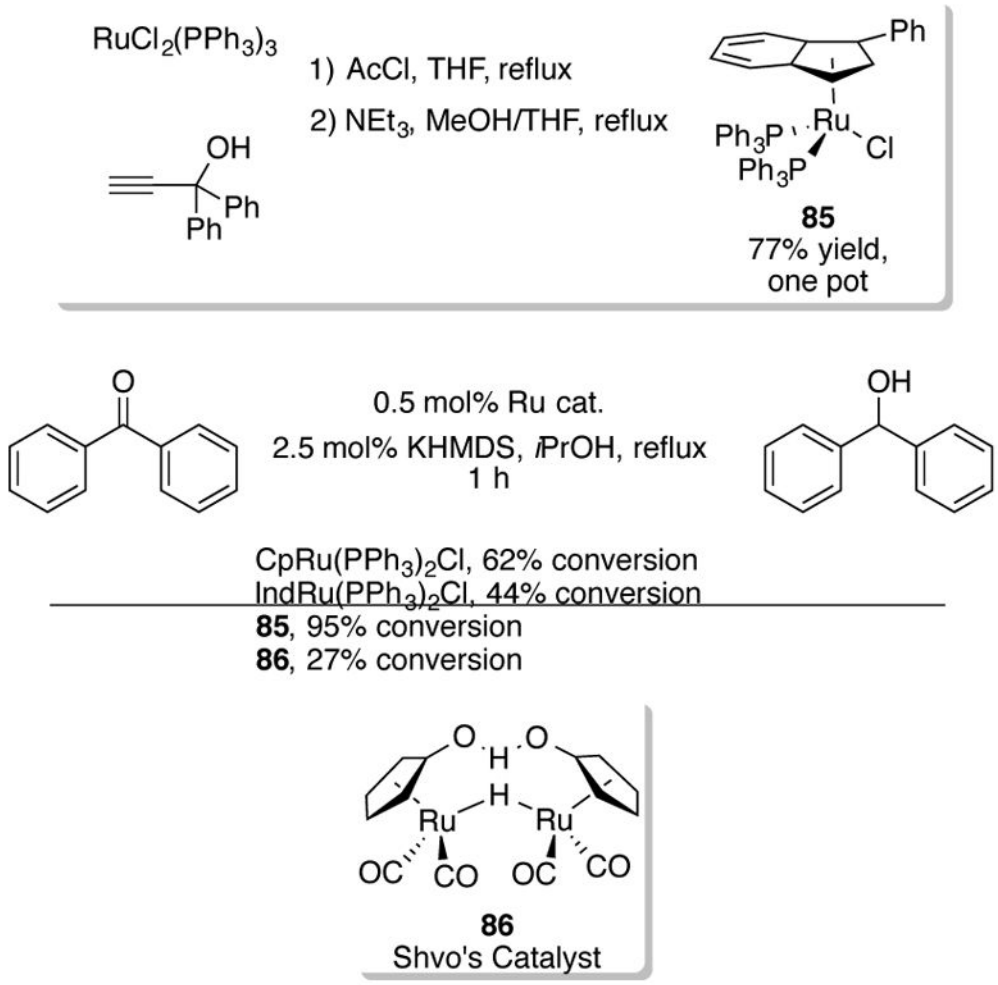

Scheme 29.

Synthesis of **85** and comparison of its activity toward transfer hydrogenation

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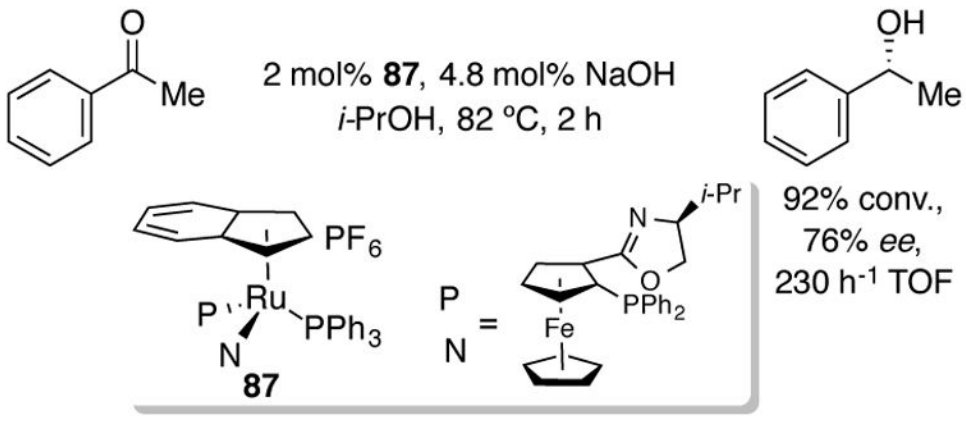
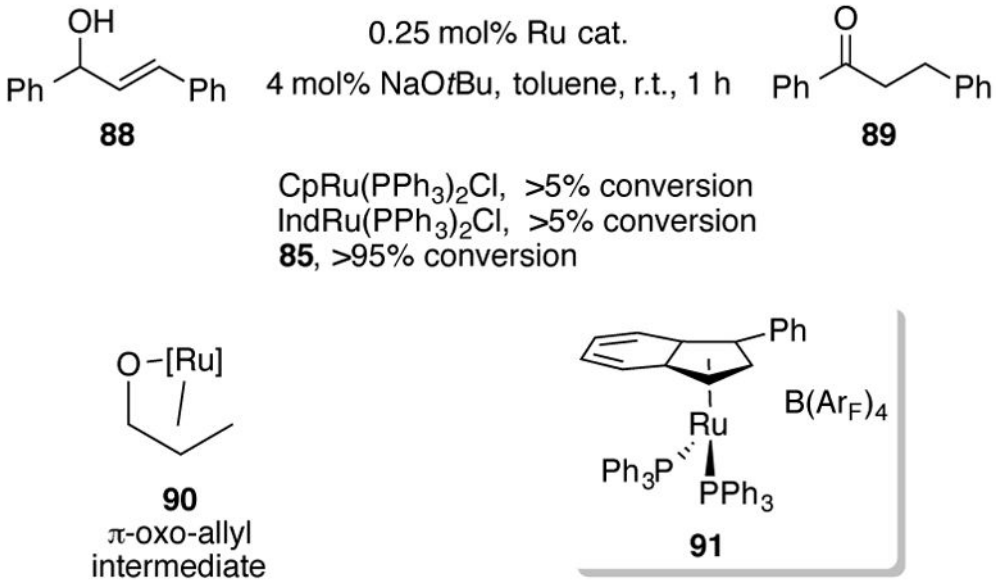


Scheme 30.
Asymmetric transfer hydrogenation with indenylruthenium PHOX complex



Scheme 31.
Redox isomerization of allyl alcohols at room temperature with **85**

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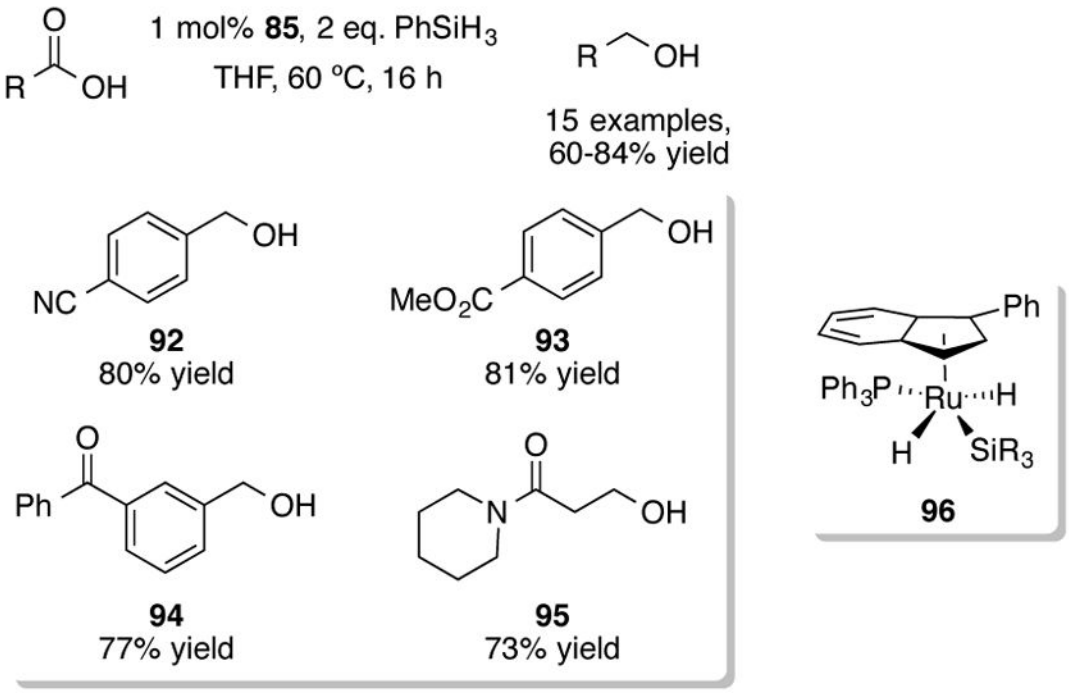

Scheme 32.
Chemoselective silane reduction of carboxylic acids with **85**

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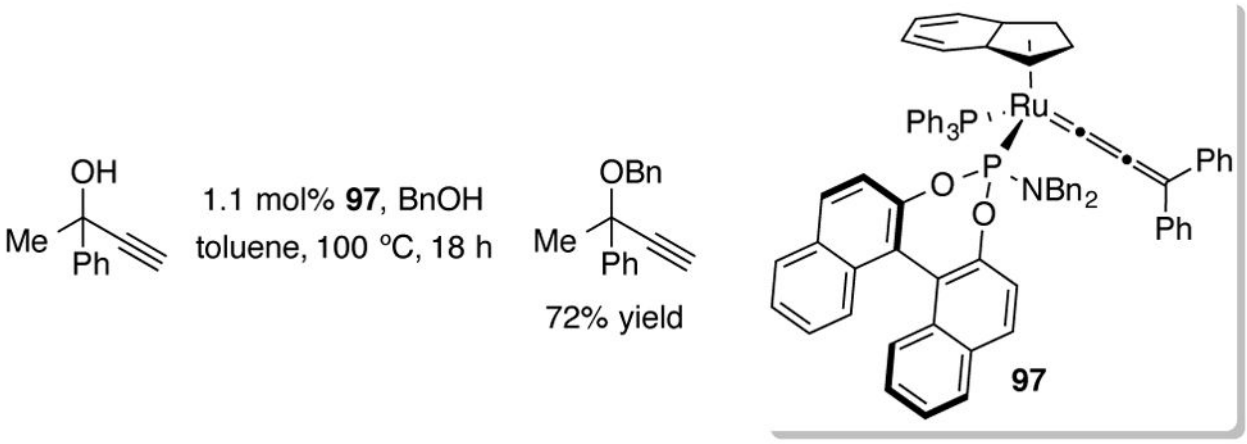

Scheme 33.
Propargyl alcohol substitution with allenylidene complex **97**

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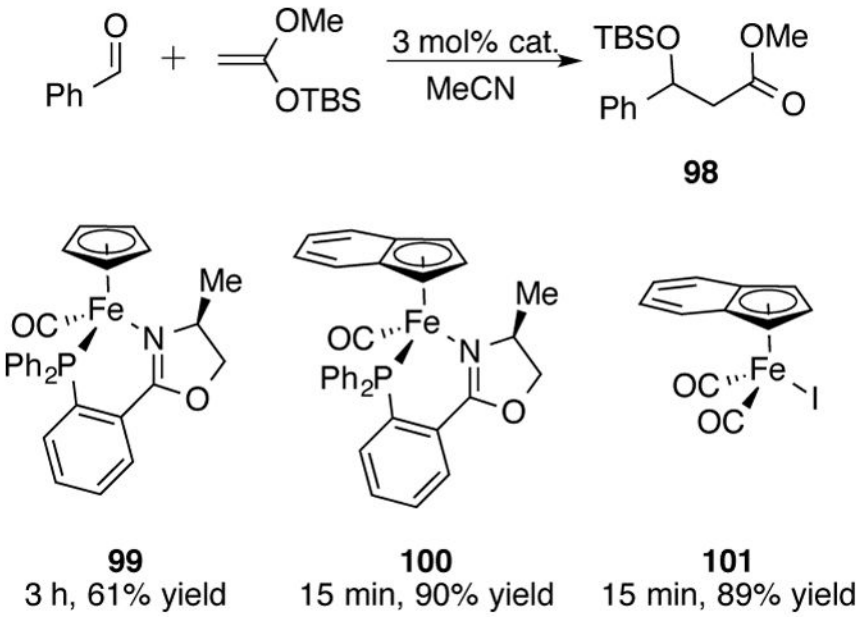

Scheme 34.
Iron-catalyzed Mukaiyama aldol reaction of benzaldehyde

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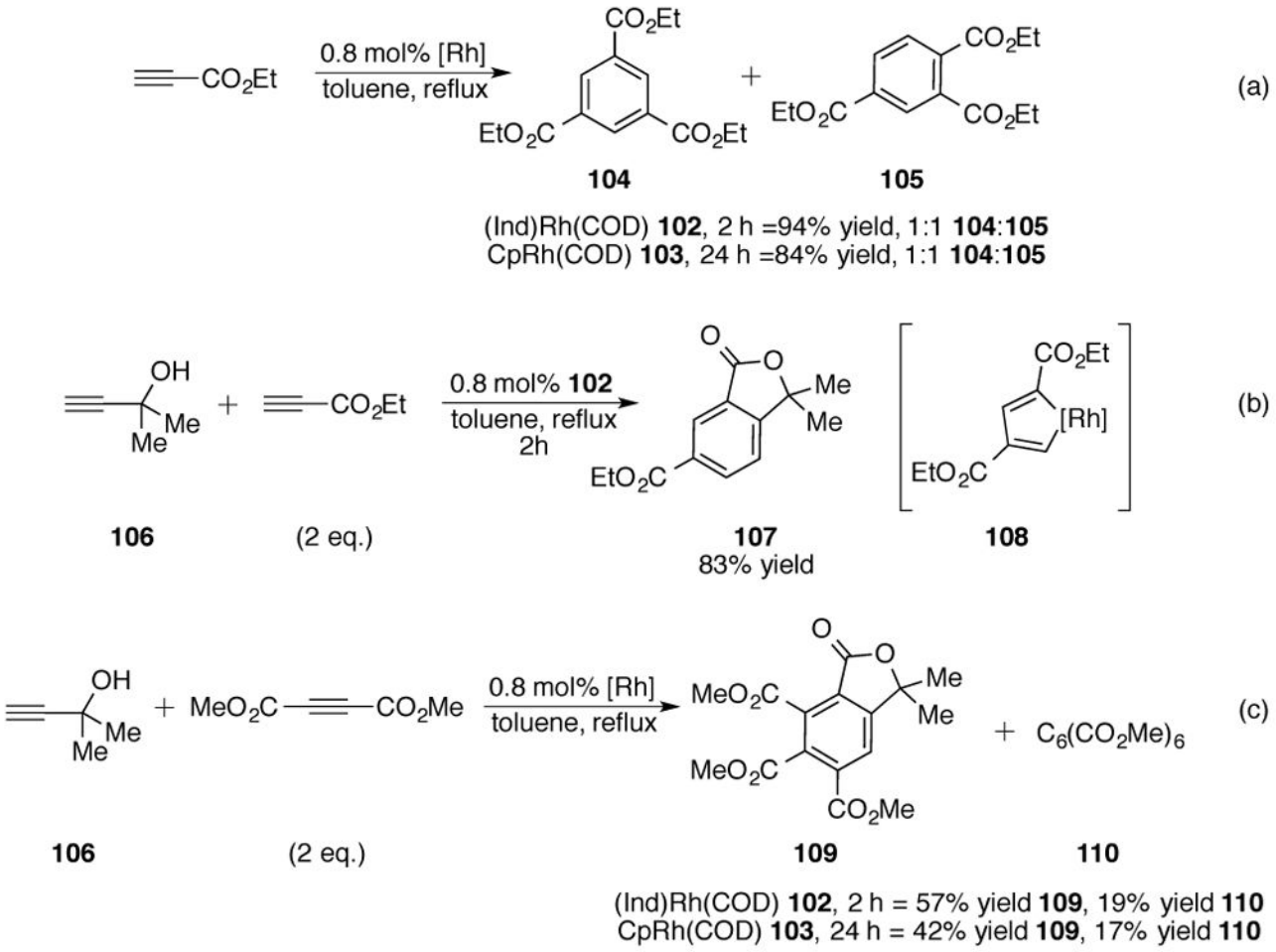
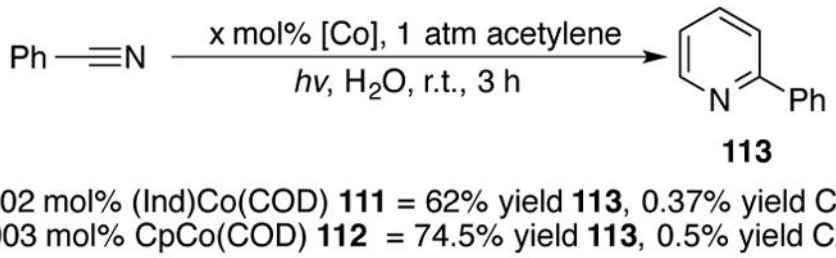


Scheme 35.

(a) Cyclotrimerization of ethyl propiolate (b) and (c) Cyclotrimerization with mixtures of unsymmetrical alkynes



0.002 mol% (Ind)Co(COD) **111** = 62% yield **113**, 0.37% yield C_6H_6
0.003 mol% CpCo(COD) **112** = 74.5% yield **113**, 0.5% yield C_6H_6

Scheme 36.
[2+2+2] cycloaddition under cobalt catalysis to make 2-substituted pyridines

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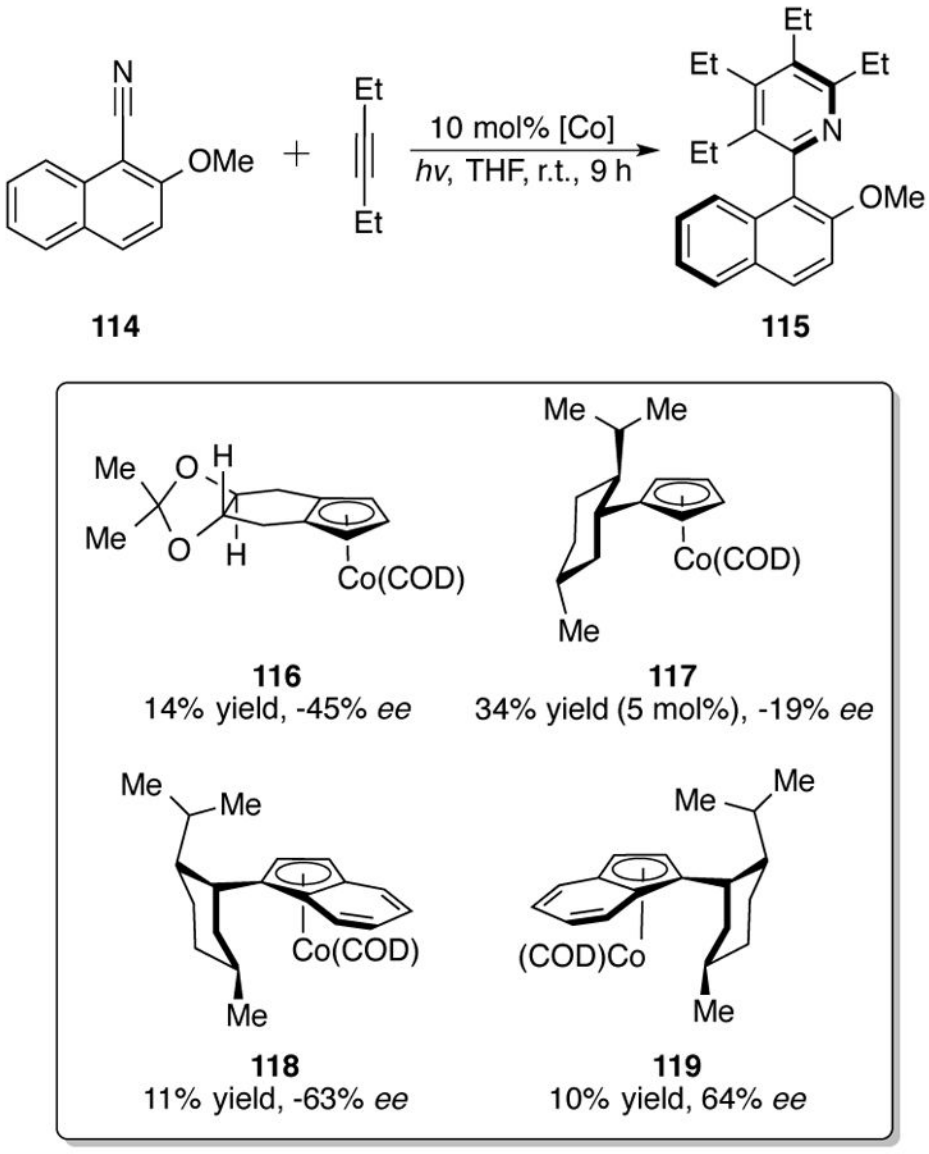

Scheme 37.
Intermolecular atroposelective syntheisis of pyridines with chiral cobalt catalysts

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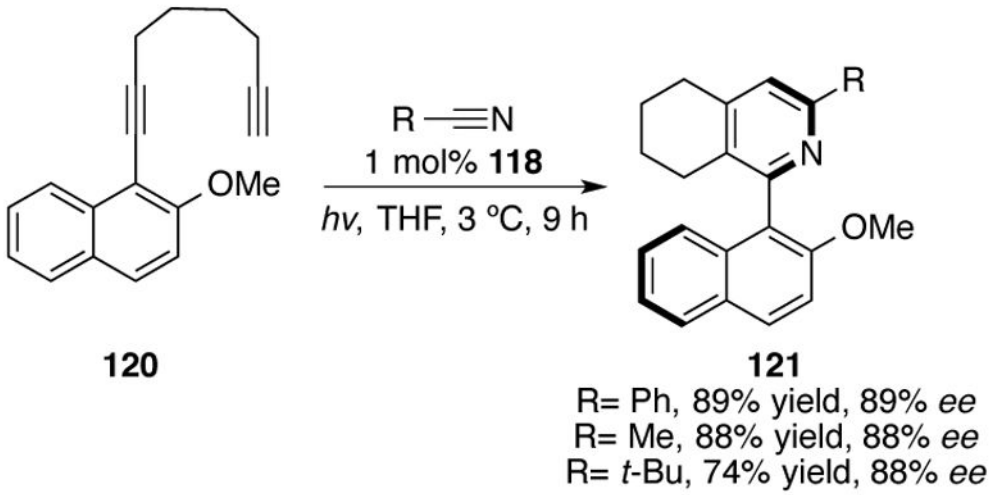

Scheme 38.

Intramolecular atroposelective syntheisis of pyridines with chiral cobalt catalysts

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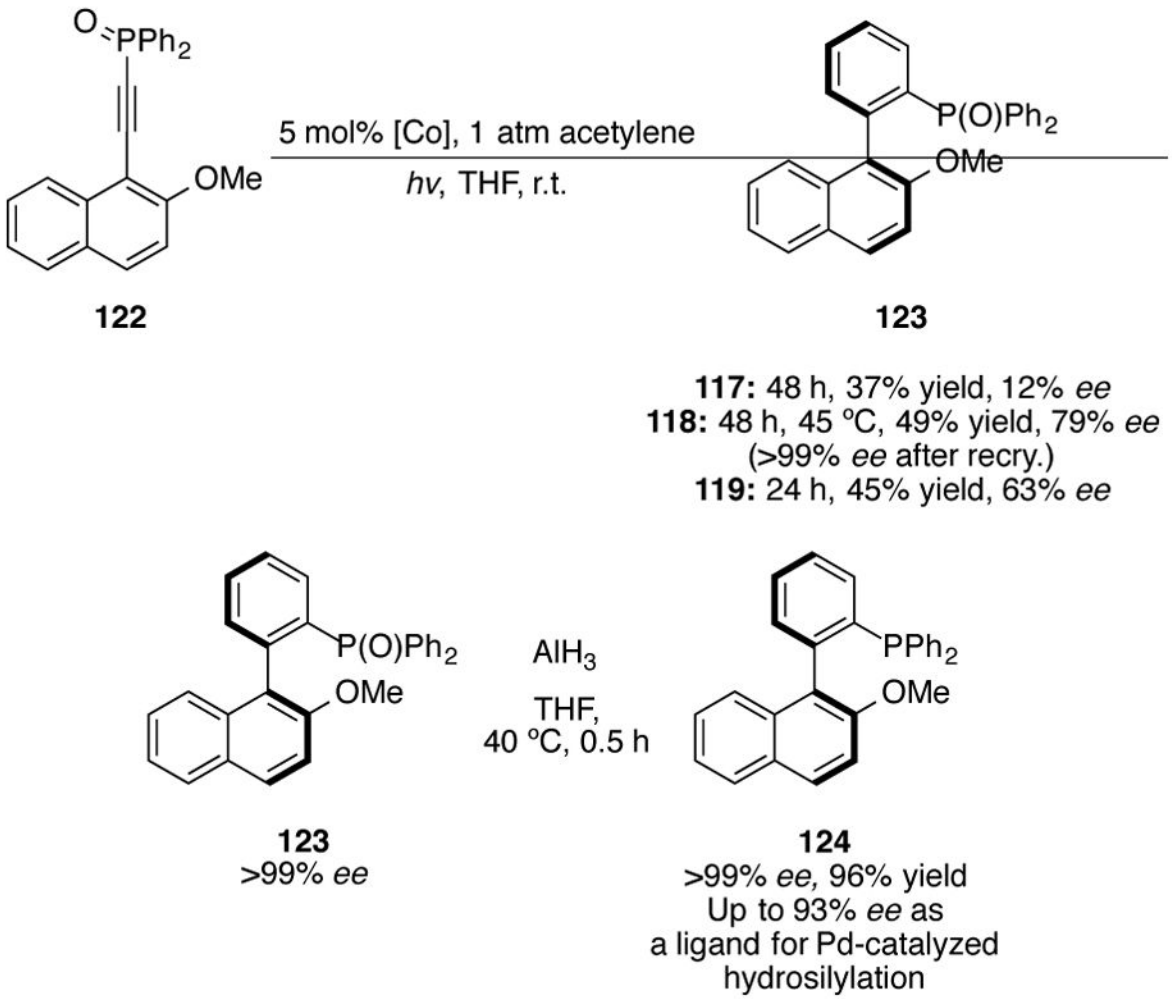

Scheme 39.
[2+2+2] cycloaddition of alkynylphosphine oxide **122**

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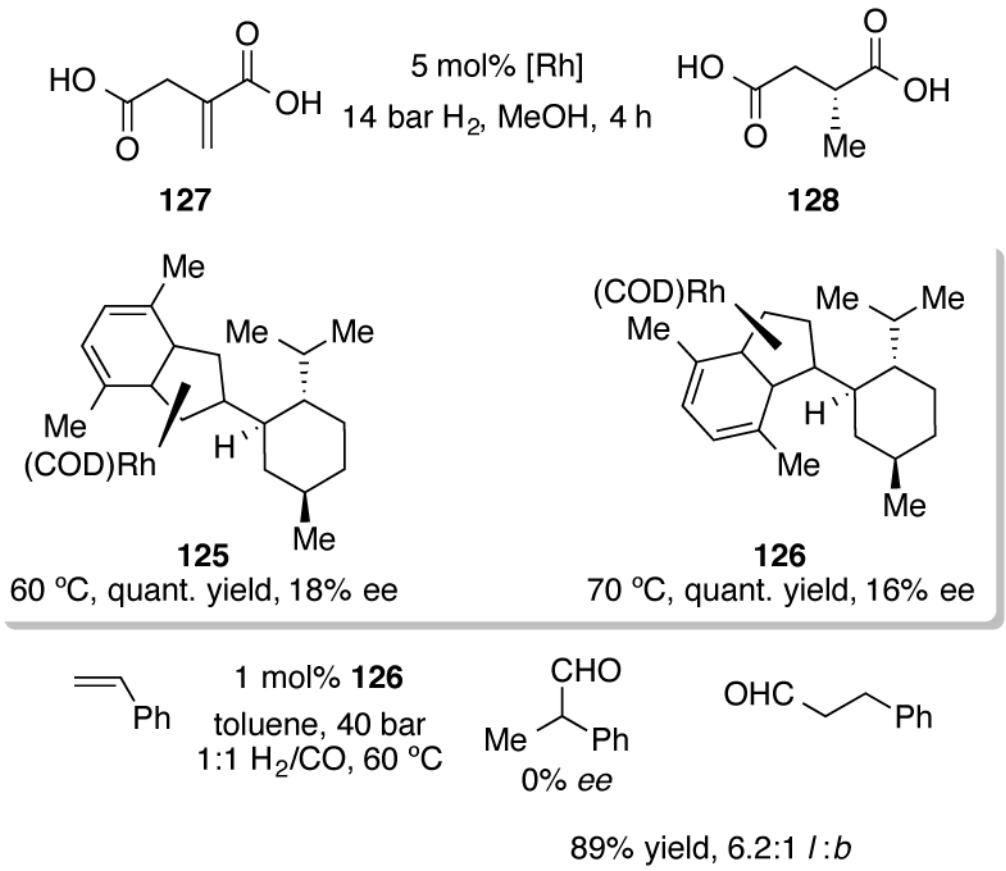
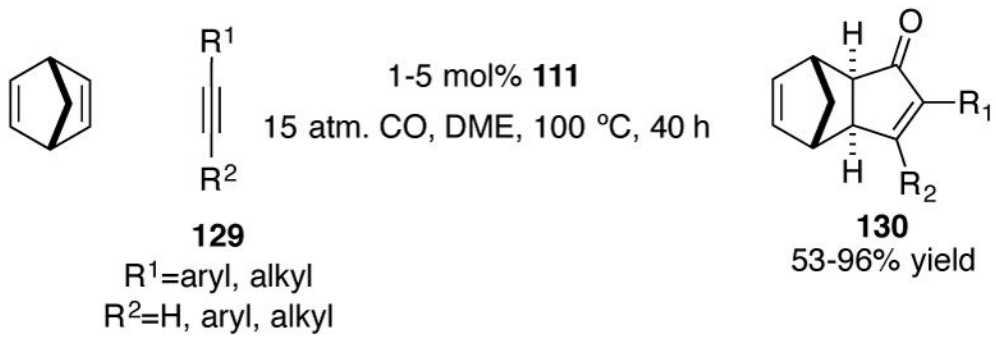


Scheme 40.

Asymmetric hydrogenation of itaconic acid **127** with chiral indenylrhodium complexes **125** and **126**



Scheme 41.
Co-catalyzed intermolecular Pauson-Khand reactions

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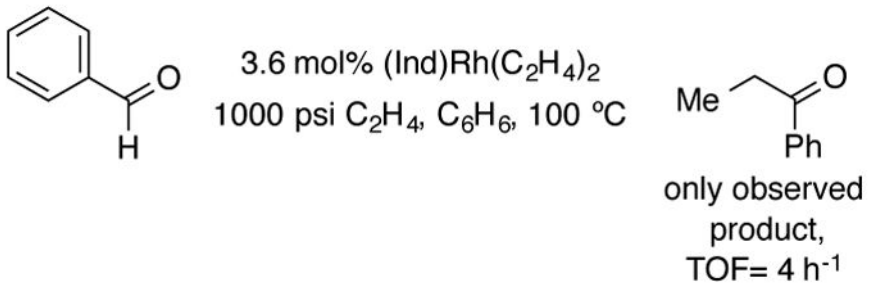

Scheme 42.
Hydroacylation of ethylene with (Ind)Rh(C_2H_4)$_2$

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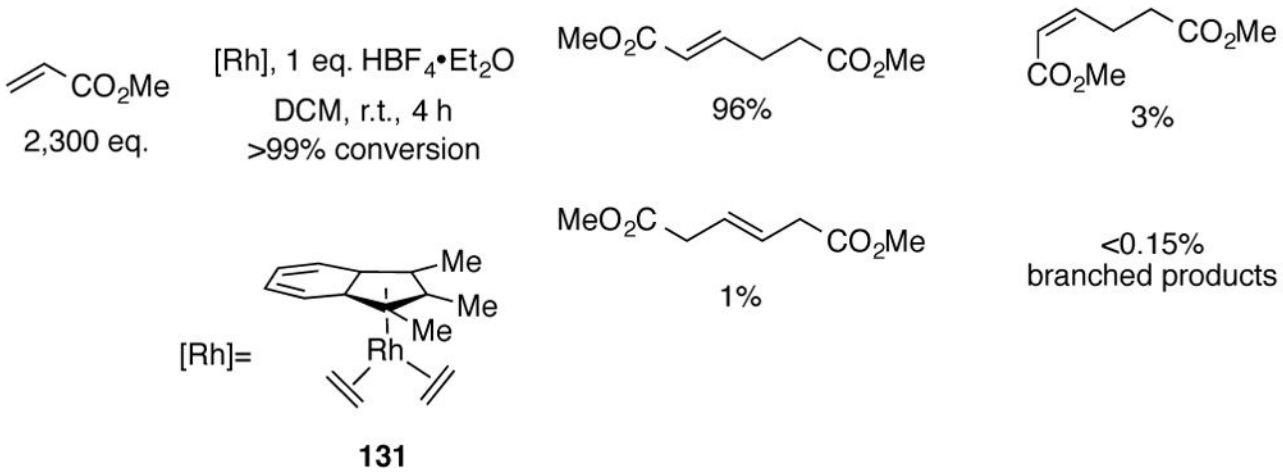

Scheme 43.
Rh-catalyzed tail-to-tail dimerization of methyl acrylate

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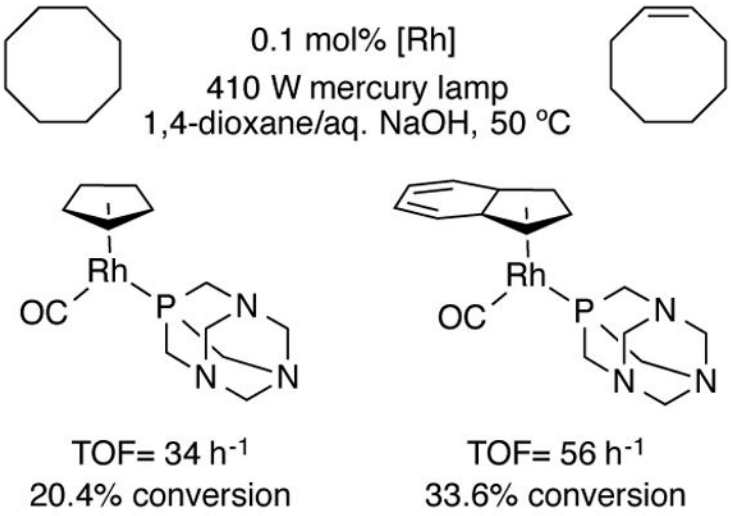
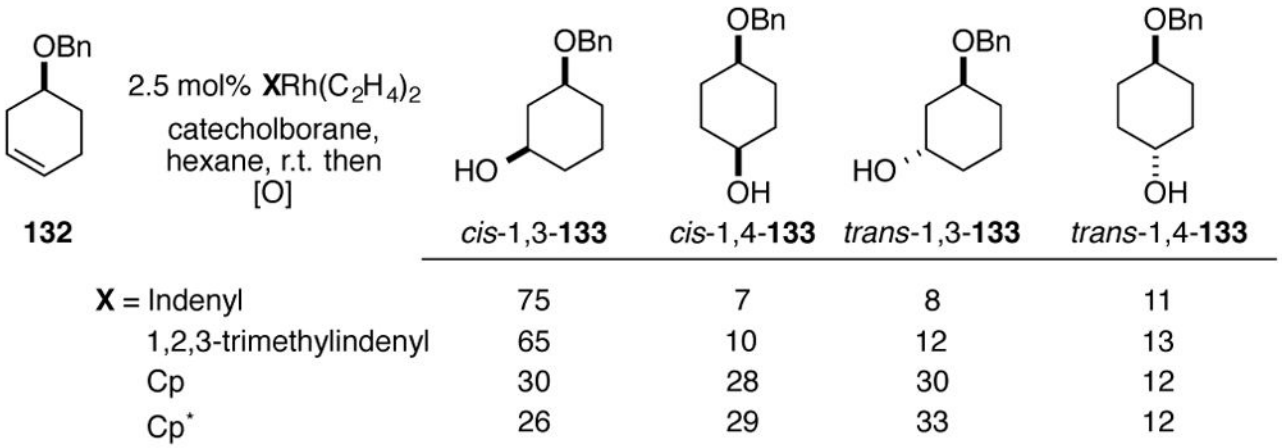


Scheme 44.
Acceptorless dehydrogenation of cyclooctane



X =	cis-1,3-133	cis-1,4-133	trans-1,3-133	trans-1,4-133
Indenyl	75	7	8	11
1,2,3-trimethylindenyl	65	10	12	13
Cp	30	28	30	12
Cp*	26	29	33	12

Scheme 45.
Rh^{I}-directed hydroboration of **132**

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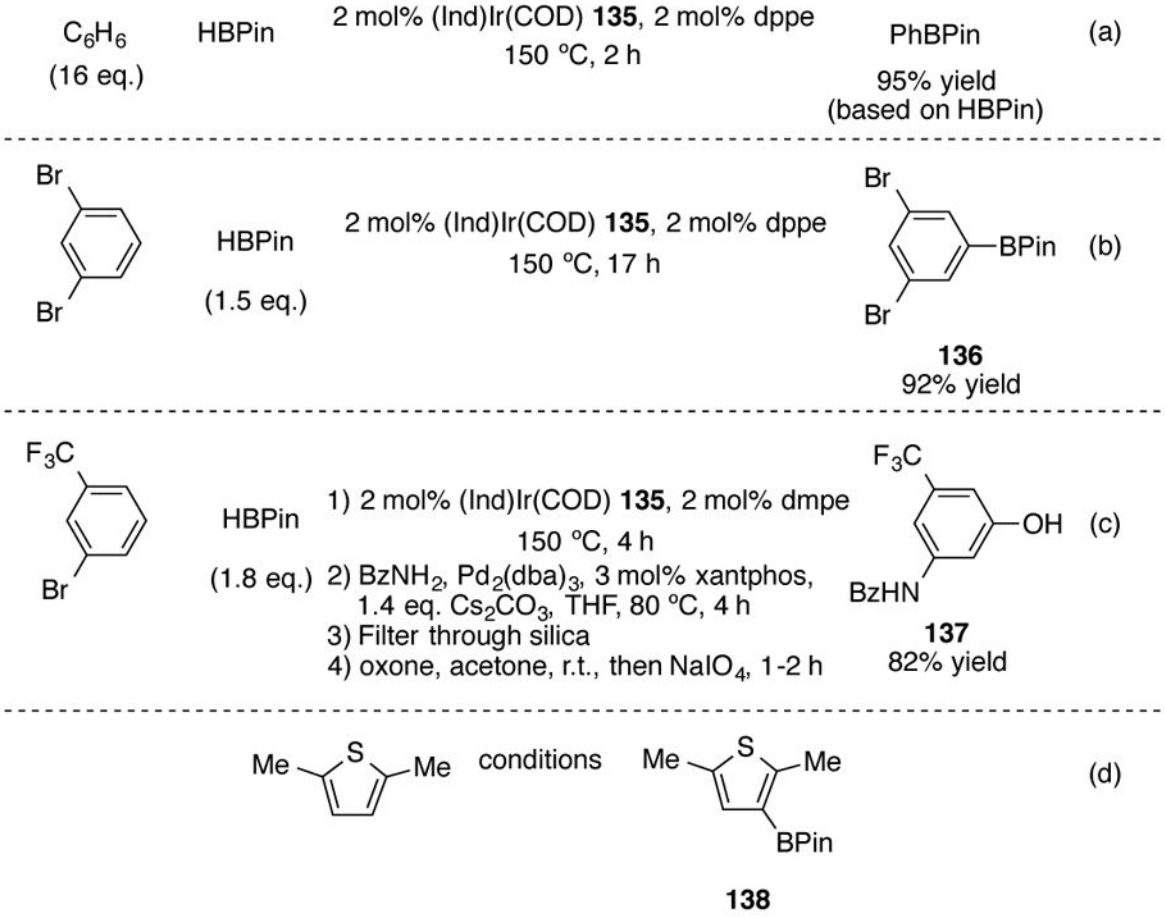
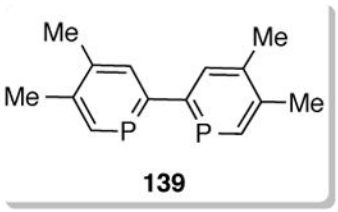


Scheme 46.

(Ind)Ir(COD)-catalyzed *meta* selective arene C-H borylation

3 mol% $[Ir(COD)(OMe)]_2$, 6 mol% dtbpy, 1.5 eq. HBPin, hexanes, r.t., 20 h, **no reaction**

2 mol% **135**, 2 mol% dmpe, 1.5 eq. HBPin, 150 °C, 16 h, **97% yield**



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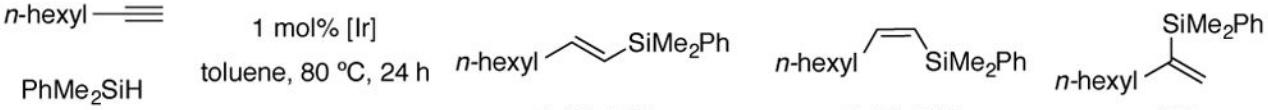

	β-(*E*)-**140**	β-(*Z*)-**140**	α–**140**
(Ind)Ir(COD) **135**, 34% yield	21	67	12
(Ind)Ir(COD) **135**, 2 mol% **139**, 96% yield	94	4	2
$[Ir(COD)_2][BF_4]$, DCM, 40 °C, 94% yield	1	98	1

Scheme 47.
Hydrosilylation of terminal alkynes with (Ind)Ir(COD) **135**

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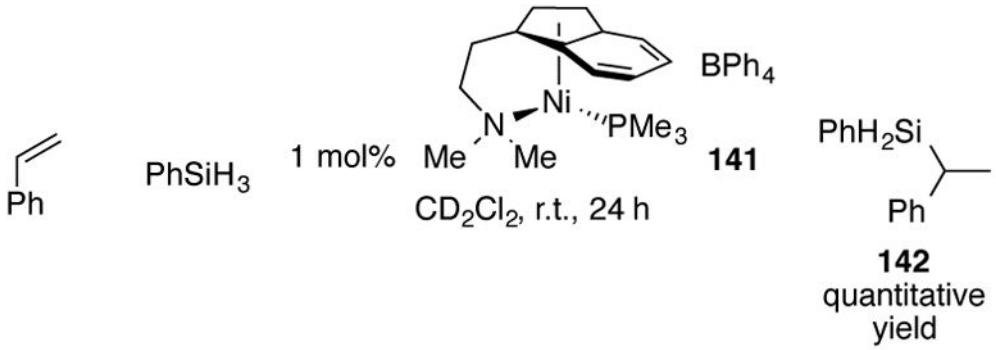
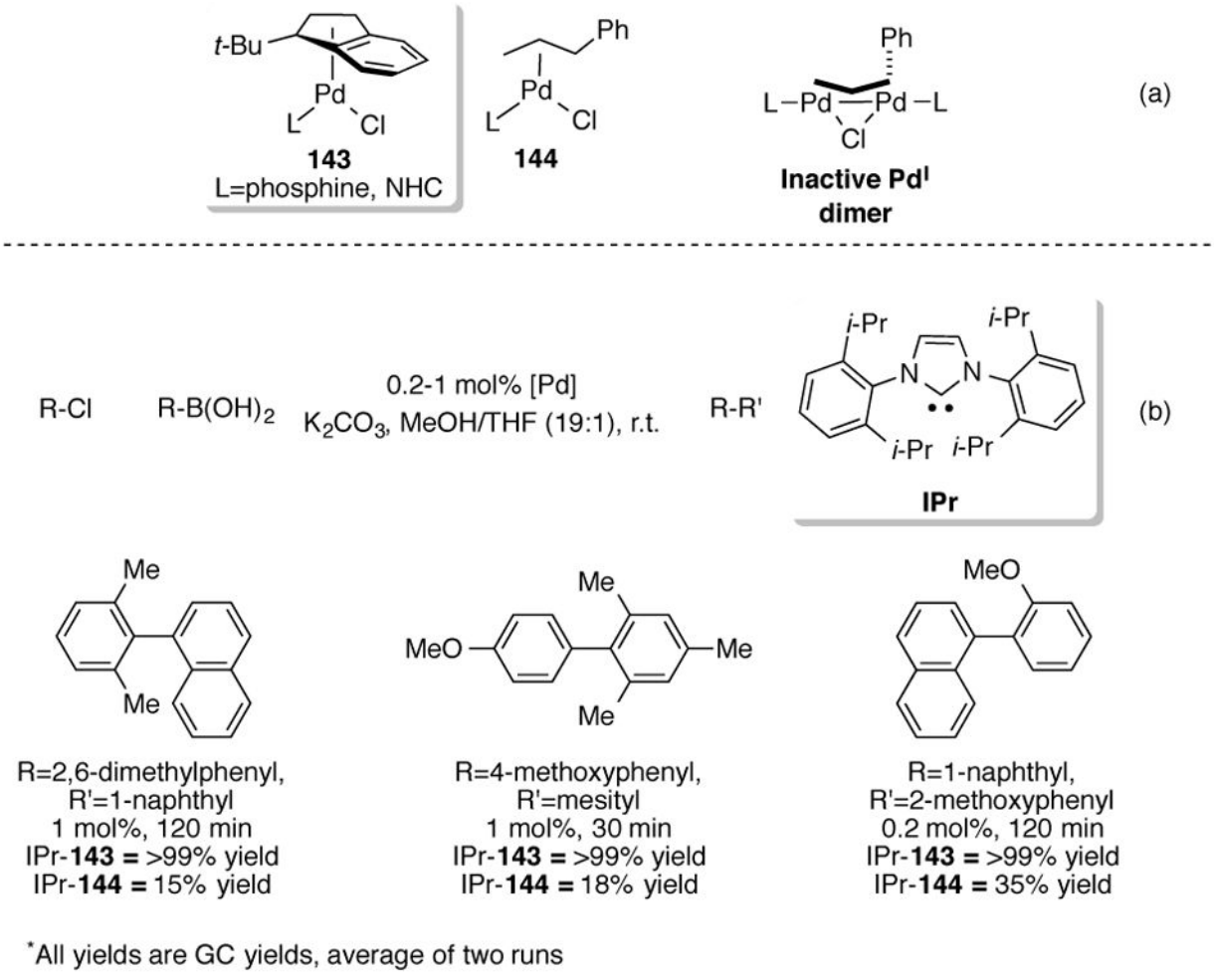


Scheme 48.
Hydrosilylation of styrene with indenylnickel complex **141**



Scheme 49.

(a) Generation of inactive Pd^{I} dimers during catalysis (b) comparison of **143** and **144** for Suzuki cross-couplings

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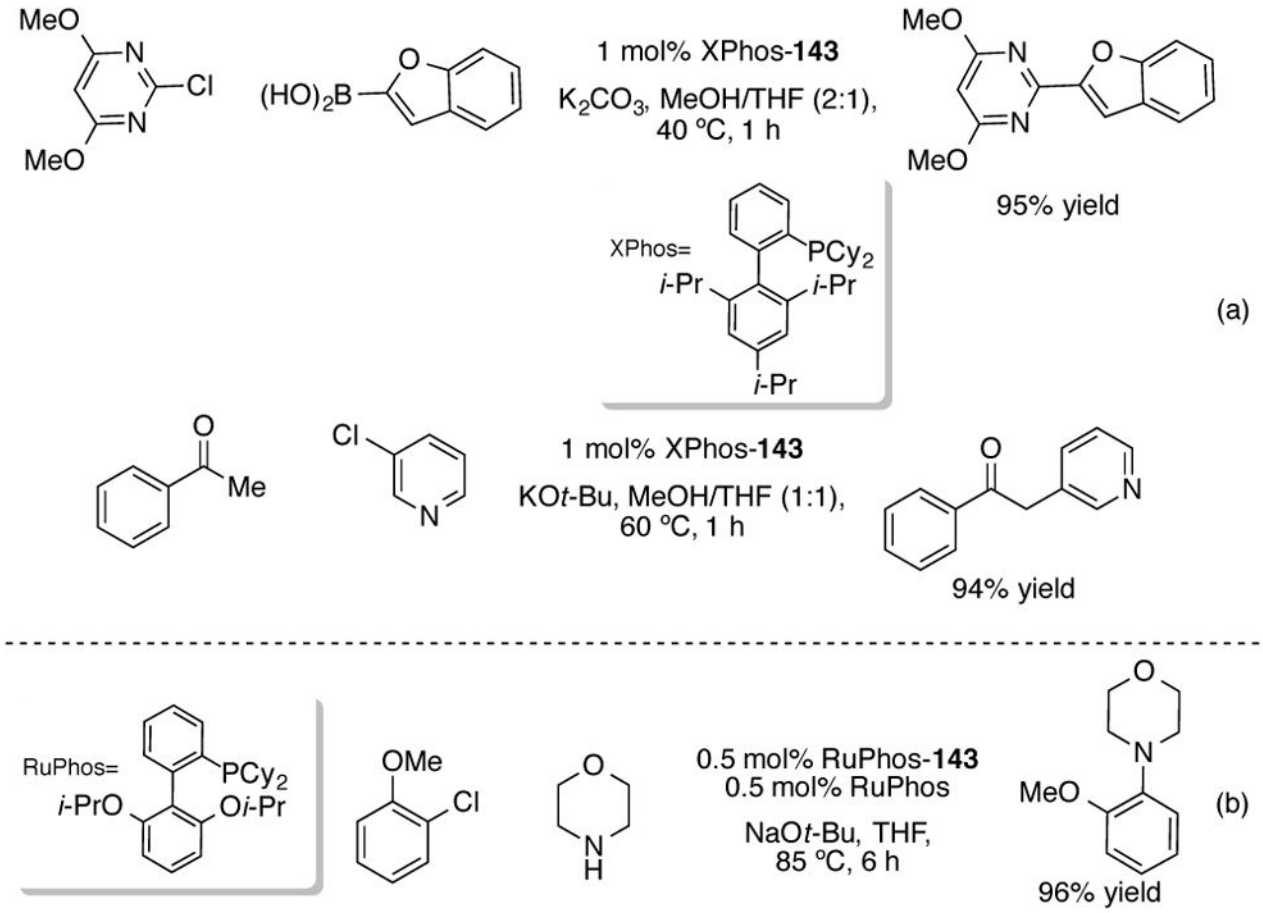

Scheme 50.

(a) Suzuki coupling of and α-arylation of ketones with XPhos-**143** (b) Buchwald-Hartwig amination with RuPhos-**143**