Chiral Switchable Catalysts for Dynamic Control of Enantioselectivity

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Chiral Switchable Catalysts for Dynamic Control of Enantioselectivity

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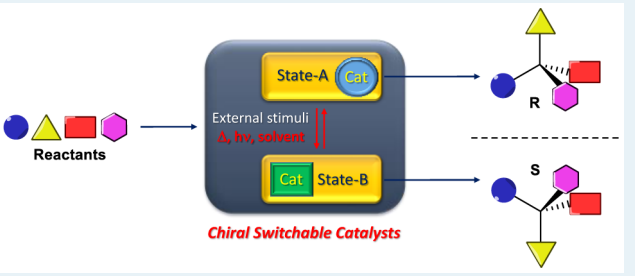
ABSTRACT: Among the artificial switchable catalysts, those catalysts whose activity can be switched by an external stimulus, only a few cases offer the possibility to develop an effective chiral switchable system that could selectively accelerate the formation of a given enantiomer in one state, whereas in the other state it prefers accelerating the formation of the opposite enantiomer. Many pharmacological investigations need both enantiomers to study potentially different activities and side effects. Thus, chiral switchable catalysts could be a very important tool to achieve this goal because their use will eliminate the need to have the two enantiomers of a designed catalyst. This perspective summarizes, discusses, and emphasizes important developments in the chiral switchable catalyst area for the dynamic control of enantioselectivity, highlighting their advantages and showing some perspectives of this field that is still in its infancy.



KEYWORDS: *chiral catalyst, switchable catalyst, enantioselectivity, dynamic control, enantiocontrol*

1. INTRODUCTION

Nowadays, one demanding task in chemistry is the design and synthesis of artificial catalysts that can compete with the catalytic proficiency of enzymes. Within this framework, in the past decade, the studies on synthesis and activity of artificial switchable metal catalysts and organocatalysts have become an intense, fervid, and challenging field of research. The peculiarity of these catalysts is that they can be generally triggered in the "on" or "off" states by several external stimuli such as light, heat, solvents, pH change, coordination events or ion influxes, redox processes, mechanical forces, or other changes in reaction conditions.[1]

However, among artificial switchable catalysts, only a few cases offer the possibility to develop an effective *chiral* switchable system that could selectively accelerate the formation of a given enantiomer in one state, whereas in the other state it accelerates the formation of the opposite enantiomer. In fact, achieving dual stereocontrol in asymmetric reactions[2] using a chiral switchable catalyst could be a very important goal in enantioselective synthesis, since it will eliminate the need to have available the two enantiomers of the designed catalyst. Such a case would practically avoid all the necessary steps for the preparation of opposite configured catalysts, thus improving the chemical sustainability of the whole catalytic process under study.

An exhaustive review by Hayashi et al. addressed the topic of enantiocontrol by changing factors other than stimuli-responding structural change of catalysts such as catalyst substituents or substrate substituents or central metal or solvents or additives or other factors.[2c]

In this Perspective, we will focus on the work on asymmetric synthesis achieved by means of the dynamic control of enantioselectivity through a chiral switchable catalyst. It is noteworthy that the time-span in which results of this work have been disclosed in the scientific literature is solely six years. The discussion on catalysts has been divided into three major classes: light- and/or heat-, redox-, and solvent-driven chiral switchable catalysts.

2. LIGHT- AND/OR HEAT-DRIVEN CHIRAL SWITCHABLE CATALYSTS

In 2011, a seminal and paradigmatic work on dynamic chiral switchable catalysts was described by Wang and 2016 Nobel Laureate Feringa.[3] On the basis of their previous experience in the synthesis of chiral crowded alkenes,[4] they designed and used the molecular motor **1** as a chiral switchable organocatalyst (Scheme 1) in the sulfa-Michael addition to α,β-unsaturated ketones, efficiently modulating both its enantioinduction and activity (Scheme 2).

The catalyst **1** is decorated with Brønsted acidic thiourea and Brønsted basic DMAP groups, which are known to cooperate in the catalysis of the sulfa-Michael addition.[5] The chiral crowded alkene moiety in **1** can move through a unidirectional rotatory cycle with a series of two photoisomerizations and two thermal isomerizations (Scheme 1). Thus, the rotation of the molecular motor can control the relative orientations of the two catalytic moieties. In particular, starting from (*R*,*R*)-(*P*,*P*)-*E*-**1** and irradiating at 312 nm at 20 °C, an *E*−*Z* photoisomerization and a helix inversion[6] from *P* to *M* take place to give (*R*,*R*)-(*M*,*M*)-*Z*-**1**, in which the two catalytic units are brought into close proximity. A thermal helix inversion at 70 °C gives the (*R*,*R*)-(*P*,*P*)-*Z*-**1** isomer, in which the two catalytic groups are still

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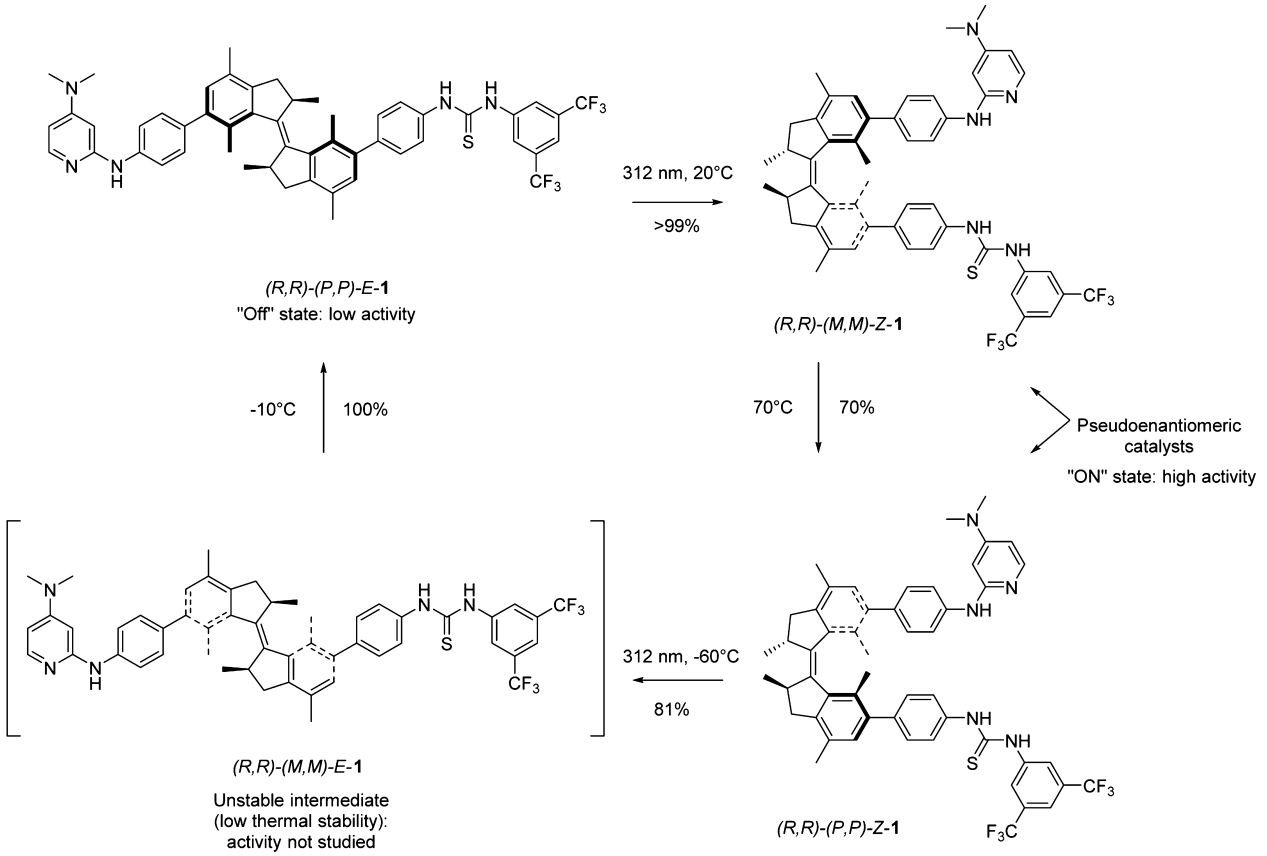
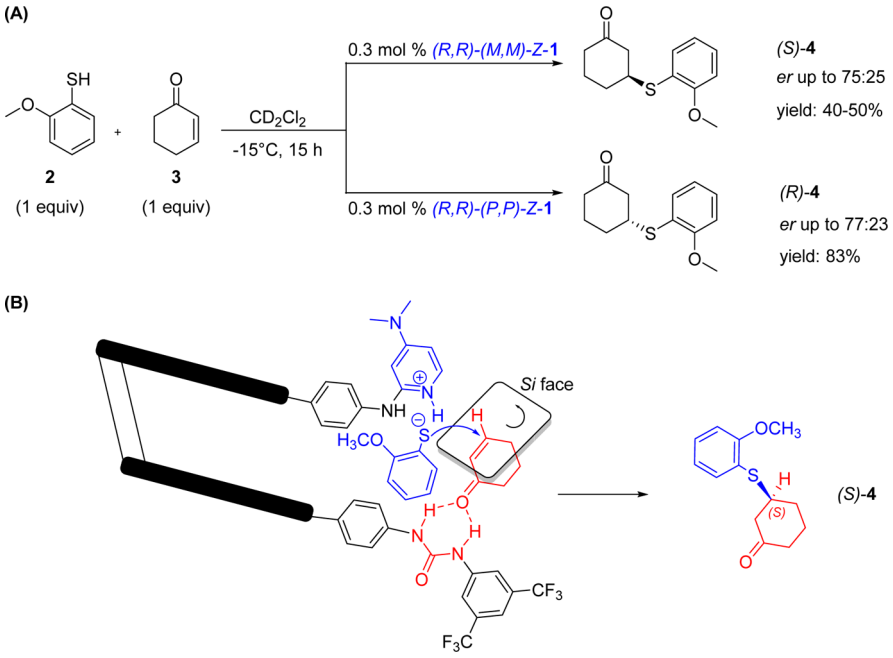
Scheme 1. Light- and Heat-Driven Chiral Switchable Catalyst 1



Scheme 2. (A) Control of the Enantioselectivity of a Sulfa-Michael Addition Employing Chiral Switchable Catalyst 1 and (B) Plausible Ternary Complex Involved in the Mechanism of Thiol Addition to Enone Catalyzed by 1



in close proximity. A photochemical step followed by thermal isomerization regenerates the original structure (*R*,*R*)-(*P*,*P*)-*E*-**1** through the intermediate (*R*,*R*)-(*M*,*M*)-*E*-**1**, which was not employed as a catalyst due to its low thermal stability. All steps of this 360° rotation of molecular motor **1** were fully studied and confirmed by a combination of chiral HPLC, circular dichroism (CD), UV−vis, and ^{1}H NMR spectroscopy. When (*R*,*R*)-(*P*,*P*)-*E*-**1** was used to catalyze the sulfa-Michael addition of 2-methoxy thiophenol **2** to cyclohexenone **3**, the adduct **4** was obtained as a racemate in very low yield (7% yield in 15 h) due to the

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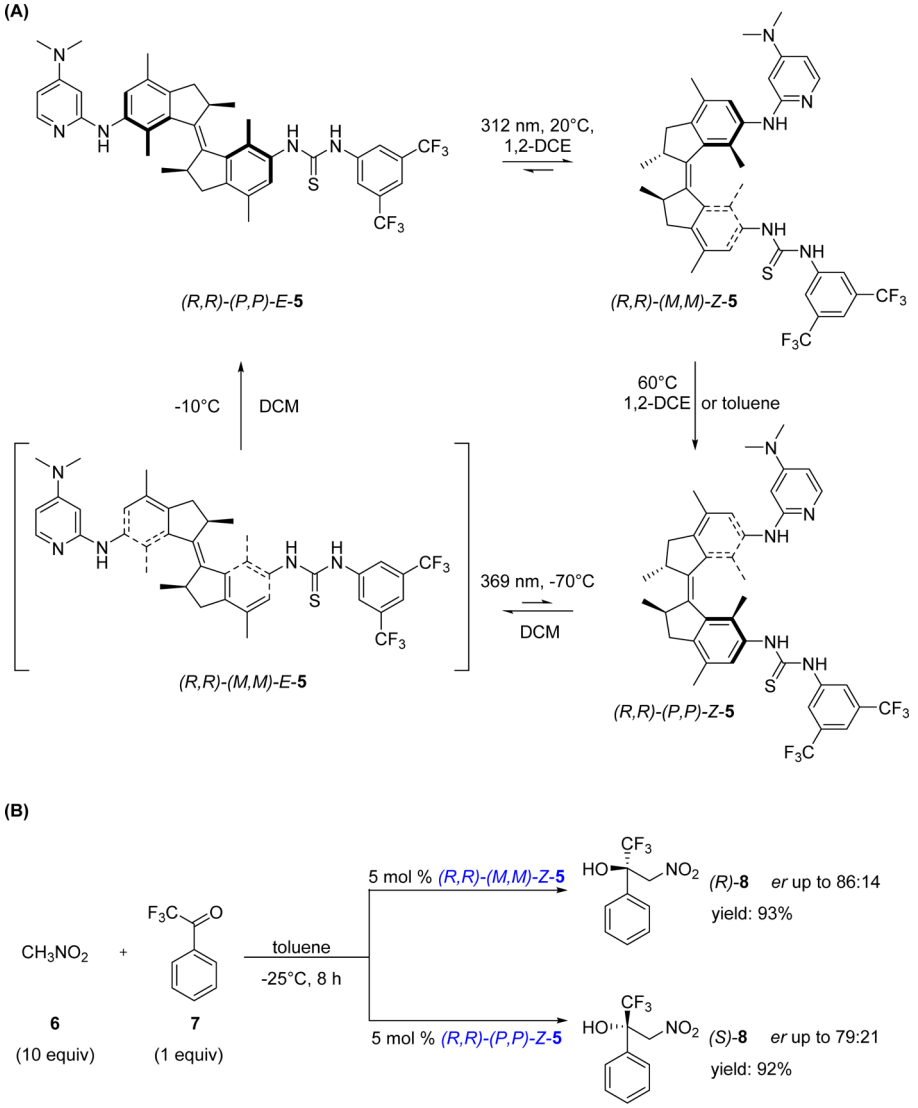
Scheme 3. (A) Light- and Heat-Driven Chiral Switchable Catalyst 5and (B) Control of the Enantioselectivity of a Henry Reaction Employing Chiral Switchable Catalyst 5



unfavorable orientation of the thiourea and DMAP catalytic moieties. On the other hand, when the catalyst (*R*,*R*)-(*M*,*M*)-*Z*-**1** was employed under the same conditions, a higher catalytic activity was achieved affording, after 15 h, the sulfa-Michael adduct (*S*)-**4** in 50% yield with an enantiomeric ratio (*er*) up to 75:25. By using the *Z* isomer of opposite helicity, (*R*,*R*)-(*P*,*P*)-*Z*-**1**, the sulfa-Michael addition proceeded even faster, giving a higher yield (83% in 15 h) and exhibiting a similar degree of enantioselectivity (*er* up to 77:23) but in favor of opposite enantiomer (*R*)-**4** (Scheme 2A). Taking into account previous mechanistic studies on bifunctional organocatalysts for sulfa-Michael addition[5,7] as well as performing basic molecular modeling studies, the authors proposed that the helicity of the catalyst determined the absolute stereochemistry of the product **4**, depending on the face (*Si* or *Re*) of cyclohexenone **3** on which the attack of 2-methoxy thiophenol (**2**) took place (Scheme 2B).

Following this approach, the same group developed a molecular motor-based dynamic organocatalyst **5** (Scheme 3A) able to accelerate the Henry reaction of nitromethane **6** with α,α,α-trifluoroketones such as trifluoroacetophenone **7**, with high control of the enantioinduction (Scheme 3B).[8] For this second-generation catalyst **5**, the same kind of isomerization steps were necessary to obtain its 360° rotation, but the phenyl spacers between the motor core and catalytic moieties were removed with respect to **1**. In fact, catalyst **1** showed poor catalytic performance in the Henry reactions both in terms of activity and stereoselectivity. Thus, it was decided to bring the catalytically active units (i.e., thiourea and DMAP) in closer proximity in order to achieve a more effective cooperative action between these two functionalities.

As in the case of **1**, the *E*-state of **5** proved to be almost inactive and without stereocontrol as a catalyst for the Henry reaction between nitromethane and α,α,α-trifluoroketones. On the other hand, the two *Z*-states ((*R*,*R*)-(*M*,*M*)-*Z*-**5** and (*R*,*R*)-(*P*,*P*)-*Z*-**5**), in which the catalytic active sites are in closer proximity, were once again effective in catalysis, affording the corresponding products with opposite enantioselectivity (*er* up to 86:14 for (*R*)-**8** and *er* up to 79:21 for (*S*)-**8**) in excellent yields (93% for (*R*)-**8** and 92% for (*S*)-**8**). For catalyst (*R*,*R*)-(*M*,*M*)-*Z*-**5**, the use of toluene as reaction media was mandatory both in catalysis and in its isomerization to (*R*,*R*)-(*P*,*P*)-*Z*-**5**, because only in this solvent

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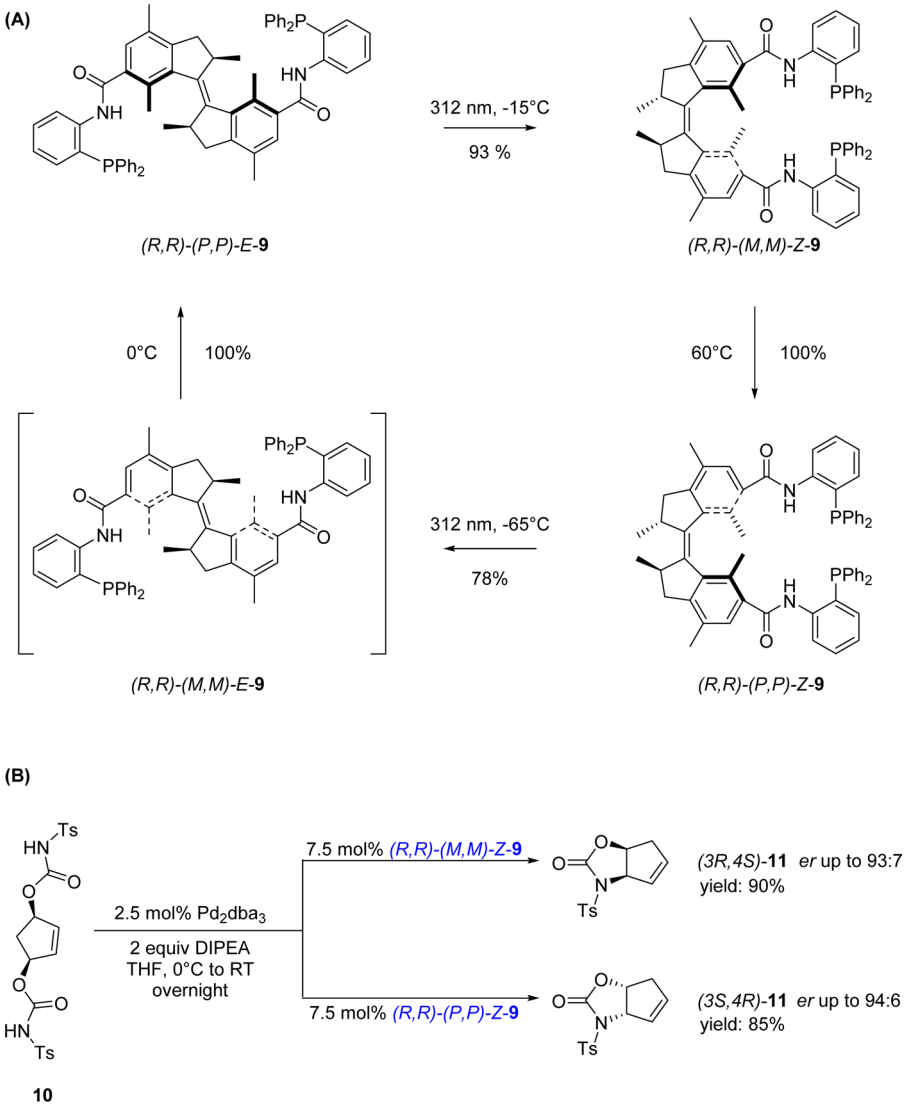
Scheme 4. (A) Light- and Heat-Driven Chiral Switchable Ligand 9 and (B) Control of the Enantioselectivity of a Pd-Catalyzed Desymmetrization Reaction Using Chiral Switchable Ligand 9



was (*R*,*R*)-(*M*,*M*)-*Z*-**5** endowed with a long half-life (156 h at room temperature).

The rotary molecular motor system **9** similar to **1** or **5**, but decorated with diphenylphosphine groups (Scheme 4A), has been successfully employed in asymmetric catalysis.[9]

In fact, light and heat-induced changes in geometry and helicity of **9** furnished a switchable ligand that exhibited excellent selectivity in the Pd-catalyzed desymmetrization reaction of meso-biscarbamate **10** (Scheme 4B). In particular, under optimized conditions, the Pd complex of ligand (*R*,*R*)-(*M*,*M*)-*Z*-**9** catalyzed the desymmetrization reaction of **10** with excellent stereocontrol, affording product (3*R*,4*S*)-**11** (*er* up to 93:7), whereas the Pd-complex of ligand (*R*,*R*)-(*P*,*P*)-*Z*-**9** afforded the opposite enantiomer (3*S*,4*R*)-**11** also with excellent enantioselectivity (*er* up to 94:6). In addition, it should be pointed out that the obtained enantioselectivities using the two *Z*-states of **9** as a ligand were comparable to those reachable with conventional chiral biphosphine ligands, such as the Trost ligand.[10] However, it should be noted that in situ switching experiments were possible only for free ligands because, in the presence of Pd, the formed active palladium complexes were photosensitive and led to a significant decrease in enantioselectivity.

In 2017, Chen et al. reported the synthesis of the chiral light- or heat-switchable helicene **12** that was used as an organocatalyst for accelerating the enantiodivergent Steglich rearrangement of O-carboxylazlactones (Scheme 5).[11]

The effective catalytic moiety in **12** is the 4-aminopyridine unit, but the helical sense (*P* or *M*) of the molecule which could be switched photochemically or thermally was found essential for achieving dual enantiocontrol in this catalysis. Irradiating (*P*)-**12** at 290 nm led to the exclusive formation of (*M*)-**12** [(*P*)-**12**/(*M*)-**12**, <1:>99]. Photoisomerization of almost pure (*M*)-**12** was then performed at 340 nm, which resulted in predominant enrichment of (*P*)-**12** [(*P*)-**12**/(*M*)-**12**, 91:9]. The diastereomerically pure (*P*)-**12** can be regenerated either by unidirectional thermo-rotation of the 91:9 (*P*)-**12**/(*M*)-**12** mixture or by unidirectional thermo-rotation of almost pure (*M*)-**12** in *p*-xylene at 130 °C for 2 h.

Both pseudoenantiomeric helicenes (*P*)-**12** and (*M*)-**12** were investigated in their diastereomerically pure forms as chiral organocatalysts in the Steglich rearrangement of several O-carboxylazlactones. In particular, under a nitrogen atmosphere using as a solvent a 1:1 mixture of 1,2-dimethoxyethane (1,2-DME)/t-amyl alcohol (tAA) at −40 °C, (*P*)-**12** revealed to be a

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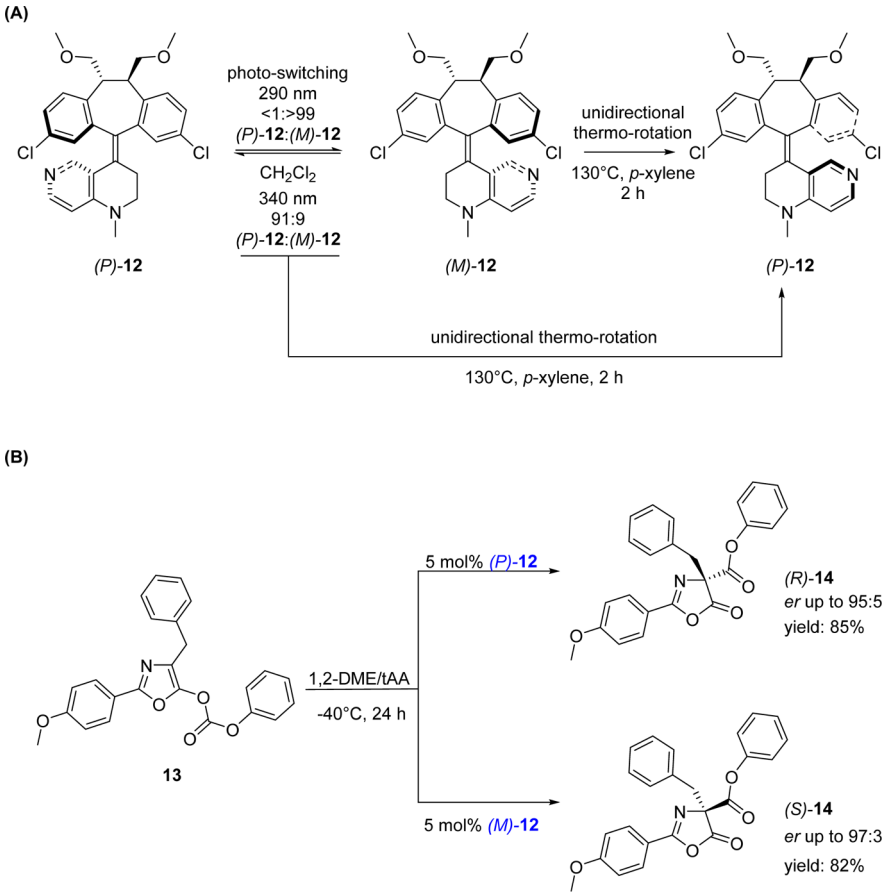
Scheme 5. (A) Light- or Heat-Driven Chiral Switchable Catalyst 12 and (B) Control of the Enantioselectivity of the Steglich Rearrangement of O-Carboxylazlactones Employing Catalyst 12



very efficient chiral catalyst for the Steglich rearrangement of **13**, giving the corresponding C-carboxylated product (*R*)-**14** in 85% yield with a high level of enantioselectivity (*er* up to 95:5). On the other hand, almost pure (*M*)-**12** catalyzed in good yield (82%) the rearrangement of **13** to give the opposite product (*S*)-**14** with the same level of enantioselectivity (*er* up to 97:3). To gain further insights into the origin of enantiocontrol of this asymmetric catalytic process, the authors carried out DFT calculations on the transition state assembly of the incipient ion pair, which would be formed between pyridinium cation **12a** and enolate anion **13a** (Scheme 6A), as postulated in previous mechanistic studies of the Steglich rearrangement.[12] The molecular simulations indicated that synclinal *Re*-face attack is favored with catalyst (*P*)-**12** due to greater HOMO−LUMO interactions with minimal stereoelectronic repulsion (Scheme 6B).

In 2015, Storch and Trapp reported an example of a stereochemically flexible diastereomeric rhodium(I) catalyst based on a *tropos* (i.e., chirally flexible) ligand.[13] Such a catalyst provided access to both enantiomeric products of asymmetric hydrogenations of prochiral (*Z*)-α-acetamidocinnamates by changing solely the applied temperature. The catalytic system was thought to be complementary to the one introduced by Mikami and Aikawa[14] in an attempt to overcome some of its limitations (Scheme 7).

Mikamiand Aikawa's approach of asymmetric (de)activation of racemic catalysts bearing a *tropos* ligand is based on the use of catalysts with stereochemically flexible ligands, for example, *tropos* biphenyls, in combination with a suitable chiral activator that forms a diastereomeric metal complex with the catalyst and shifts the equilibrium toward one diastereoisomer. In this way, the chiral activator could not only control the chirality of racemic catalysts but also lead to the formation of a catalytic species with higher enhanced catalytic properties. However, a limitation of this elegant approach is that the activator with opposite configuration is required to obtain the opposite enantiomeric product, because the absolute configuration of the activator determines the chirality of the product. To overcome this limitation, Storch and Trapp proposed to functionalize a *tropos* biphenyl ligand core with a homochiral auxiliary substituent as the chiral directing group. By binding this auxiliary to the ligand's core, the chiral information is continuously transferred to the stereochemically flexible chiral axis of the *tropos* biphenyl, which shifts the stereoisomeric ratio away from the 1:1 equilibrium. The stereogenic center of the chiral auxiliary has to be located in proximity to the linking group in order to maximize stereoselective interactions. In addition, the chiral auxiliary has to possess an expanded aryl group that aligns the adjacent phenyl rings of the metal bound diphenylphosphine group. The effective catalyst is then obtained by coordination of a metal precursor to the pair of diastereomeric ligand cores, thus freezing the equilibrium ratio of the stereoisomers. Eventually, the ratio of epimerizing diastereomers could be, in principle, controlled by external parameters such as temperature.

Following this principle, the authors synthesized the stereochemically flexible ligand 2,2′-bis(diphenylphosphino)-[1,1′-biphenyl]-3,3′-diol **15** as the chiral ligand core (as a racemate, Scheme 8A). Ligand **15** was functionalized with (*S*)-naproxen as

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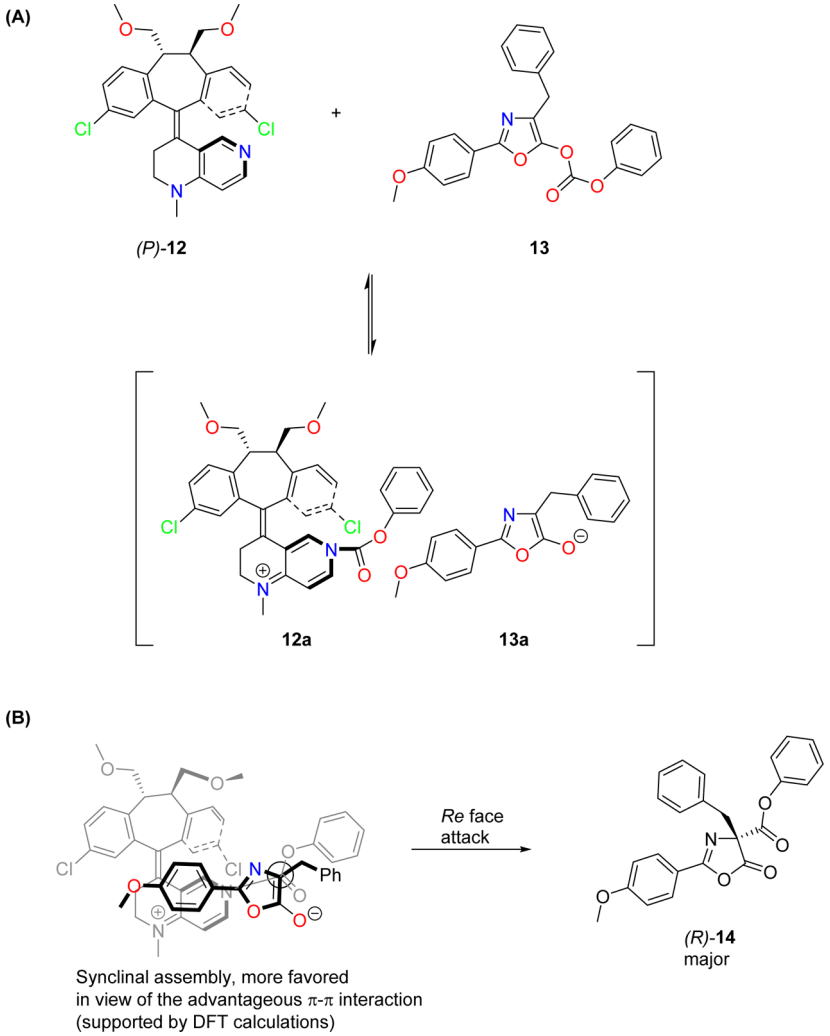
Scheme 6. (A) Formation of a Stabilized Ion Pair between Pyridinium Cation 12a and Enolate Anion 13a and (B) Plausible Transition State Assemblies of Steglich Rearrangement Employing Catalyst (*P*)-12 As Supported by DFT Calculations



the chiral auxiliary to afford the modified diastereomeric ligands (R_{ax},*S*,*S*)-**16** and (S_{ax},*S*,*S*)-**16**, thus shifting the ligand equilibrium ratio from 50:50 (for **15**) to 61:39 (for **16**) as a result of a central-to-axial chirality transfer of the chiral auxiliary to the axially chiral biphenyl core. Binding the (R_{ax},*S*,*S*)-**16** and (S_{ax},*S*,*S*)-**16** ligands to rhodium afforded the diastereomeric catalysts (R_{ax},*S*,*S*)-**17** and (S_{ax},*S*,*S*)-**17**, respectively. Complexation of the rhodium resulted in the freezing of the diastereomeric ratio, which did not undergo any change at room temperature. Interestingly, by heating at 70 °C for 6 h the diastereomeric mixture (R_{ax},*S*,*S*)-**17**/(S_{ax},*S*,*S*)-**17** (61:39) yielded the minor isomer (S_{ax},*S*,*S*)-**17** with a purity greater than 99%. The reaction progress was followed by $^{31}P\{^{1}H\}$ and ^{1}H NMR spectroscopy. Hence, according to this behavior, to come back to the initial diastereomeric (R_{ax},*S*,*S*)-**17**/(S_{ax},*S*,*S*)-**17** ratio of 61:39, the system would require decomplexation of rodhium, ligand re-equilibration, and recomplexation with rodhium, because the diasteromeric ratio catalyst (R_{ax},*S*,*S*)-**17**/(S_{ax},*S*,*S*)-**17** remains <1:>99 upon cooling.

The catalytic properties of either the (R_{ax},*S*,*S*)-**17**/(S_{ax},*S*,*S*)-**17** (61:39) mixture or almost pure complex (S_{ax},*S*,*S*)-**17** were assessed in the asymmetric hydrogenation of a prochiral substrate such as the (*Z*)-methyl-α-acetamidocinnamate (MAC, **18**; Scheme 8B). Upon optimization of hydrogenation conditions, the use of the mixture complexes (R_{ax},*S*,*S*)-**17**/(S_{ax},*S*,*S*)-**17** (61:39) as catalysts in $CDCl_3$ at −40 °C and under an initial hydrogen pressure of 10 atm gave the complete conversion of substrate **18** in the N-acetylphenylalanine methyl ester **19** enriched in the enantiomer *R* (*er* up to 87:13). This enantiomeric excess of 74% is equivalent to an amplification factor (f_{amp}) of 3.4, f_{amp} being defined as the ratio of the enantiomeric excess of the reaction product and the diastereomeric excess of the catalyst. This nonlinear chiral amplification[15] is a significant result because it demonstrates that small deviations from a 1:1 equilibrium of a proposed catalytic system seems to be enough to generate high stereoselectivity. In contrast, using the almost pure (S_{ax},*S*,*S*)-**17** as a catalyst, under similar conditions but at a higher temperature (−10 °C), the opposite enantiomer (*S*)-**19** was obtained with an *er* up to 96:4.

Although the chiral switchability of catalyst **17** is "unidirectional," the concept proposed by Trapp would in principle be directly transferable to other kinds of asymmetric catalyzed reactions. Moreover, the achievement of a reversal enantioselectivity by using solely a temperature control is a rather rare phenomenon in asymmetric synthesis or catalysis.[16]

3. REDOX-DRIVEN CHIRAL SWITCHABLE CATALYSTS

In 2012, a redox-driven chiral switchable catalyst was reported by Canary and co-workers (Scheme 9).[17] Inspired by their previous s9

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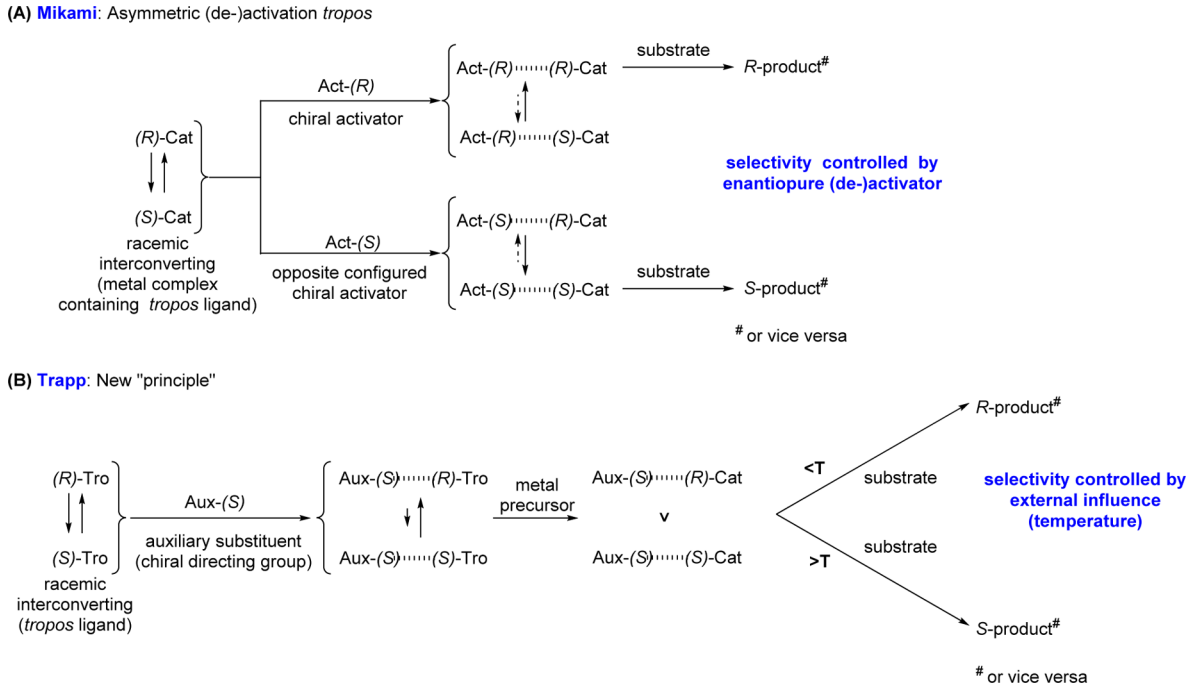
Scheme 7. (A) Principle of Asymmetric (De-)activation Proposed by Mikami and Aikawa and (B) Principle of Temperature-Controlled Bidirectional Enantioselectivity Proposed by Storch and Trapp



work,[18] the catalyst design is based on a complex derived from multidentate ligand **20**, which comes from the commercially available L-methioninol. Ligand **20** is able to complex either Cu(II) or Cu(I) salts, affording respectively the bisurea complexes Δ-**21** and Λ-**21**, which might undergo innersphere ligand rearrangement upon one-electron reduction or oxidation of copper. The metal complex catalysts **21** were able to deliver opposite enantiomers for a nitro-Michael addition reaction, depending on the oxidation state of the copper atom (that is Δ-**21** or Λ-**21**).

When the copper atom is in its oxidized state (Cu^{II}), catalyst Δ-**21** promotes the addition of diethyl malonate **22** to *trans*-β-nitrostyrene **23** to form the nitro-Michael adduct (*S*)-**24** in 55% yield (75% conversion) with *er* up to 86:14. On the other hand, when the copper atom in its Cu^{I} reduced state, Λ-**21** catalyzed the formation of the opposite enantiomer (*R*)-**24** in 40% yield with *er* up to 85:15. In situ reduction of Cu^{II} catalyst Δ-**21** to Cu^{I} Λ-**21** was possible by L-ascorbic acid reduction. Employing the product of in situ reduction in the nitro-Michael addition afforded the opposite product enantiomer (*R*)-**24**. Moreover, it is remarkable that the same *er* (85:15) of the product (*R*)-**24** was obtained with a slightly higher yield (43%) with respect to that obtained via the preformed Cu(I) complex. However, in the discussion of this work there is not a clear explanation on how the helix inversion of **21** could influence the handedness of the products of catalysis. In this regard, in a following paper,[19] Canary and co-workers pointed out that the urea groups were the only active functionalities influencing catalysis while the copper ion was used to control the handedness of the scaffold's helical structure. By combining molecular modeling, crystal structure, and kinetic data, they suggested that only one urea moiety of **21** likely binds the nitrostyrene substrate while blocking the *Re*-face of the nitrostyrene in the transition state. The ability to guide the handedness of the nitro-Michael product based on the helical state of catalyst **21** was also demonstrated with other solvents, bases, and nitrostyrene/malonate substrates, even though the achieved enatioselectivities were not improved.

Canary's group demonstrated that catalyst **21** is capable of independent, dial-in control of the absolute stereochemistry when two similar nitrostyrenes were used for the Michael addition reactions. In fact, by in situ oxidation and reduction of the catalyst, it was possible to access all four possible stereoisomers for the nitroalkane products (Scheme 10).[20] s10

By choosing a pair of nitrostyrenes such as **23** and *trans*-2,3-dimethoxy-β-nitrostyrene **25** having a large difference in reaction rate with diethyl malonate (**22**), using Δ-**21** as a catalyst, it was possible to obtain products of opposite absolute stereochemistry such as (*S*)-**24** and (*R*)-**26**. In particular it was ascertained that, after 3 h, nitrostyrene **23** was mostly consumed and the Δ-**21** catalyst state could be instantaneously switched in situ to Λ-**21** employing L-ascorbic acid. Allowing then the system to react for an additional 24 h, the product (*S*)-**24** was obtained in 52% yield with *er* up to 77.5:22.5 while product (*R*)-**26** was obtained in 90% yield with *er* up to 57:43. In contrast, by starting the reaction with Λ-**21** as a catalyst and switching it to Δ-**21** in situ, after 3 h, using the ceric ammonium nitrate (CAN) as an oxidizing agent, the other two possible stereoisomers were obtained: (*R*)-**24** in 51% yield with *er* up to 82:18 and (*S*)-**26** in 48% yield but only *er* 51:49. Although the *er* of (*S*)-**26** was very low, the change in *er* was however appreciable, confirming at least the principle that through those two dynamic catalysis it is possible to have access to all four stereochemical permutations for a nitro-Michael addition. The low yields of both products were ascribed to side reactions of the substrate with the oxidizing agent CAN.[21]

4. SOLVENT-DRIVEN CHIRAL SWITCHABLE CATALYSTS

Suginome and co-workers reported in 2010 that a high-molecular-weight (about 1000-mer) random copolymer of poly(quinoxaline-2,3-diyl) **27**, bearing both coordinating diphenylphosphino pendants and (*R*)-2-butoxymethyl side

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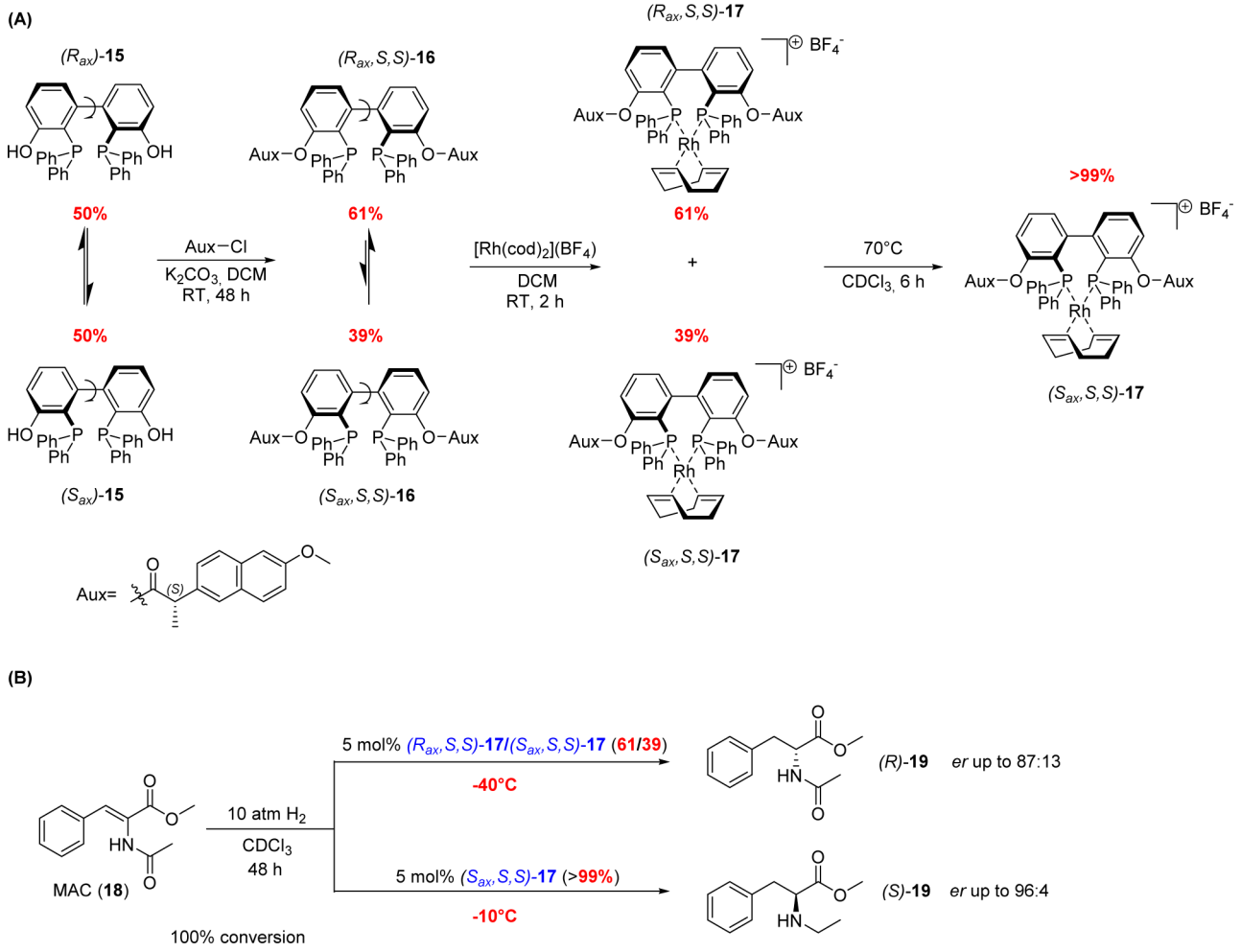
Scheme 8. (A) Synthesis of Heat-Driven Chiral Catalyst 17 and (B) Control of the Enantioselectivity in the Asymmetric Hydrogenation of (*Z*)-Methyl-α-acetamidocinnamate (18) to N-Acetylphenylalanine Methyl Ester (19) Using Catalyst 17



chains, showed a solvent-driven switch of its own helicity (Scheme 11) and could serve as a chiral ligand in the asymmetric hydrosilylation of styrene (Scheme 12).[22] In fact, these kinds of copolymers generally do not have prefixed chiral axes or stereogenic centers in the main-chains but adopt a right- or left-handed helical structure on the basis of homogeneous axial chirality between the quinoxaline rings, which is induced thermodynamically by chiral side chains or pendants.[23] In particular, copolymer **27** adopted an almost pure *P*-helical structure in chloroform, but dissolving it in a mixture of 1,1,2-trichloroethane(TCE)/toluene (2:1) induces a gradual inversion of the helical sense that turned it almost entirely to an *M*-helix after 6 h at 60 °C.

By employing ligand (*P*)-**27** in palladium catalyzed hydrosilylation of styrene, the product (*S*)-**31** was obtained in 94% yield with *er* up to 98.5:1.5 without the use of a solvent. In contrast, using ligand (*M*)-**27** for the same reaction but in a mixture of 1,1,2-TCE/toluene (3:1) as a solvent, the opposite enantiomer (*R*)-**31** was produced in 93% yield with *er* up to 96.5:3.5. In this case, the use of a 1,1,2-TCE/toluene mixture (3:1) as reaction media was found to be mandatory for maintaining the left-handed helical structure of ligand (*M*)-**27** during the longer reaction time (72 h) required for the reaction.

In the hydrosilylation reaction carried out under neat conditions, polymeric ligand (*P*)-**27** formed with palladium an insoluble complex, which was found to be easily separable from the reaction mixture. The complex could be reused seven times without a loss of enantioselectivities and with almost complete retention of the initial palladium load.

High-molecular-weight helically chiral polyquinoxaline-based phosphines (*P*)-**28** (see Scheme 11) have been employed for other palladium-catalyzed reactions such as asymmetric Suzuki−Miyaura cross-coupling (SMC) of 1-bromo-2-naphthalenephosphonic esters and *o*-substituted phenylboronic acids to afford axially chiral biaryls such as biarylphosphinates (Scheme 13).[24]

In particular, employing ligand (*P*)-**28** in SMC of 1-bromo-2-naphthalenephosphonic dimethyl ester **32** and (2,3-dimethylphenyl)boronic acid **33**, at 40 °C in a mixture of THF/water (10:1) with K_3PO_4 and $[PdCl(\pi\text{-allyl})]_2$, the axially chiral biaryl (*S*)-**34** was achieved in 78% yield with *er* up to 99:1. Of note, the enantioselectivities were higher than those obtained by Yin and Buchwald in one of the first examples of a catalytic enantioselective cross-coupling procedure for the preparation of functionalized biaryls, using KenPhos as a chiral ligand.[25] Moreover, enantioselectivities were comparable to those reported in other related works.[26] As in (*P*)-**27**, the helical sense of (*P*)-**28** was found to be switchable, and the left-handed helical polymer ligand (*M*)-**28** was obtained by heating at 60 °C for 24 h a 1,1,2-TCE/THF (3:1) solution of (*P*)-**28**. Using ligand (*M*)-**28** in SMC of **32** and **33** with K_3PO_4 and Pd_2dba_3 as a base and a Pd source, respectively, the opposite enantiomer (*R*)-**34** was obtained with an *er* of 90:10, even though the reaction yield

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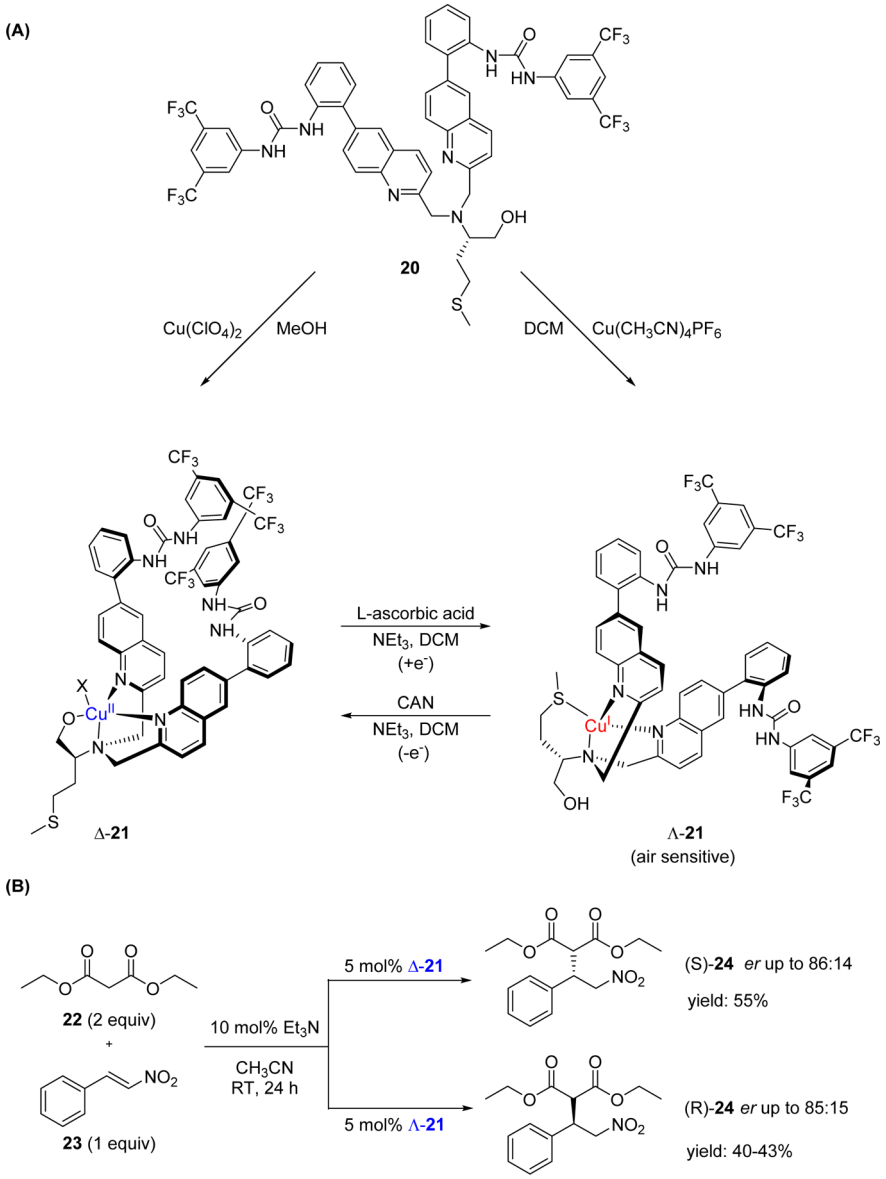
Scheme 9. (A) Synthesis of Redox-Driven Chiral Switchable Catalyst 21 and (B) Control of the Enantioselectivity of a Nitro-Michael Addition Using Catalyst 21



was moderate (59%). Also in this case, the use of a chlorinated solvent such as 1,1,2-TCE was necessary to maintain the left-handed helical structure of ligand (*M*)-**28** during the course of the reaction.

The chiral switchable ligand **29** (see Scheme 11) was active in Pd-catalyzed asymmetric silaborative cleavage of *meso*-methyl-
s14 enecyclopropanes (Scheme 14).[27]

By reacting, at 50 °C in toluene, the bicyclic *meso*-methylenecyclopropane **35** (7-methylenebicyclo[4.1.0]heptane) with the silylborane **36** in the presence of a catalytic amount of both palladium source and ligand (*P*)-**29**, the silaboration product (1*S**,2*S**)-**37** was obtained in good yield (84%) and high enantioselectivity (*er* up to 98:2). Hence, ligand (*P*)-**29** was switched to a left-handed helical ligand (*M*)-**29** by dissolving it in a 3:1 mixture of 1,1,2-TCE and toluene at 60 °C for 24 h. Upon the use of a palladium complex of the inverted (*M*)-**29**, under the same reaction conditions employed for (*P*)-**29**, the asymmetric silaborative cleavage of **35** with **36**, leading to the opposite enantiomer (1*R**,2*R**)-**37**, was found to be significantly slower. The reaction rate could be reasonably improved under solvent-free reaction conditions, but enantioselectivity decreased (*er* 87.5:12.5), likely due to an *M*-to-*P* helix reinversion during the reaction at 50 °C. Eventually, by using a small amount of 1,1,2-TCE as an additive, which was necessary to maintain the left-handed helical structure of (*M*)-**29** during the reaction, the enantiomer (1*R**,2*R**)-**37** was obtained in similar yield (80%) and higher enantioselectivity (*er* up to 95.5:4.5) with respect to (1*S**,2*S**)-**37**.

The chiral switchable ligand (*P*)-**29** bearing 4-$CF_3C_6H_4$ groups (see Scheme 11) was found effective in the asymmetric SMC of 1-bromo-2-naphthoate derivatives and arylboronic acid (Scheme 15).[28]
s15

This asymmetric SMC of the naphthyl bromide bearing a 2,4-dimethyl-3-pentyl ester **38** and 1-pyreneboronic acid **39** afforded the corresponding axially chiral biaryl product (*S*)-**40** in high yield (96%) and high enantioselectivity (*er* up to 97.5:2.5). However, the presence of a bulky ester group such as 2,4-dimethyl-3-pentyl ester in naphthoate substrates was found

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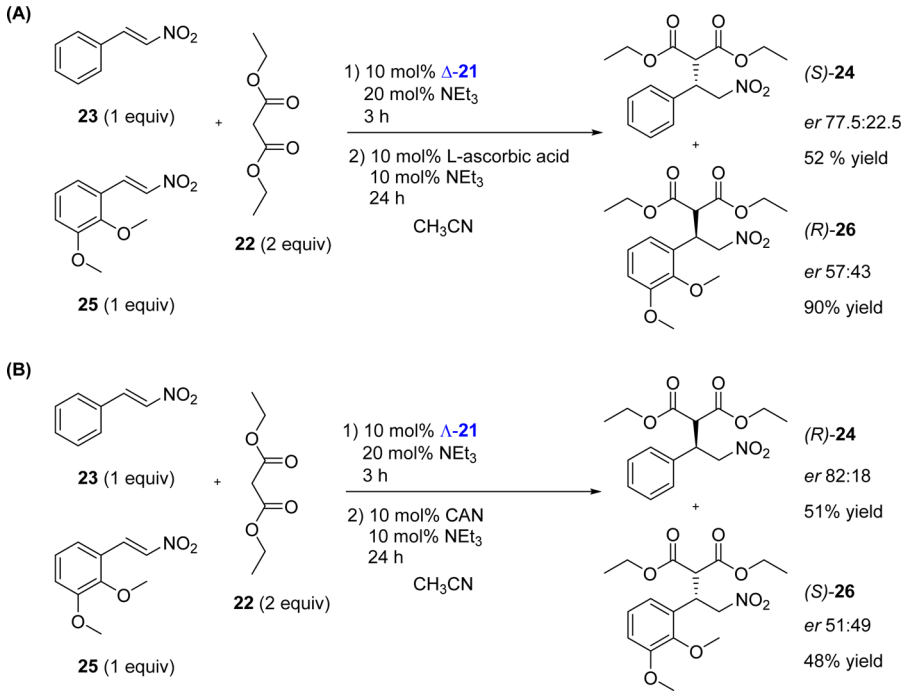
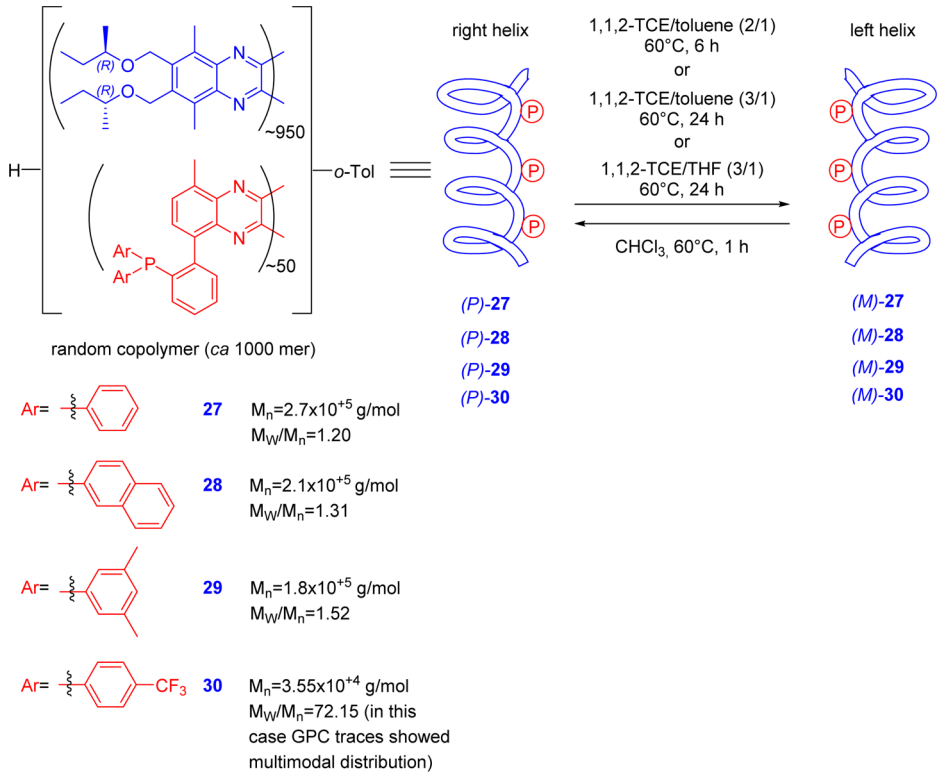
Scheme 10. Dynamic Catalysis Performed with Catalysts 21: (A) Dynamic Catalysis Starting from Δ-21 (Which Was Switched after 3 h to Λ-21) to Obtain Products of Opposite Absolute Stereochemistry: (*S*)-24 and (*R*)-26 and (B) Dynamic Catalysis Starting from Λ-21 (Which Was Switched after 3 h to Δ-21) to Obtain Products of Opposite Absolute Stereochemistry: (*R*)-24 and (*S*)-26



Scheme 11. Structure of Solvent-Driven Chiral Switchable Polymeric Ligands 27, 28, 29, and 30



crucial to achieving high enantioselectivities. In addition, this ester functionality can be readily converted into other functional groups. Stereocomplementary synthesis of the opposite enantiomer product (*R*)-**40** was achieved by employing the helically inverted ligand (*M*)-**30**, which was obtained by heating (*P*)-**30** in a mixture of 1,1,2-TCE/THF (3:1) at 60 °C for 24 h. (*R*)-**37** was obtained in high yield (93%) with high enantioselectivity (*er* up to 95.5:4.5). The presence of 1,1,2-TCE in the reaction medium was found again to be mandatory to maintaining the left-handed helical structure of (*M*)-**30**.

As the use of halogenated solvents has to be avoided in Pd-catalyzed reactions such as SMC, it was demonstrated that a

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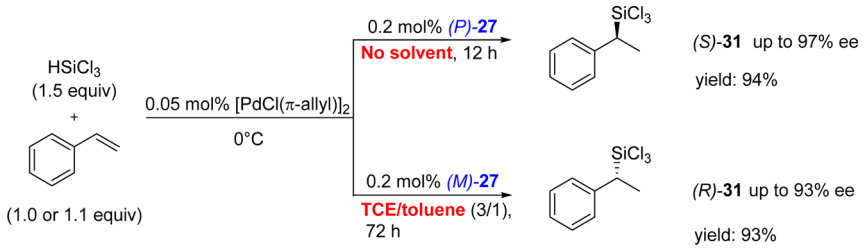
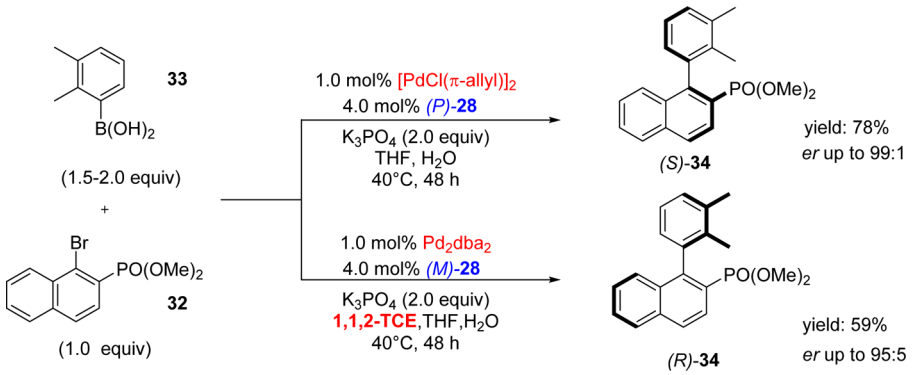
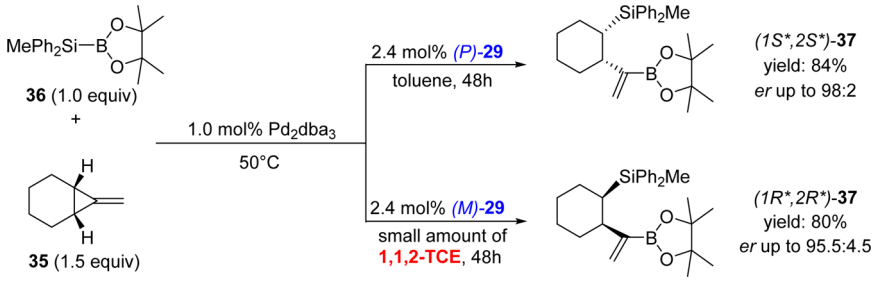
Scheme 12. Control of the Enantioselectivity of a Palladium Catalyzed Asymmetric Hydrosilylation Using Solvent-Driven Chiral Switchable Ligand 27



Scheme 13. Control of the Enantioselectivity of an Asymmetric Suzuki−Miyaura Cross-Coupling Using the Solvent-Driven Chiral Switchable Ligand 28



Scheme 14. Control of the Enantioselectivity of a Palladium Catalyzed Asymmetric Silaborative Cleavage Using the Solvent-Driven Chiral Switchable Ligand 29



random copolymer (about 1050-mer) of poly(quinoxaline-2,3-diyl) bearing L-lactic acid groups with pentyl esters as side chains and diphenylphosphino pendants **41** could be used as a chiral switchable polymeric ligand for asymmetric SMC also in ethereal solvents (Scheme 16).[29]

The ligand **41** showed an effective solvent-dependent helix inversion between 1,2-dimethoxyethane (1,2-DME, *M*-helix) and methyl *tert*-butyl ether (MTBE, *P*-helix) by heating it for 24 h at 60 °C. Thus, by carrying out the SMC of compound **32** and 1-naphthyl-boronic acid **42** at 40 °C with K_3PO_4 and Pd_2dba_3, both enantiomeric biaryls were obtained in high *er* employing 1,2-DME (*er* up to 95.5:4.5 for (*R*)-**43**) and MTBE (*er* up to 96.5:3.5 for (*S*)-**43**) as solvents, albeit the yields were moderate (45% for (*R*)-**43**, and 71% for (*S*)-**43**). However, the enantioselectivities are comparable to those previously obtained with ligands **28** and **30** using as solvents either THF or a mixture 1,1,2-TCE/THF.

The solvent-dependent helical inversion of copolymers of poly(quinoxaline-2,3-diyl) was proven also in hydrocarbon solvents. In particular, the random copolymer (about 1000-mer) of poly(quinoxaline-2,3-diyl) containing (*S*)-3-octyloxymethyl side chains and diphenylphosphino pendants **44** exhibited solvent-dependent helical inversion switching from *n*-octane to cyclooctane (Scheme 17).[30]

By employing ligand (*M*)-**44** in palladium catalyzed hydrosilylation of styrene in *n*-octane, the product (*R*)-**31** was afforded in 88% yield with *er* up to 97:3. When the same reaction was carried out in cyclooctane, causing a switch of the helical sense from (*M*)-**44** to (*P*)-**44**, the product (*S*)-**31** with opposite stereochemistry was obtained in 89% yield with *er* up to 95:5.

Last but not least, Suginome and co-workers demonstrated that the supramolecular approach of helical majority rules[31] is applicable to the random copolymer (about 1000-mer) of poly(quinoxaline-2,3-diyl) containing octan-2-yloxy side chains and diphenylphosphino pendants **45**, in which the chiral side chains were derived from (*R*)-2-octanol with a low enantiomeric purity (23%; Scheme 18).[32]

Measurement of the CD spectrum in chloroform of **45** revealed that the amplification of chirality due to majority rules was enough for adopting a right-handed helical structure: (*P*)-**45** (screw-sense excess >99%). As in the case previously discussed, the screw-sense was easily inverted to the left (*M*)-**45** by heating (*P*)-**45** in a mixture (3:1) of 1,1,2-TCE and toluene or 1,1,2-TCE

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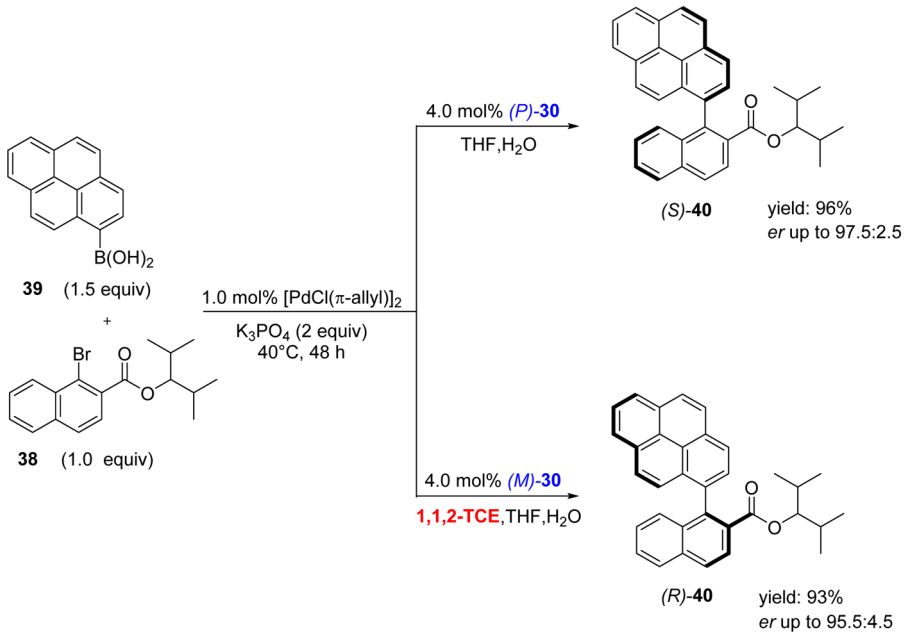
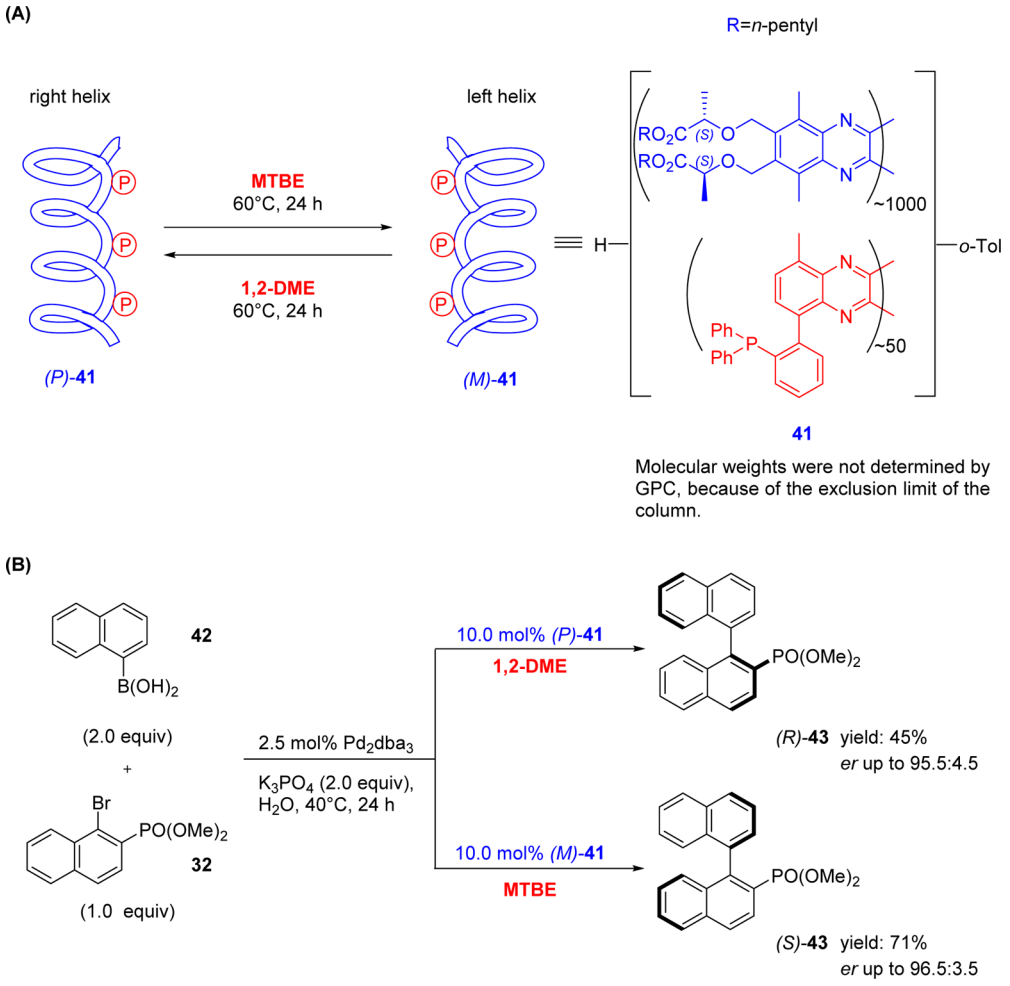
Scheme 15. Control of the Enantioselectivity of an Asymmetric Suzuki−Miyaura Cross-Coupling Using the Solvent-Driven Chiral Switchable Ligand 30



Scheme 16. (A) Structure of the Solvent-Driven Chiral Switchable Polymeric Ligand 41 and (B) Control of the Enantioselectivity of an Asymmetric Suzuki−Miyaura Cross-Coupling Using Ligand 41



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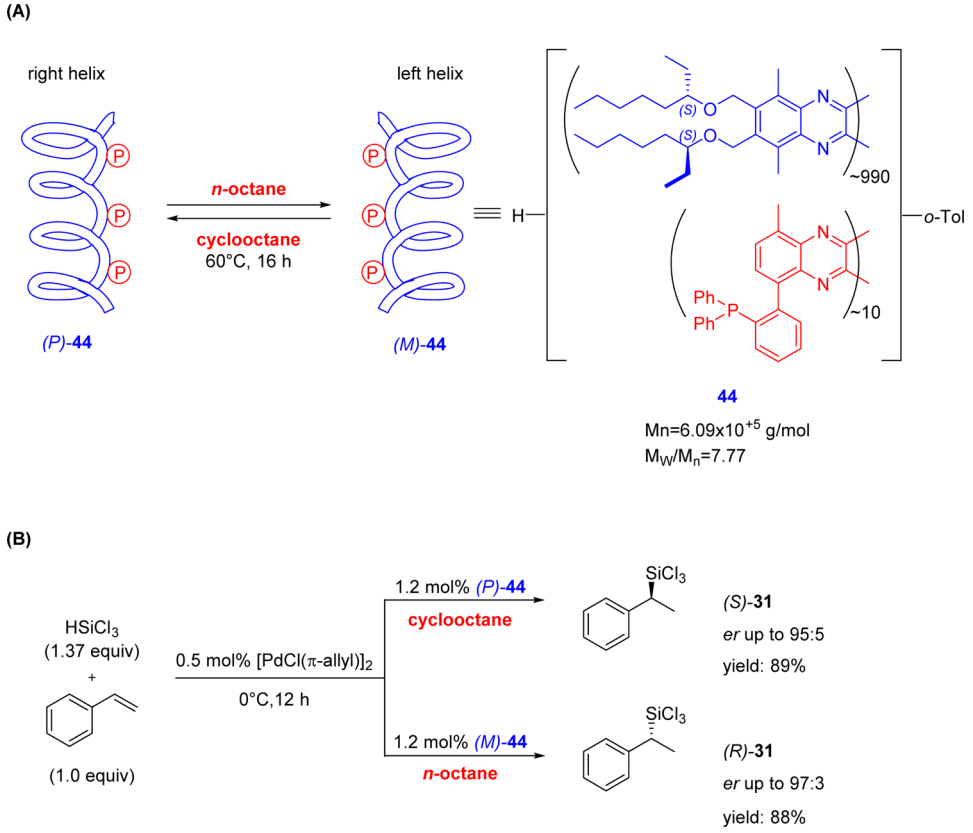
Scheme 17. (A) Structure of the Solvent-Driven Chiral Switchable Polymeric Ligand 44 and (B) Control of the Enantioselectivity of a Palladium Catalyzed Asymmetric Hydrosilylation Using Ligand 44



and THF at 60 °C for 24 h. The polymeric ligand **45** was efficiently employed in both asymmetric hydrosilylation of *β*-methylstyrene **46** and asymmetric SMC of **32** and **42**. By using (*P*)-**45** in hydrosilylation of **46** without solvent, the product (*S*)-**47** was afforded in 89% yield with *er* up to 97:3, while when the helical sense was switched from (*P*)-**45** to (*M*)-**45** the opposite enantiomer (*R*)-**47** was afforded in 90% yield with *er* up to 97.5:2.5 employing 1,1,2-TCE/toluene (3:1) as a reaction medium. As to the asymmetric SMC of **32** and **42**, such a reaction carried out in the presence of (*P*)-**45** or (*M*)-**45** confirmed the obtainment of an asymmetric amplification. In particular, in the presence of (*P*)-**45**, the axially chiral product (*S*)-**43** was obtained in 41% yield with high enantioselectivity (*er* up to 96.5:3.5). When (*M*)-**45** with inverted helical chirality was used, the opposite product (*R*)-**43** was afforded in 74% yield with the same level of enantioselectivity (*er* up to 96:4). As expected, the assistance of 1,1,2-TCE in the reaction media was found to be mandatory to maintain the left-handed helical structure of the ligand.

Finally, it should be noted that other catalytic systems have been demonstrated to exhibit solvent-dependent stereoselectivity,[33] but in all of these cases the nature of the catalyst is not switchable. In some cases, the origin of solvent-dependent stereodiscrimination has been attributed to effects of the enthalpy−entropy compensation or addition of other additives or charge stabilization factor of solvents.

5. SUMMARY AND OUTLOOK

In this Perspective, we addressed the very recent achievement reached in chiral switchable catalysis to obtain dynamic dual enantiocontrol in asymmetric synthesis. Since many pharmacological investigations often need both enantiomers to study potentially different activities and side effects,[34] attaining dual enantiocontrol using this approach could become very attractive, and moreover it could eliminate the need for a parallel synthesis of the opposite enantiomer of the designed catalyst.

Three different conceptual approaches have been presented according to the trigger employed to obtain the stereochemical control of the reaction. In the first one, based on light- and/or heat- driven chiral switchable catalysts, Wang and Feringa's catalysts **1**, **5**, and **9** have been dealt with. These catalysts are in principle the most elegant candidates as chiral switchable catalysts because they possess a three-way switch: in the first one the catalyst is in its *off* state (no activity), while in the other two the catalyst is in its *on* state, giving opposite stereochemistry of the products. However, these catalysts sometimes showed complications in their isomerization steps necessary for the switchability. Nevertheless, there are no doubts that their design paved the way to the dynamic control of enantioselectivity using a single switchable catalytic source.

In the second approach, based on redox-driven chiral switchable catalysts, the metal complex **21** proposed by Canary and co-workers has offered a new way to think about chiral switchable catalysts. Compound **21** represents simultaneously an organocatalyst and transition metal complex. In fact, the urea groups are the active functionalities influencing the catalytic activity, while the oxidation state of metal is the tool to control the helical preference allowing the desired dual stereocontrol.

In the third approach, based on solvent-driven chiral switchable catalysts, several copolymers of poly(quinoxaline-2,3-diyl) bearing chiral side chains and diarylphosphino pendants proposed by Suginome's group have been discussed as chiral

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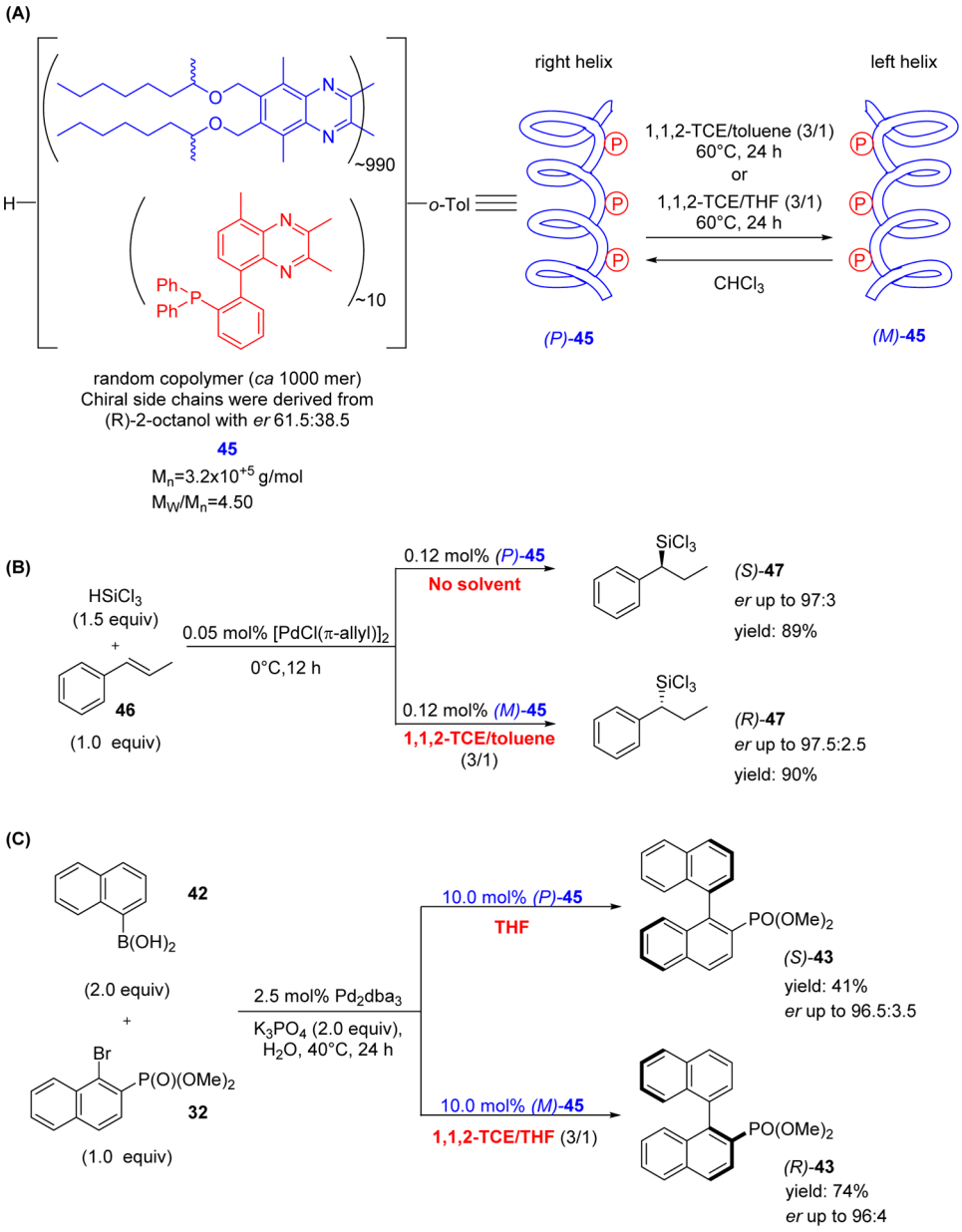
Scheme 18. (A) Structure of the Solvent-Driven Chiral Switchable Polymeric Ligand 45, (B) Control of the Enantioselectivity of a Palladium Catalyzed Asymmetric Hydrosilylation Using Ligand 45, and (C) Control of the Enantioselectivity of an Asymmetric Suzuki−Miyaura Cross-Coupling Using Ligand 45



switchable ligands for accelerating asymmetric palladium catalyzed reactions. The results achieved with the ligand **45**, in which the chiral side chains derived from (*R*)-2-octanol with low enantiomeric purity (23%), are noteworthy because the dynamic nature of its helical preference not only allows for the dual enantiocontrol of the reaction but also leads to enantiomerically enriched products with *er* higher than that of the chiral catalyst (a phenomenon referred to as amplification of chirality).

In conclusion, the chemistry dealt with herein represents today only a proof of principle. Nevertheless, the progress in the field of metal catalysis, organocatalysis, organic synthesis, and supramolecular chemistry will hopefully stimulate and inspire "brave" researchers to put forth further efforts aimed at broadening the availability of chiral switchable catalysts. The door is open; it will need to open the way further!

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Notes

The authors declare no competing financial interest.

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