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Chiral Switchable Catalysts for Dynamic Control of Enantioselectivity

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1 Chiral Switchable Catalysts for Dynamic Control of Enantioselectivity

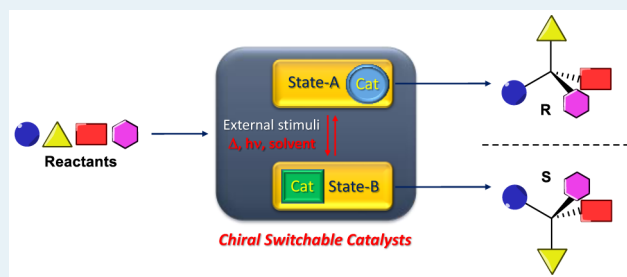
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5 **ABSTRACT:** Among the artificial switchable catalysts, those
6 catalysts whose activity can be switched by an external stimulus,
7 only a few cases offer the possibility to develop an effective chiral
8 switchable system that could selectively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

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



16 chiral switchable catalyst area for the dynamic control of enantioselectivity, highlighting their advantages and showing some
17 perspectives of this field that is still in its infancy.

1. INTRODUCTION

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

30 However, among artificial switchable catalysts, only a few cases
31 offer the possibility to develop an effective *chiral* switchable
32 system that could selectively accelerate the formation of a given
33 enantiomer in one state, whereas in the other state it accelerates
34 the formation of the opposite enantiomer. In fact, achieving dual
35 stereocontrol in asymmetric reactions² using a chiral switchable
36 catalyst could be a very important goal in enantioselective
37 synthesis, since it will eliminate the need to have available the two
38 enantiomers of the designed catalyst. Such a case would
39 practically avoid all the necessary steps for the preparation of
40 opposite configured catalysts, thus improving the chemical
41 sustainability of the whole catalytic process under study.

42 An exhaustive review by Hayashi et al. addressed the topic of
43 enantiocontrol by changing factors other than stimuli-respond-
44 ing structural change of catalysts such as catalyst substituents or
45 substrate substituents or central metal or solvents or additives or
46 other factors.^{2c}

47 In this Perspective, we will focus on the work on asymmetric
48 synthesis achieved by means of the dynamic control of
49 enantioselectivity through a chiral switchable catalyst. It is
50 noteworthy that the time-span in which results of this work have

been disclosed in the scientific literature is solely six years. The
51 discussion on catalysts has been divided into three major classes:
52 light- and/or heat-, redox-, and solvent-driven chiral switchable
53 catalysts.
54

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

55
56 In 2011, a seminal and paradigmatic work on dynamic chiral
57 switchable catalysts was described by Wang and 2016 Nobel
58 Laureate Feringa.³ On the basis of their previous experience in
59 the synthesis of chiral crowded alkenes,⁴ they designed and used
60 the molecular motor **1** as a chiral switchable organocatalyst
61 (Scheme 1) in the sulfa-Michael addition to α,β -unsaturated
62 ketones, efficiently modulating both its enantioinduction and
63 activity (Scheme 2).
64

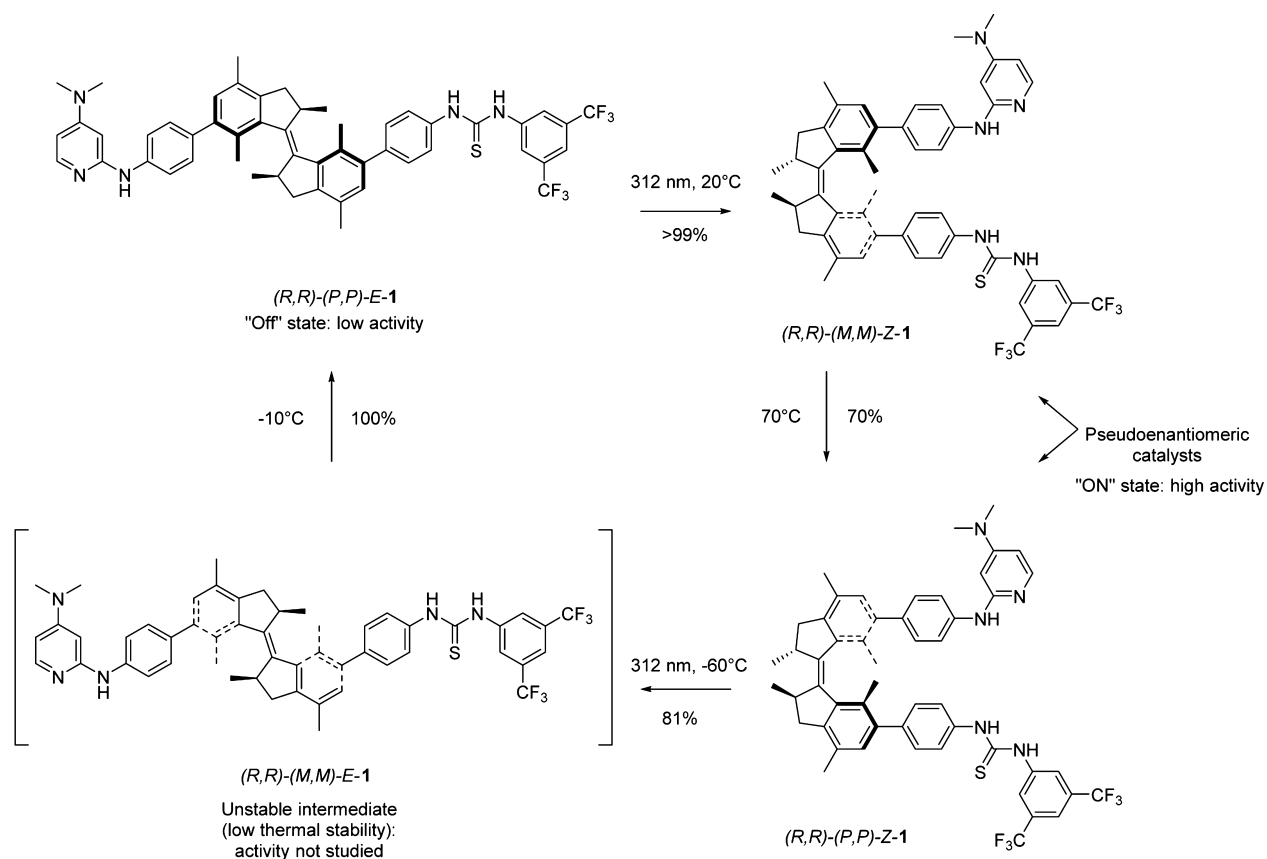
65 The catalyst **1** is decorated with Brønsted acidic thiourea and
66 Brønsted basic DMAP groups, which are known to cooperate in
67 the catalysis of the sulfa-Michael addition.⁵ The chiral crowded
68 alkene moiety in **1** can move through a unidirectional rotatory
69 cycle with a series of two photoisomerizations and two thermal
70 isomerizations (Scheme 1). Thus, the rotation of the molecular
71 motor can control the relative orientations of the two catalytic
72 moieties. In particular, starting from (R,R)-(P,P)-E-**1** and
73 irradiating at 312 nm at 20 °C, an E–Z photoisomerization
74 and a helix inversion⁶ from P to M take place to give (R,R)-
75 (M,M)-Z-**1**, in which the two catalytic units are brought into
76 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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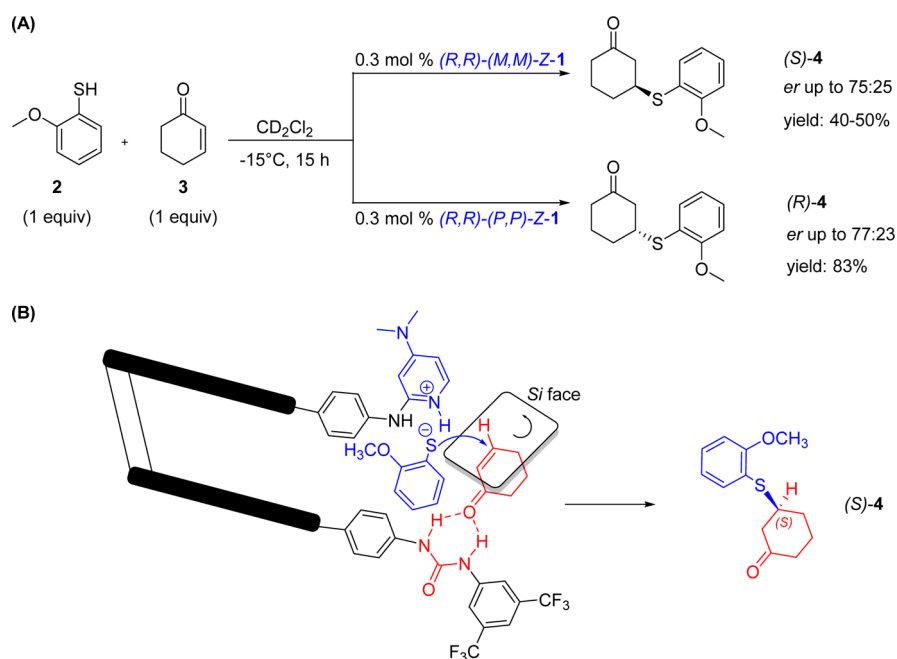
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Scheme 1. Light- and Heat-Driven Chiral Switchable Catalyst 1

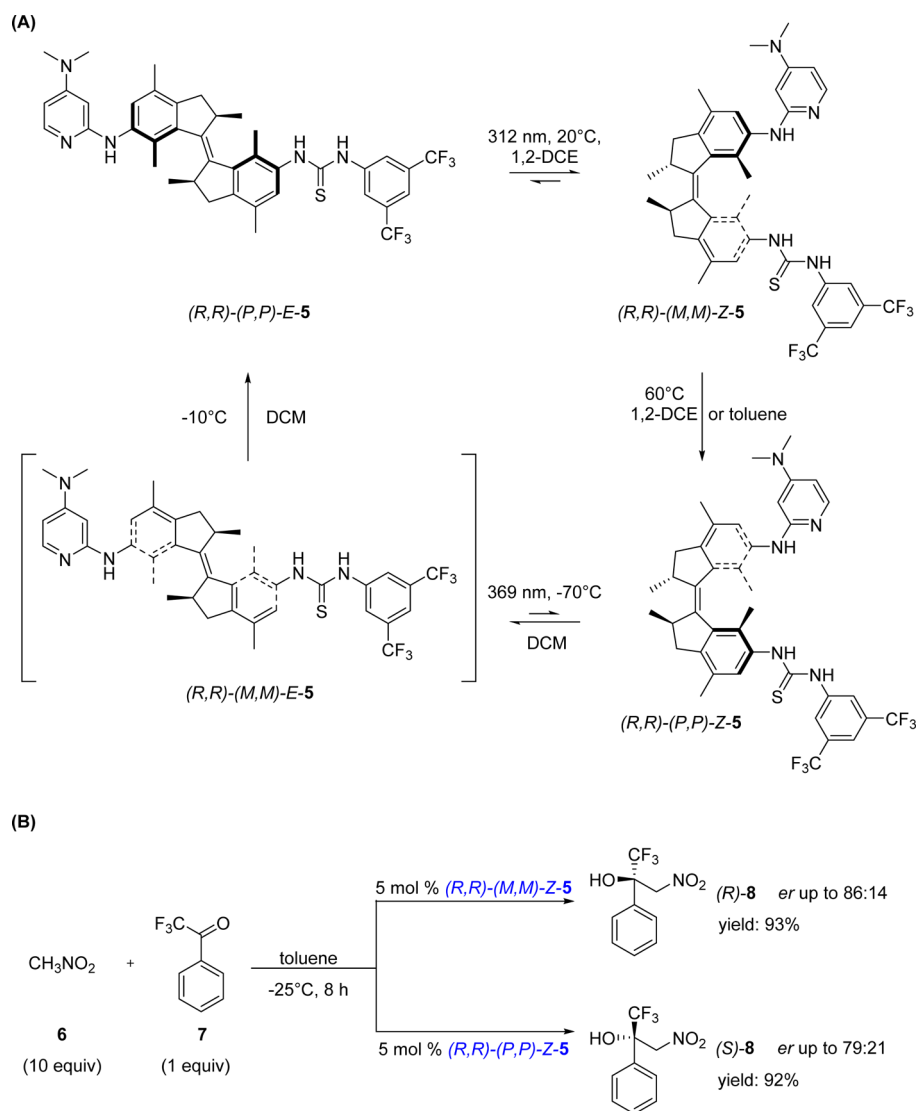


Scheme 2. (A) Control of the Enantioselectivity of a Sulfa-Michael Addition Employing Chiral Switchable Catalyst 1 and (B) Plausible Ternary Complex Involved in the Mechanism of Thiol Addition to Enone Catalyzed by 1



77 in close proximity. A photochemical step followed by thermal
78 isomerization regenerates the original structure (*R,R*)-(*P,P*)-*E*-1
79 through the intermediate (*R,R*)-(*M,M*)-*E*-1, which was not
80 employed as a catalyst due to its low thermal stability. All steps of
81 this 360° rotation of molecular motor 1 were fully studied and

confirmed by a combination of chiral HPLC, circular dichroism 82
(CD), UV-vis, and ¹H NMR spectroscopy. When (*R,R*)-(*P,P*)- 83
E-1 was used to catalyze the sulfa-Michael addition of 2-methoxy 84
thiophenol 2 to cyclohexenone 3, the adduct 4 was obtained as a 85
racemate in very low yield (7% yield in 15 h) due to the 86

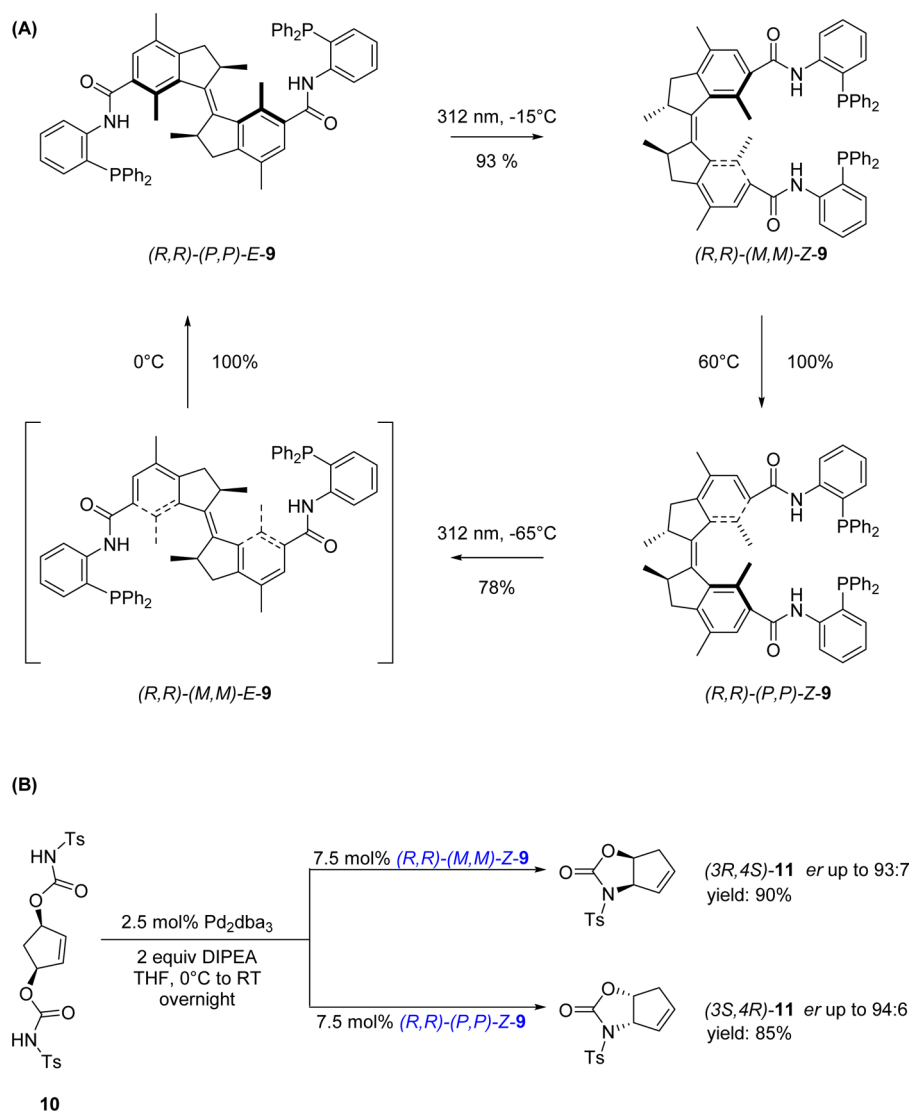
Scheme 3. (A) Light- and Heat-Driven Chiral Switchable Catalyst Sand (B) Control of the Enantioselectivity of a Henry Reaction Employing Chiral Switchable Catalyst 5


87 unfavorable orientation of the thiourea and DMAP catalytic
 88 moieties. On the other hand, when the catalyst (R,R)-(M,M)-Z-1
 89 was employed under the same conditions, a higher catalytic
 90 activity was achieved affording, after 15 h, the sulfa-Michael
 91 adduct (S)-4 in 50% yield with an enantiomeric ratio (*er*) up to
 92 75:25. By using the Z isomer of opposite helicity, (R,R)-(P,P)-Z-
 93 1, the sulfa-Michael addition proceeded even faster, giving a
 94 higher yield (83% in 15 h) and exhibiting a similar degree of
 95 enantioselectivity (*er* up to 77:23) but in favor of opposite
 96 enantiomer (R)-4 (Scheme 2A). Taking into account previous
 97 mechanistic studies on bifunctional organocatalysts for sulfa-
 98 Michael addition^{5,7} as well as performing basic molecular
 99 modeling studies, the authors proposed that the helicity of the
 101 4, depending on the face (*Si* or *Re*) of cyclohexenone 3 on which
 102 the attack of 2-methoxy thiophenol (2) took place (Scheme 2B).
 103 Following this approach, the same group developed a
 104 molecular motor-based dynamic organocatalyst 5 (Scheme 3A)
 105 able to accelerate the Henry reaction of nitromethane 6 with
 106 α,α,α -trifluoroketones such as trifluoroacetophenone 7, with
 107 high control of the enantioinduction (Scheme 3B).⁸ For this

second-generation catalyst 5, the same kind of isomerization 108
 steps were necessary to obtain its 360° rotation, but the phenyl 109
 spacers between the motor core and catalytic moieties were 110
 removed with respect to 1. In fact, catalyst 1 showed poor 111
 catalytic performance in the Henry reactions both in terms of 112
 activity and stereoselectivity. Thus, it was decided to bring the 113
 catalytically active units (i.e., thiourea and DMAP) in closer 114
 proximity in order to achieve a more effective cooperative action 115
 between these two functionalities. 116

As in the case of 1, the *E*-state of 5 proved to be almost inactive 117
 and without stereocontrol as a catalyst for the Henry reaction 118
 between nitromethane and α,α,α -trifluoroketones. On the other 119
 hand, the two *Z*-states ((R,R)-(M,M)-Z-5 and (R,R)-(P,P)-Z-5), 120
 in which the catalytic active sites are in closer proximity, were 121
 once again effective in catalysis, affording the corresponding 122
 products with opposite enantioselectivity (*er* up to 86:14 for (R)- 123
 8 and *er* up to 79:21 for (S)-8) in excellent yields (93% for (R)- 124
 8 and 92% for (S)-8). For catalyst (R,R)-(M,M)-Z-5, the use of 125
 toluene as reaction media was mandatory both in catalysis and in 126
 its isomerization to (R,R)-(P,P)-Z-5, because only in this solvent 127

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**



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

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

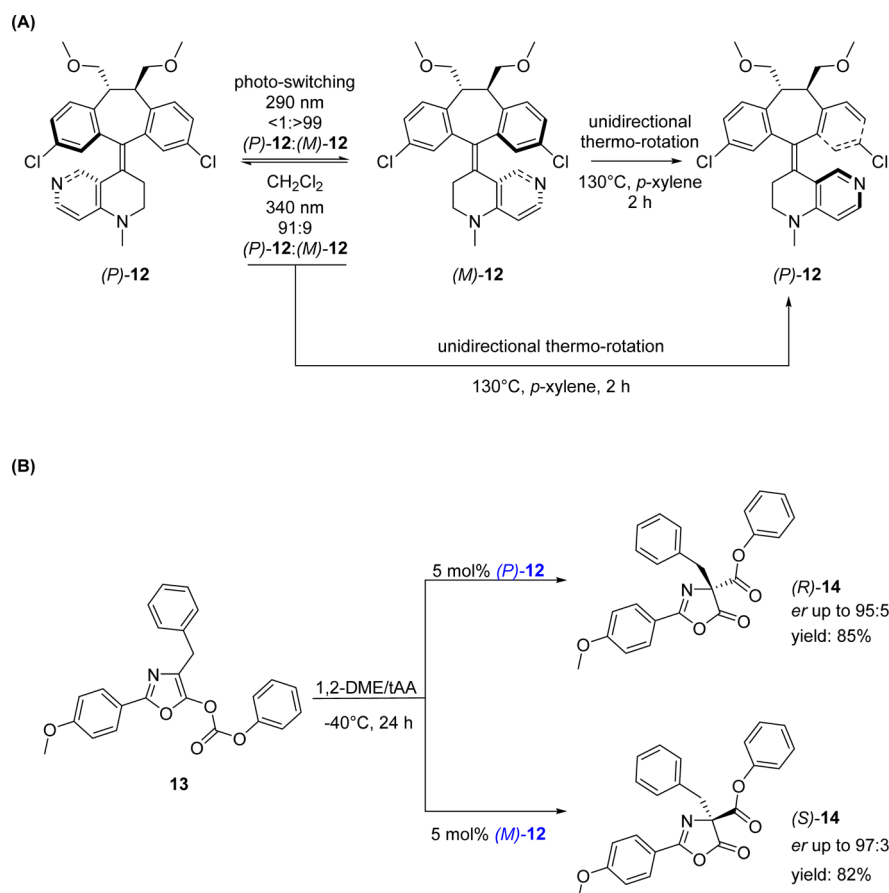
133 In fact, light and heat-induced changes in geometry and
134 helicity of **9** furnished a switchable ligand that exhibited excellent
135 selectivity in the Pd-catalyzed desymmetrization reaction of
136 meso-biscarbamate **10** (Scheme 4B). In particular, under
137 optimized conditions, the Pd complex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

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



172 very efficient chiral catalyst for the Steglich rearrangement of **13**,
 173 giving the corresponding C-carboxylated product (R)-**14** in 85%
 174 yield with a high level of enantioselectivity (*er* up to 95:5). On the
 175 other hand, almost pure (M)-**12** catalyzed in good yield (82%)
 176 the rearrangement of **13** to give the opposite product (S)-**14** with
 177 the same level of enantioselectivity (*er* up to 97:3). To gain
 178 further insights into the origin of enantiocontrol of this
 179 asymmetric catalytic process, the authors carried out DFT
 180 calculations on the transition state assembly of the incipient ion
 181 pair, which would be formed between pyridinium cation **12a** and
 182 enolate anion **13a** (Scheme 6A), as postulated in previous
 183 mechanistic studies of the Steglich rearrangement.¹² The
 184 molecular simulations indicated that synclinal *Re*-face attack is
 185 favored with catalyst (P)-**12** due to greater HOMO–LUMO
 186 interactions with minimal stereoelectronic repulsion (Scheme
 187 6B).

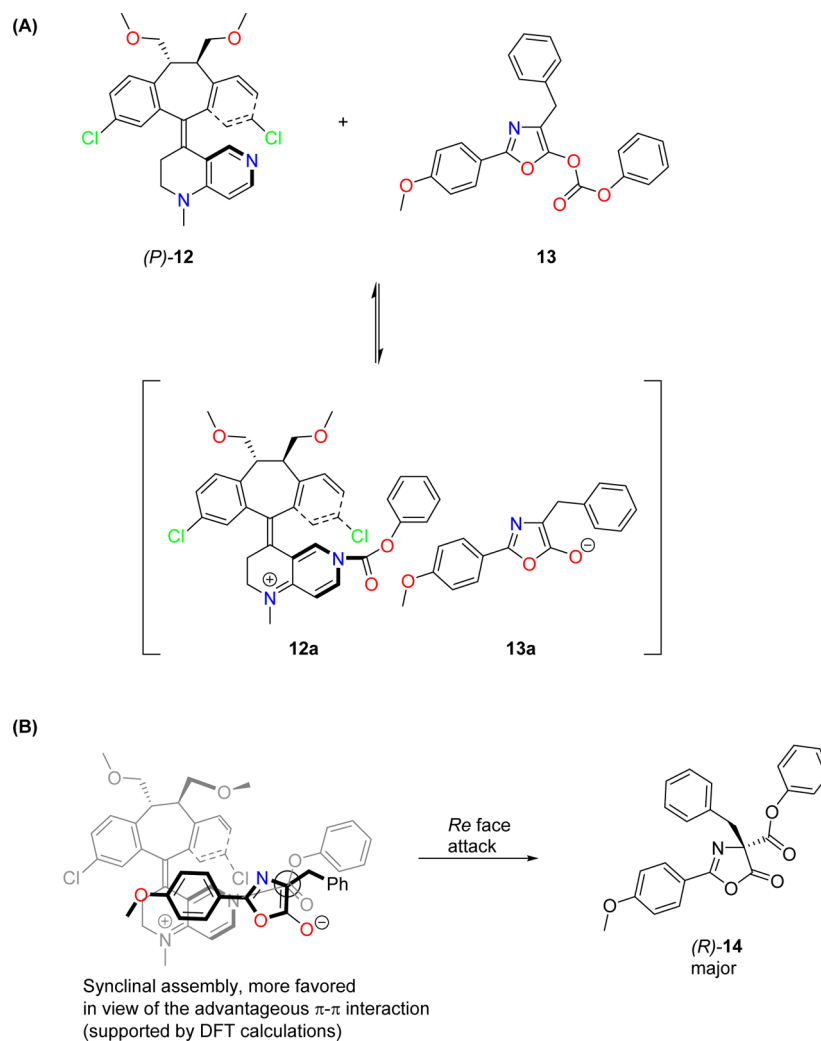
188 In 2015, Storch and Trapp reported an example of a
 189 stereochemically flexible diastereomeric rhodium(I) catalyst
 190 based on a *tropos* (i.e., chirally flexible) ligand.¹³ Such a catalyst
 191 provided access to both enantiomeric products of asymmetric
 192 hydrogenations of prochiral (*Z*)- α -acetamidocinnamates by
 193 changing solely the applied temperature. The catalytic system
 194 was thought to be complementary to the one introduced by
 195 Mikami and Aikawa¹⁴ in an attempt to overcome some of its
 196 limitations (Scheme 7).

197 Mikami and Aikawa's approach of asymmetric (de)activation
 198 of racemic catalysts bearing a *tropos* ligand is based on the use of
 199 catalysts with stereochemically flexible ligands, for example,
 200 *tropos* biphenyls, in combination with a suitable chiral activator

201 that forms a diastereomeric metal complex with the catalyst and 201
 202 shifts the equilibrium toward one diastereoisomer. In this way, 202
 203 the chiral activator could not only control the chirality of racemic 203
 204 catalysts but also lead to the formation of a catalytic species with 204
 205 higher enhanced catalytic properties. However, a limitation of 205
 206 this elegant approach is that the activator with opposite 206
 207 configuration is required to obtain the opposite enantiomeric 207
 208 product, because the absolute configuration of the activator 208
 209 determines the chirality of the product. To overcome this 209
 210 limitation, Storch and Trapp proposed to functionalize a *tropos* 210
 211 biphenyl ligand core with a homochiral auxiliary substituent as 211
 212 the chiral directing group. By binding this auxiliary to the ligand's 212
 213 core, the chiral information is continuously transferred to the 213
 214 stereochemically flexible chiral axis of the *tropos* biphenyl, which 214
 215 shifts the stereoisomeric ratio away from the 1:1 equilibrium. The 215
 216 stereogenic center of the chiral auxiliary has to be located in 216
 217 proximity to the linking group in order to maximize stereo- 217
 218 selective interactions. In addition, the chiral auxiliary has to 218
 219 possess an expanded aryl group that aligns the adjacent phenyl 219
 220 rings of the metal bound diphenylphosphine group. The effective 220
 221 catalyst is then obtained by coordination of a metal precursor to 221
 222 the pair of diastereomeric ligand cores, thus freezing the 222
 223 equilibrium ratio of the stereoisomers. Eventually, the ratio of 223
 224 epimerizing diastereomers could be, in principle, controlled by 224
 225 external parameters such as temperature. 225

226 Following this principle, the authors synthesized the stereo- 226
 227 chemically flexible ligand 2,2'-bis(diphenylphosphino)-[1,1'- 227
 228 biphenyl]-3,3'-diol **15** as the chiral ligand core (as a racemate, 228
 229 **15** was functionalized with (S)-naproxen as 229 s8

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



230 the chiral auxiliary to afford the modified diastereomeric ligands
 231 ($R_{ax,S,S}$)-16 and ($S_{ax,S,S}$)-16, thus shifting the ligand equilibrium
 232 ratio from 50:50 (for 15) to 61:39 (for 16) as a result of a central-
 233 to-axial chirality transfer of the chiral auxiliary to the axially chiral
 234 biphenyl core. Binding the ($R_{ax,S,S}$)-16 and ($S_{ax,S,S}$)-16 ligands
 235 to rhodium afforded the diastereomeric catalysts ($R_{ax,S,S}$)-17 and
 236 ($S_{ax,S,S}$)-17, respectively. Complexation of the rhodium resulted
 237 in the freezing of the diastereomeric ratio, which did not undergo
 238 any change at room temperature. Interestingly, by heating at 70
 239 °C for 6 h the diastereomeric mixture ($R_{ax,S,S}$)-17/($S_{ax,S,S}$)-17
 240 (61:39) yielded the minor isomer ($S_{ax,S,S}$)-17 with a purity
 241 greater than 99%. The reaction progress was followed by $^{31}\text{P}\{^1\text{H}\}$
 242 and ^1H NMR spectroscopy. Hence, according to this behavior, to
 243 come back to the initial diastereomeric ($R_{ax,S,S}$)-17/($S_{ax,S,S}$)-17
 244 ratio of 61:39, the system would require decomplexation of
 245 rhodium, ligand re-equilibration, and recomplexation with
 246 rhodium, because the diastereomeric ratio catalyst ($R_{ax,S,S}$)-17/
 247 ($S_{ax,S,S}$)-17 remains <1: >99 upon cooling.

248 The catalytic properties of either the ($R_{ax,S,S}$)-17/($S_{ax,S,S}$)-17
 249 (61:39) mixture or almost pure complex ($S_{ax,S,S}$)-17 were
 250 assessed in the asymmetric hydrogenation of a prochiral
 251 substrate such as the (*Z*)-methyl- α -acetamidocinnamate
 252 (MAC, 18; Scheme 8B). Upon optimization of hydrogenation
 253 conditions, the use of the mixture complexes ($R_{ax,S,S}$)-17/

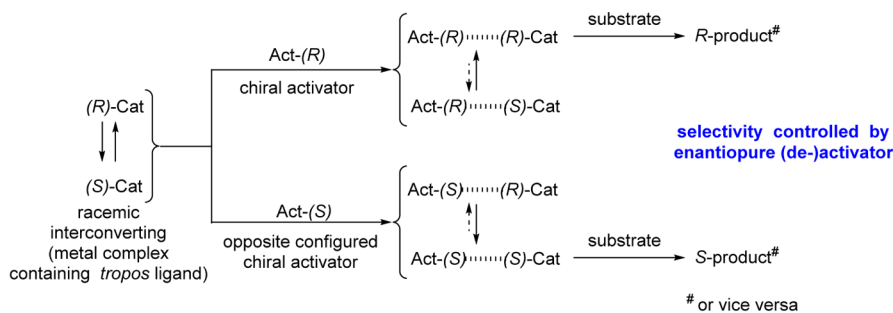
($S_{ax,S,S}$)-17 (61:39) as catalysts in CDCl_3 at -40 °C and under 254
 an initial hydrogen pressure of 10 atm gave the complete 255
 conversion of substrate 18 in the *N*-acetylphenylalanine methyl 256
 ester 19 enriched in the enantiomer *R* (*er* up to 87:13). This 257
 enantiomeric excess of 74% is equivalent to an amplification 258
 factor (f_{amp}) of 3.4, f_{amp} being defined as the ratio of the 259
 enantiomeric excess of the reaction product and the diastereo- 260
 meric excess of the catalyst. This nonlinear chiral amplification¹⁵ 261
 is a significant result because it demonstrates that small 262
 deviations from a 1:1 equilibrium of a proposed catalytic system 263
 seems to be enough to generate high stereoselectivity. In 264
 contrast, using the almost pure ($S_{ax,S,S}$)-17 as a catalyst, under 265
 similar conditions but at a higher temperature (-10 °C), the 266
 opposite enantiomer (*S*)-19 was obtained with an *er* up to 96:4. 267
 Although the chiral switchability of catalyst 17 is “unidirectional,” 268
 the concept proposed by Trapp would in principle be 269
 directly transferable to other kinds of asymmetric catalyzed 270
 reactions. Moreover, the achievement of a reversal enantiose- 271
 lectivity by using solely a temperature control is a rather rare 272
 phenomenon in asymmetric synthesis or catalysis.¹⁶ 273

3. REDOX-DRIVEN CHIRAL SWITCHABLE CATALYSTS

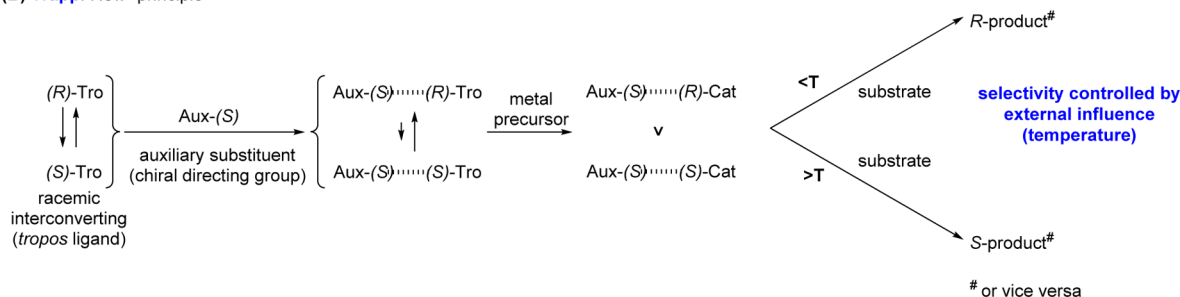
In 2012, a redox-driven chiral switchable catalyst was reported by 274
 Canary and co-workers (Scheme 9).¹⁷ Inspired by their previous 275 89

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

(A) Mikami: Asymmetric (de-)activation *tropos*



(B) Trapp: New "principle"



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 enantioselectivities were not improved.

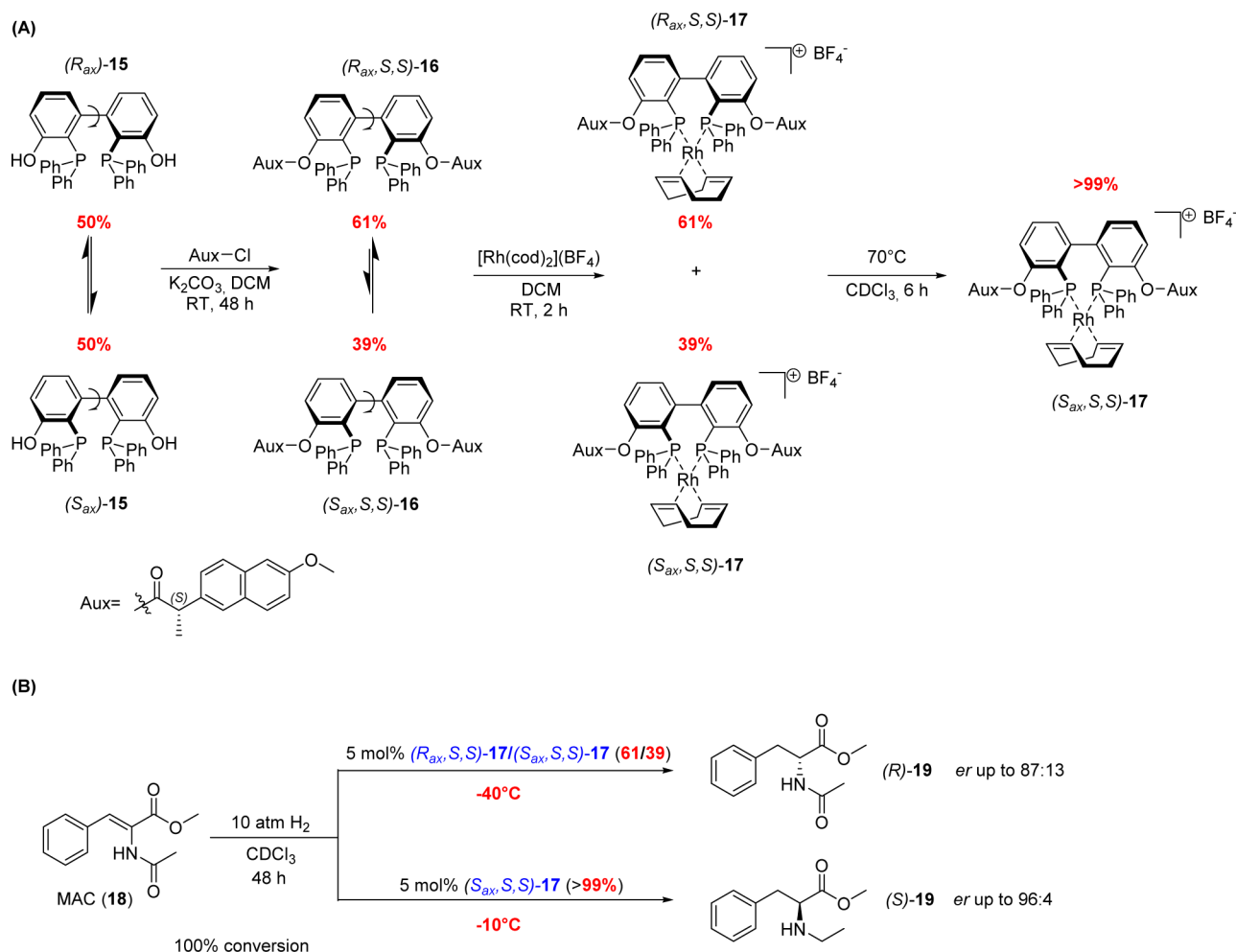
Canary's group demonstrated that catalyst **21** is capable of independent, dial-in control of the absolute stereochemistry when two similar nitrostyrenes were used for the Michael addition reactions. In fact, by in situ oxidation and reduction of the catalyst, it was possible to access all four possible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

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

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



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

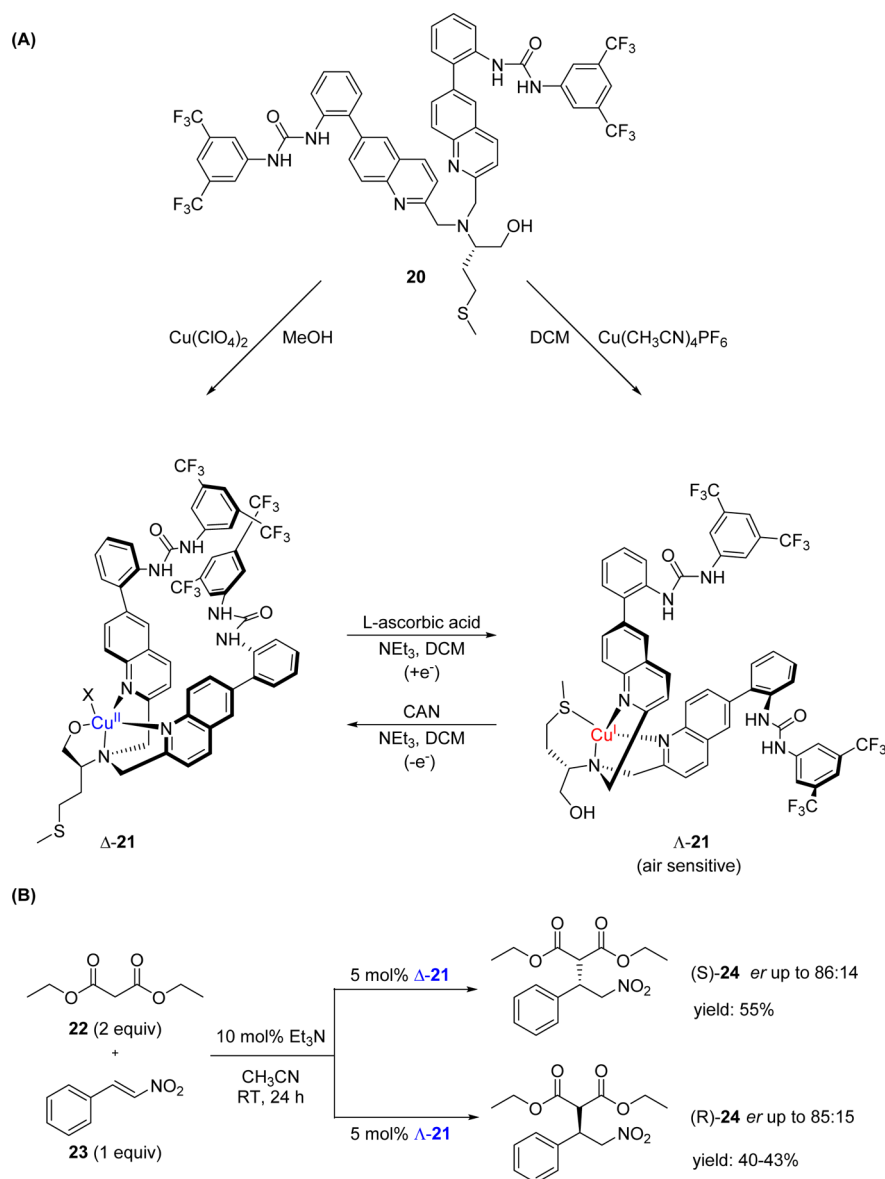
358 By employing ligand (*P*)-27 in palladium catalyzed hydro-
 359 silylation of styrene, the product (*S*)-31 was obtained in 94%
 360 yield with *er* up to 98.5:1.5 without the use of a solvent. In
 361 contrast, using ligand (*M*)-27 for the same reaction but in a
 362 mixture of 1,1,2-TCE/toluene (3:1) as a solvent, the opposite
 363 enantiomer (*R*)-31 was produced in 93% yield with *er* up to
 364 96.5:3.5. In this case, the use of a 1,1,2-TCE/toluene mixture
 365 (3:1) as reaction media was found to be mandatory for
 366 maintaining the left-handed helical structure of ligand (*M*)-27
 367 during the longer reaction time (72 h) required for the reaction.
 368 In the hydrosilylation reaction carried out under neat
 369 conditions, polymeric ligand (*P*)-27 formed with palladium an
 370 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-naphthalenephos-
 phonic 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 K₃PO₄ and [PdCl(π -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 K₃PO₄ and Pd₂dba₃ 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

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**



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

401 The chiral switchable ligand **29** (see Scheme 11) was active in
402 Pd-catalyzed asymmetric silaborative cleavage of *meso*-methyl-
403 encyclopropanes (Scheme 14).²⁷

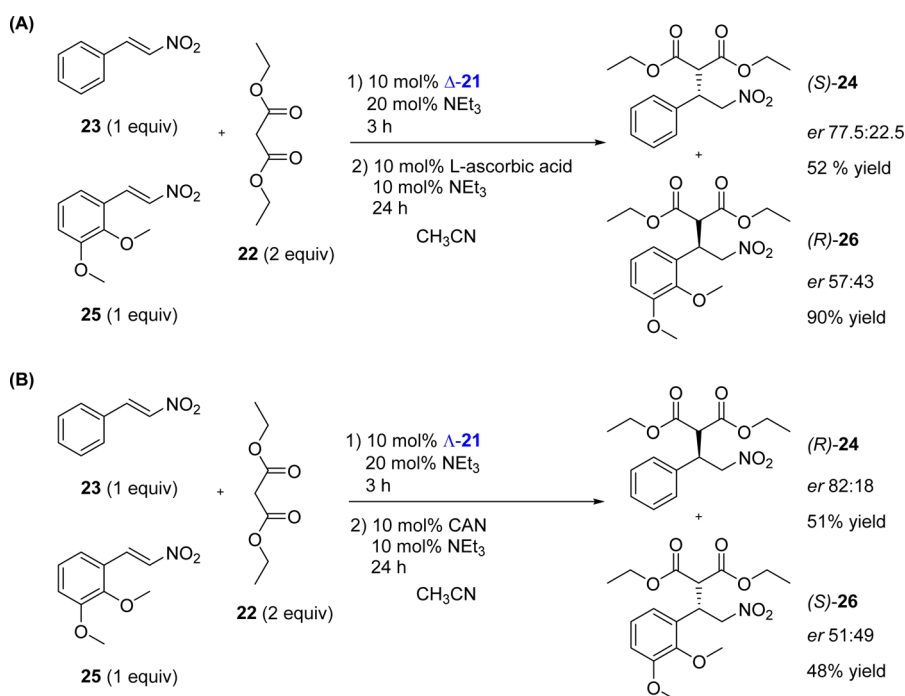
404 By reacting, at 50 °C in toluene, the bicyclic *meso*-
405 methylenecyclopropane **35** (7-methylenebicyclo[4.1.0]heptane)
406 with the silylborane **36** in the presence of a catalytic amount of
407 both palladium source and ligand (*P*)-**29**, the silaboration
408 product (1*S**,2*S**)-**37** was obtained in good yield (84%) and
409 high enantioselectivity (*er* up to 98:2). Hence, ligand (*P*)-**29** was
410 switched to a left-handed helical ligand (*M*)-**29** by dissolving it in
411 a 3:1 mixture of 1,1,2-TCE and toluene at 60 °C for 24 h. Upon
412 the use of a palladium complex of the inverted (*M*)-**29**, under the
413 same reaction conditions employed for (*P*)-**29**, the asymmetric
414 silaborative cleavage of **35** with **36**, leading to the opposite
415 enantiomer (1*R**,2*R**)-**37**, was found to be significantly slower.

The reaction rate could be reasonably improved under solvent- 416
free reaction conditions, but enantioselectivity decreased (*er* 417
87.5:12.5), likely due to an *M*-to-*P* helix reinversion during the 418
reaction at 50 °C. Eventually, by using a small amount of 1,1,2- 419
TCE as an additive, which was necessary to maintain the left- 420
handed helical structure of (*M*)-**29** during the reaction, the 421
enantiomer (1*R**,2*R**)-**37** was obtained in similar yield (80%) 422
and higher enantioselectivity (*er* up to 95.5:4.5) with respect to 423
(1*S**,2*S**)-**37**. 424

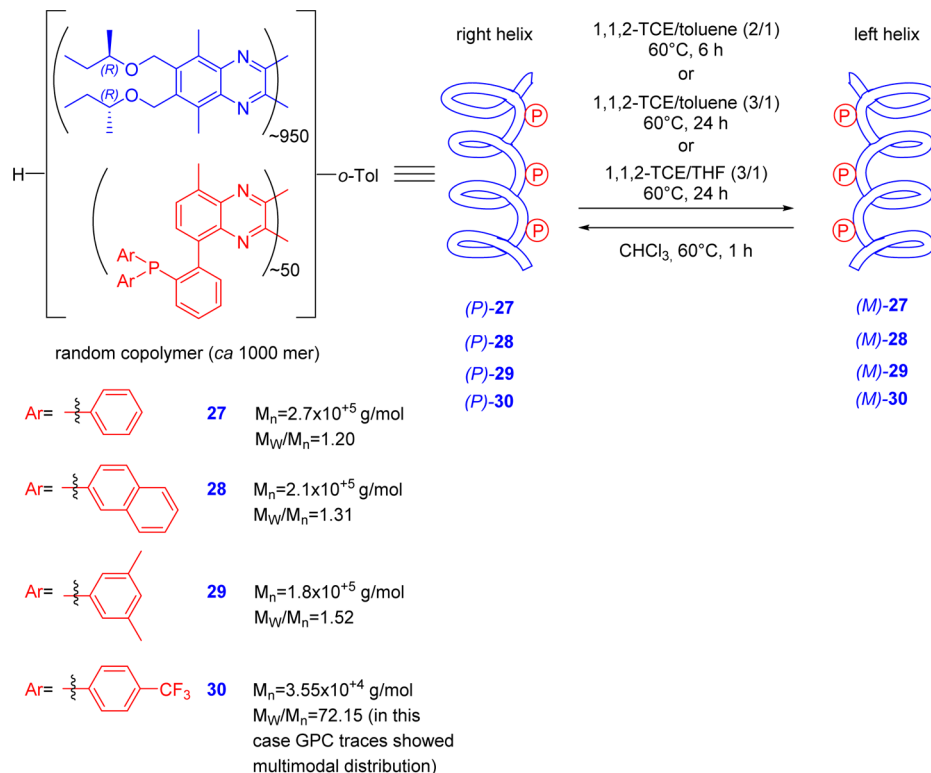
The chiral switchable ligand (*P*)-**29** bearing 4- $\text{CF}_3\text{C}_6\text{H}_4$ 425
groups (see Scheme 11) was found effective in the asymmetric 426
SMC of 1-bromo-2-naphthoate derivatives and arylboronic acid 427
(Scheme 15).²⁸ 428 s15

This asymmetric SMC of the naphthyl bromide bearing a 2,4- 429
dimethyl-3-pentyl ester **38** and 1-pyreneboronic acid **39** afforded 430
the corresponding axially chiral biaryl product (*S*)-**40** in high 431
yield (96%) and high enantioselectivity (*er* up to 97.5:2.5). 432
However, the presence of a bulky ester group such as 2,4- 433
dimethyl-3-pentyl ester in naphthoate substrates was found 434

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

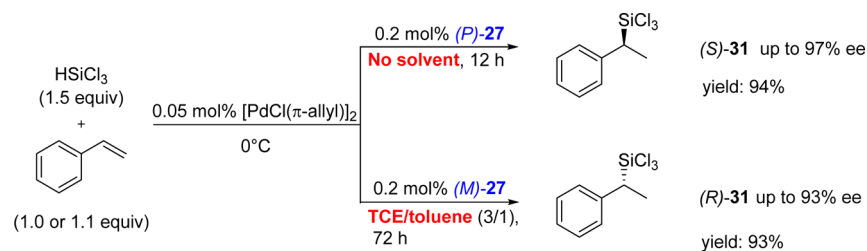


435 crucial to achieving high enantioselectivities. In addition, this
436 ester functionality can be readily converted into other functional
437 groups. Stereocomplementary synthesis of the opposite
438 enantiomer product (*R*)-40 was achieved by employing the
439 helically inverted ligand (*M*)-30, which was obtained by heating
440 (*P*)-30 in a mixture of 1,1,2-TCE/THF (3:1) at 60 °C for 24 h.

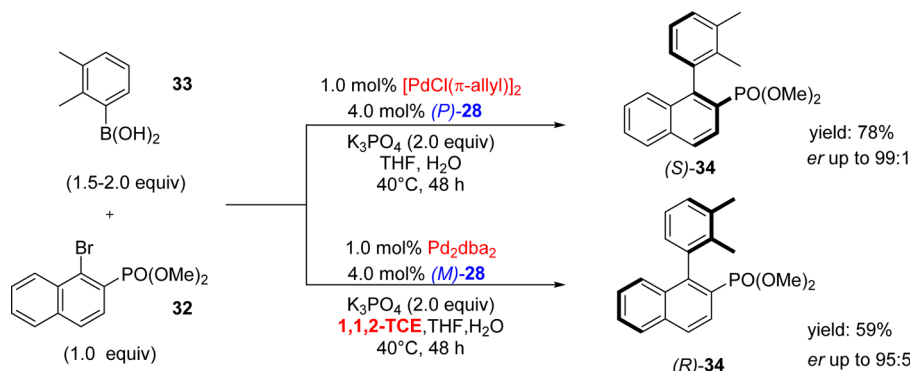
(*R*)-37 was obtained in high yield (93%) with high
441 enantioselectivity (*er* up to 95.5:4.5). The presence of 1,1,2-
442 TCE in the reaction medium was found again to be mandatory to
443 maintaining the left-handed helical structure of (*M*)-30. 444

As the use of halogenated solvents has to be avoided in Pd-
445 catalyzed reactions such as SMC, it was demonstrated that a 446

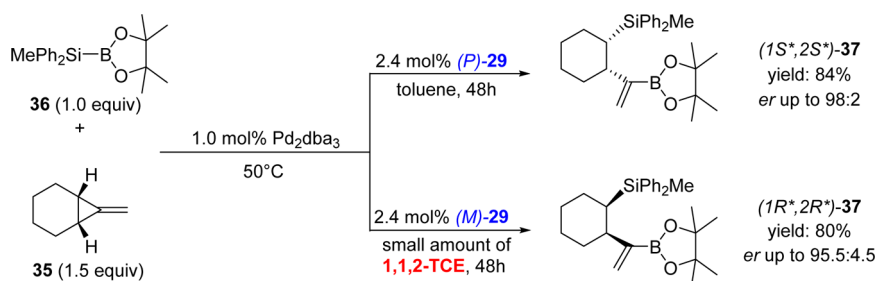
Scheme 12. Control of the Enantioselectivity of a Palladium Catalyzed Asymmetric Hydrosilylation Using Solvent-Driven Chiral Switchable Ligand 27



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



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

452 The ligand **41** showed an effective solvent-dependent helix
453 inversion between 1,2-dimethoxyethane (1,2-DME, *M*-helix)
454 and methyl *tert*-butyl ether (MTBE, *P*-helix) by heating it for 24 h
455 at 60 °C. Thus, by carrying out the SMC of compound **32** and 1-
456 naphthyl-boronic acid **42** at 40 °C with K₃PO₄ and Pd₂dba₃, both
457 enantiomeric biaryls were obtained in high *er* employing 1,2-
458 DME (*er* up to 95.5:4.5 for (*R*)-**43**) and MTBE (*er* up to 96.5:3.5
459 for (*S*)-**43**) as solvents, albeit the yields were moderate (45% for
460 (*R*)-**43**, and 71% for (*S*)-**43**). However, the enantioselectivities
461 are comparable to those previously obtained with ligands **28** and
462 **30** using as solvents either THF or a mixture 1,1,2-TCE/THF.

463 The solvent-dependent helical inversion of copolymers of
464 poly(quinoxaline-2,3-diyl) was proven also in hydrocarbon
465 solvents. In particular, the random copolymer (about 1000-
466 mer) of poly(quinoxaline-2,3-diyl) containing (*S*)-3-octylox-
467 ymethyl side chains and diphenylphosphino pendants **44**

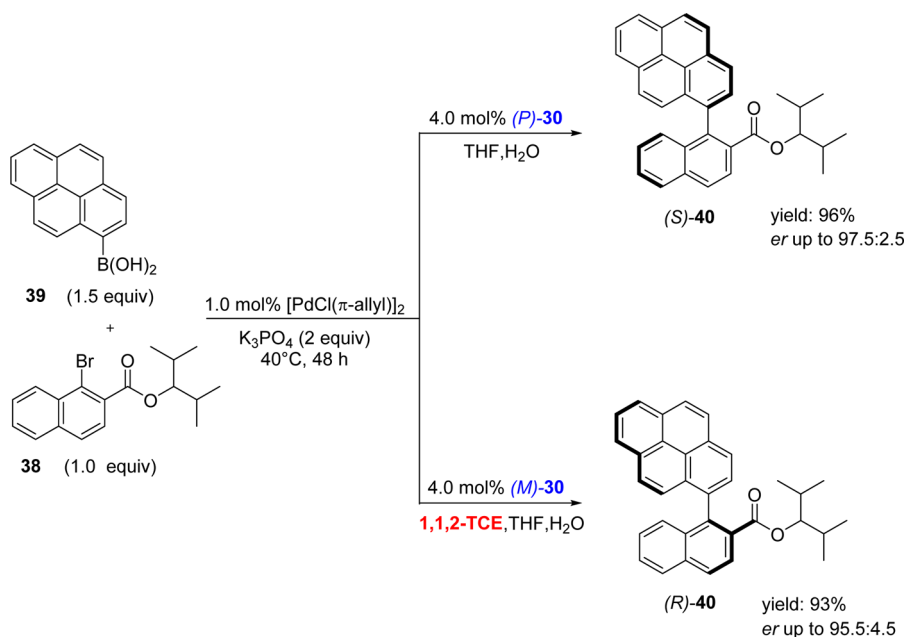
exhibited solvent-dependent helical inversion switching from *n*- 468
octane to cyclooctane (Scheme 17).³⁰ 469 s17

By employing ligand (*M*)-**44** in palladium catalyzed hydro- 470
silylation of styrene in *n*-octane, the product (*R*)-**31** was afforded 471
in 88% yield with *er* up to 97:3. When the same reaction was 472
carried out in cyclooctane, causing a switch of the helical sense 473
from (*M*)-**44** to (*P*)-**44**, the product (*S*)-**31** with opposite 474
stereochemistry was obtained in 89% yield with *er* up to 95:5. 475

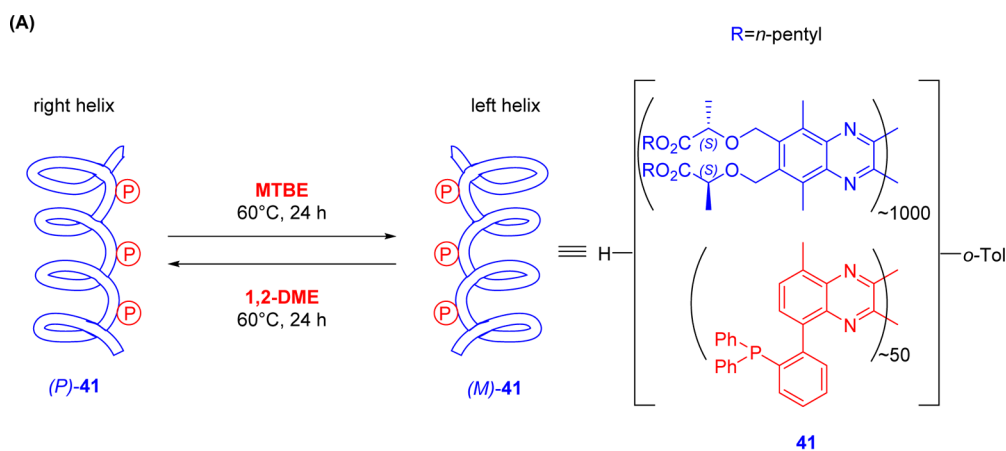
Last but not least, Suginome and co-workers demonstrated 476
that the supramolecular approach of helical majority rules³¹ is 477
applicable to the random copolymer (about 1000-mer) of 478
poly(quinoxaline-2,3-diyl) containing octan-2-yloxy side chains 479
and diphenylphosphino pendants **45**, in which the chiral side 480
chains were derived from (*R*)-2-octanol with a low enantiomeric 481
purity (23%; Scheme 18).³² 482 s18

Measurement of the CD spectrum in chloroform of **45** 483
revealed that the amplification of chirality due to majority rules 484
was enough for adopting a right-handed helical structure: (*P*)-**45** 485
(screw-sense excess >99%). As in the case previously discussed, 486
the screw-sense was easily inverted to the left (*M*)-**45** by heating 487
(*P*)-**45** in a mixture (3:1) of 1,1,2-TCE and toluene or 1,1,2-TCE 488

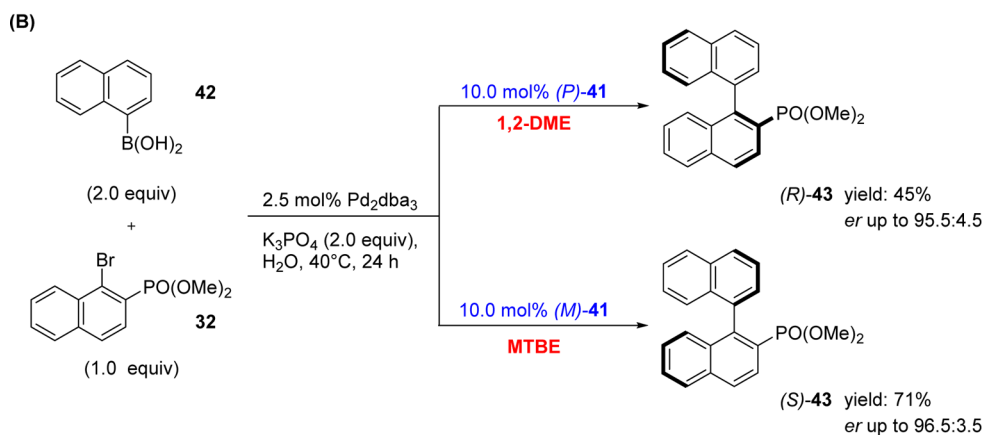
Scheme 15. Control of the Enantioselectivity of an Asymmetric Suzuki–Miyaura Cross-Coupling Using the Solvent-Driven Chiral Switchable Ligand 30

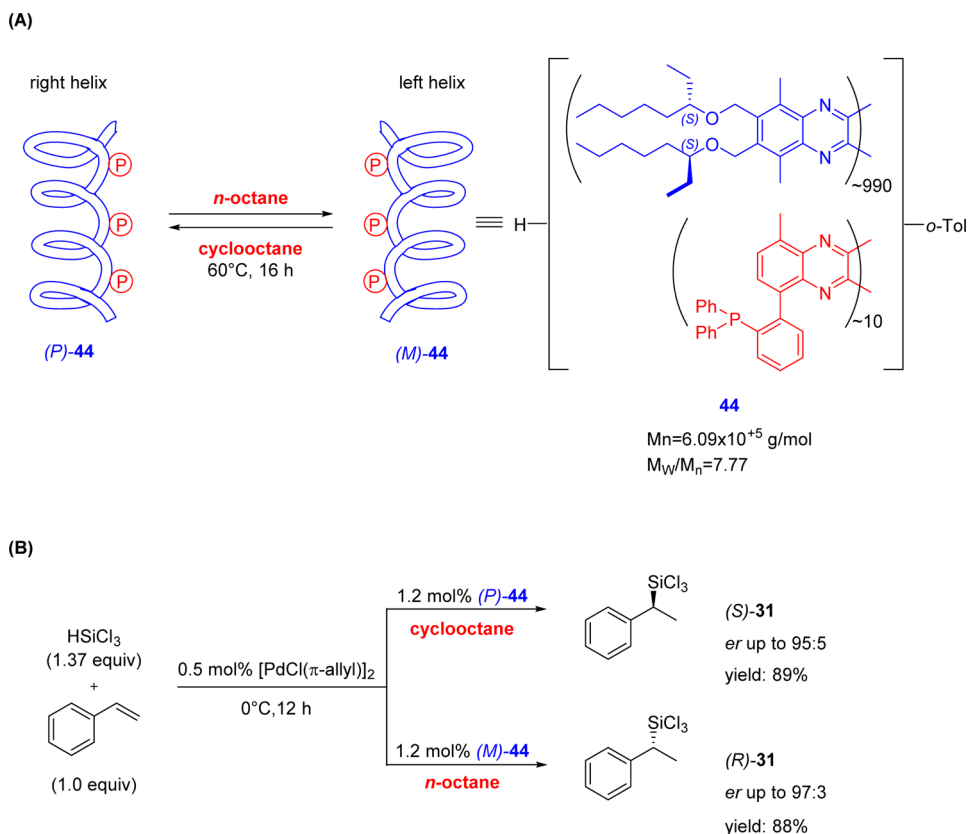


Scheme 16. (A) Structure of the Solvent-Driven Chiral Switchable Polymeric Ligand 41 and (B) Control of the Enantioselectivity of an Asymmetric Suzuki–Miyaura Cross-Coupling Using Ligand 41



Molecular weights were not determined by GPC, because of the exclusion limit of the column.



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**

489 and THF at 60 °C for 24 h. The polymeric ligand **45** was
 490 efficiently employed in both asymmetric hydrosilylation of β -
 491 methylstyrene **46** and asymmetric SMC of **32** and **42**. By using
 492 (*P*)-**45** in hydrosilylation of **46** without solvent, the product (*S*)-
 493 **47** was afforded in 89% yield with *er* up to 97:3, while when the
 494 helical sense was switched from (*P*)-**45** to (*M*)-**45** the opposite
 495 enantiomer (*R*)-**47** was afforded in 90% yield with *er* up to
 496 97.5:2.5 employing 1,1,2-TCE/toluene (3:1) as a reaction
 497 medium. As to the asymmetric SMC of **32** and **42**, such a
 498 reaction carried out in the presence of (*P*)-**45** or (*M*)-**45**
 499 confirmed the obtainment of an asymmetric amplification. In
 500 particular, in the presence of (*P*)-**45**, the axially chiral product
 501 (*S*)-**43** was obtained in 41% yield with high enantioselectivity (*er*
 502 up to 96.5:3.5). When (*M*)-**45** with inverted helical chirality was
 503 used, the opposite product (*R*)-**43** was afforded in 74% yield with
 504 the same level of enantioselectivity (*er* up to 96:4). As expected,
 505 the assistance of 1,1,2-TCE in the reaction media was found to be
 506 mandatory to maintain the left-handed helical structure of the
 507 ligand.

508 Finally, it should be noted that other catalytic systems have
 509 been demonstrated to exhibit solvent-dependent stereoselectiv-
 510 ity,³³ but in all of these cases the nature of the catalyst is not
 511 switchable. In some cases, the origin of solvent-dependent
 512 stereodiscrimination has been attributed to effects of the
 513 enthalpy–entropy compensation or addition of other additives
 514 or charge stabilization factor of solvents.

5. SUMMARY AND OUTLOOK

515 In this Perspective, we addressed the very recent achievement
 516 reached in chiral switchable catalysis to obtain dynamic dual
 517 enantiocontrol in asymmetric synthesis. Since many pharmaco-

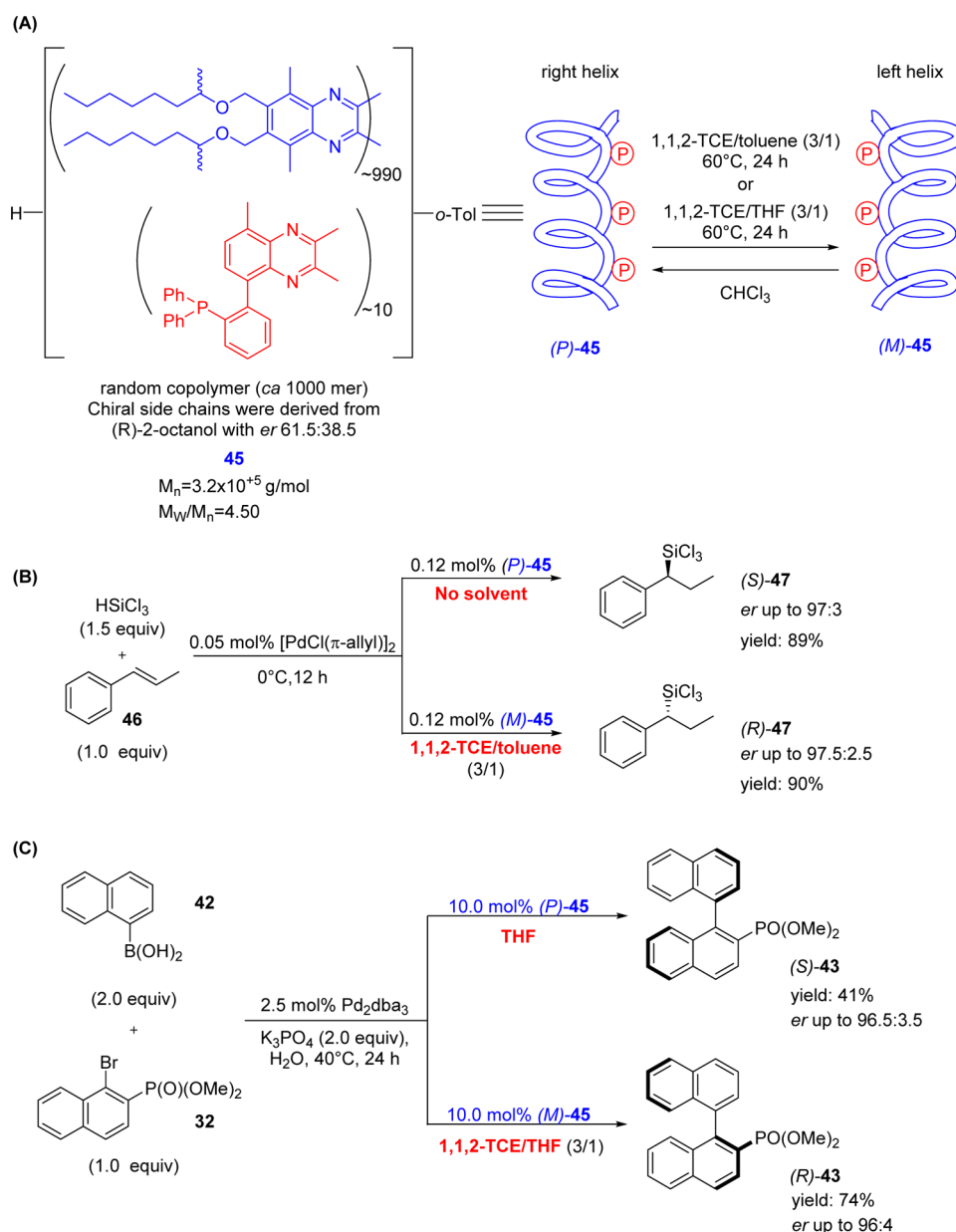
logical investigations often need both enantiomers to study
 potentially different activities and side effects,³⁴ attaining dual
 enantiocontrol using this approach could become very attractive,
 and moreover it could eliminate the need for a parallel synthesis
 of the opposite enantiomer of the designed 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

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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