Asymmetric Catalysis

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The Even-Handed Approach: Strategies for the Deployment of Racemic Chiral Catalysts

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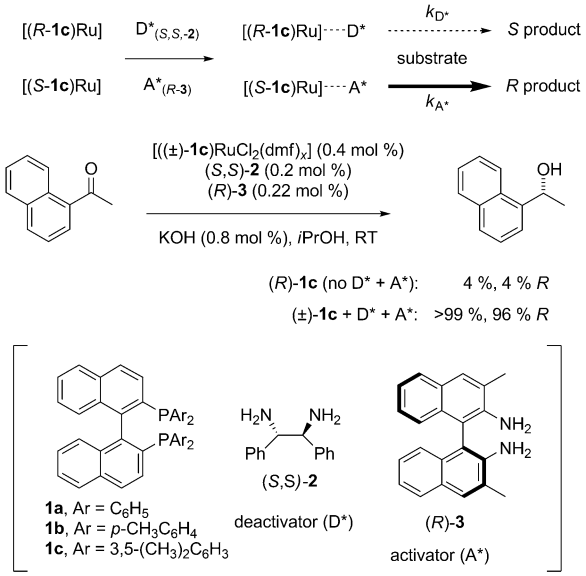
***A**symmetric catalysis is predominantly associated with the use of enantiomerically pure chiral ligands and catalysts. Although racemic chiral catalysts have been employed quite extensively in polymerization, their utility in mainstream organic synthesis and catalyst development has arguably been rather overlooked. This Minireview collates various themes for the strategic application of racemic ligands and catalysts, ranging from the estimation of selectivity and determination of enantiomeric excess, through to control of regio- and stereochemical outcomes, and mechanistic studies. What emerges is a clear picture that, in isolation or in concert with enantiopure catalysts, the "even-handed" approach has much to offer.*

1. Introduction

Although mechanistic insight and high-throughput methods increasingly contribute to the intuition, screening, and serendipity that are currently central to asymmetric catalysis, the synthesis of the requisite novel ligands and catalysts can be the limiting factor. Homogeneous asymmetric catalysis, for example, remains heavily dependent on precious metals, yet it is frequently the enantiopure ligand that commands the most expense. Herein, we review applications involving the racemic form of chiral ligands. This "even-handed" approach can be of considerable utility in synthesis, a liberating method for novel-catalyst screening, and can powerfully augment mechanistic investigations involving the enantiopure form of the catalyst.

Before we discuss turnover by racemic catalyst systems, we consider "preferential discrimination", one of the best-developed alternatives to the direct use of enantiopure catalysts. This very powerful approach has been extensively reviewed,[1] and we only illustrate it briefly by reference to asymmetric hydrogenation using 2,2′-bis(diarylphosphano)-1,1′-binaphthalene (binap) ligands (**1**; Scheme 1).[2] In asymmetric deactivation, a single enantiomer of a chiral "poison" (D*) selectively deactivates one enantiomer of the racemic catalyst (Scheme 1), thus leaving the opposite enantiomer free to catalyze the desired reaction. The concept was pioneered by Brown et al.[3] and further explored by Faller and Tokunaga[4] in the Ru-catalyzed kinetic resolution of 2-cyclohexenol, where (1*S*,2*R*)-ephedrine was found to selectively deactivate the *S* enantiomer of [((±)-**1a**)$RuCl_2$-$(dmf)_x$].



Scheme 1. Activation–deactivation strategy employing diamines as a selective deactivator (D*; **2**) and activator (A*; **3**) in the Ru-catalyzed asymmetric transfer hydrogenation using racemic xylylbinap (±)-**1c**. dmf = dimethylformamide.

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Asymmetric activation is the antithetical approach and can even be effective with a substoichiometric amount of activator (A*). For example, Noyori, Mikami, and co-workers[5] demonstrated that the *R* enantiomer in [((±)-**1b**)$RuCl_2$-$(dmf)_x$] is selectively activated by diamine (*S*,*S*)-**2** to give a new catalyst that displays higher activity and selectivity than the enantiomerically pure catalyst. Activation and deactivation can be applied in tandem to maximize the differential activity of what were the two enantiomeric forms of the catalysts.

A prime example comes from Mikami et al.,[6] where (*S*,*S*)-**2** and (*R*)-**3** simultaneously activate and deactivate the *R* and the *S* enantiomers of [(**1c**)$RuCl_2(dmf)_x$], respectively, to engender a highly effective enantioselective hydrogenation of ketonic substrates (Scheme 1).

2. Polymerization

Historically it has been in the area of polymerization where racemic chiral catalysts have been most widely applied. This stems predominantly from the need to control relative rather than absolute configuration in the propagation of the polymerization, an ideal application for parallel turnover by enantiomeric catalysts, particularly when the monomer is chiral and racemic.

2.1. Prochiral Monomers

The presence of multiple active sites in the heterogeneous first-generation Ziegler–Natta catalysts, prompted the development of homogeneous, single-site, chiral catalysts capable of isospecific propylene polymerization.[7] In 1984 Ewen[8] explored the correlation between metallocene chirality and isotacticity in propylene polymerization using the racemic indenyl complex **4**.[9] Shortly after, the more stable metallocene systems **5** and **6**[10] were found to give *i*PP in much higher yield. A vast number of catalysts have now been explored,[11] and we highlight just a few examples in Scheme 2. Racemic catalysts have also been employed for stereocontrolled ring-opening metathesis polymerization (ROMP). For example, racemic Mo/alkylidene (±)-**14** effects ROMP of *meso* norbornadienes **15a** and **15b**,[17] such that the propagating intermediate repeatedly desymmetrizes the inserted bicycle with the same sense of asymmetric induction, thus maintaining isotacticity in the growing polymer chain (**16**; Scheme 3).

2.2. Chiral Monomers

The combination of a chiral monomer with a chiral catalyst leads naturally to the possibility of match/mismatch effects, and thus a kinetic resolution as polymerization proceeds. The outcome with a racemic catalyst is then a parallel kinetic resolution, in which the two enantiomers of monomer feed separate growing polymer chains at equal rates. A prime example of this is ring-opening polymerization (ROP) of lactide (**17**) to give polylactic acid (PLA), an important biodegradable polymer derived from renewable resources (Scheme 4). For the preparation of stereoregular highly crystalline polymers, enantiomerically pure L-**17** was initially required. However, the high cost of this material led to the development of racemic Al/salen catalysts *rac*-**18ab** and (±)-**19** that polymerize D,L-**17** to isotactic stereocomplex or stereoblock D,L-PLA (Scheme 4) with higher crystallinity than L-PLA.[18–22] A similar parallel kinetic resolution phenomenon is operative in the generation of isotactic polyethers from racemic terminal epoxides (**20**) using racemic (±)-**21** (Scheme 5).[23]

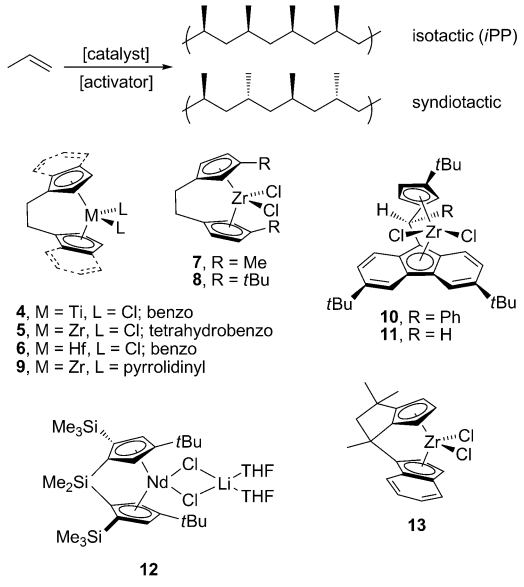
Louise Evans obtained her MSci (First Class) from the University of Bristol in 2007, after spending her third year working for DuPont (USA). She was then awarded a University of Bristol Scholarship to conduct research into palladium-catalyzed asymmetric allylic alkylation, under the supervision of Professor Guy Lloyd-Jones. She obtained her PhD in 2010 and is currently conducting post-doctoral studies with Professor Dudley Shallcross at Bristol; these are centered around the investigation of atmospheric chemistry, and include collaboration with Professor Lloyd-Jones for the synthesis of isotopically labelled alkyl halogen compounds and organonitrates.

Neil Hodnett obtained his MSci (First Class) in 1999 from the University of Bristol, having spent his third year studying at the Université de Montpellier II (France). He obtained his PhD from Bristol in 2003 under the supervision of Professor Guy Lloyd-Jones, where he contributed to the development of a method for screening racemic catalysts. In 2003 he joined the group of Professor Véronique Gouverneur at the University of Oxford to research a sequential antibody-catalyzed kinetic resolution/Pd-catalyzed oxidative ring-closure strategy for the synthesis of enantioenriched dihydropyranones. In 2004 he joined the Chemical Development group at GlaxoSmithKline where he continues to work today.

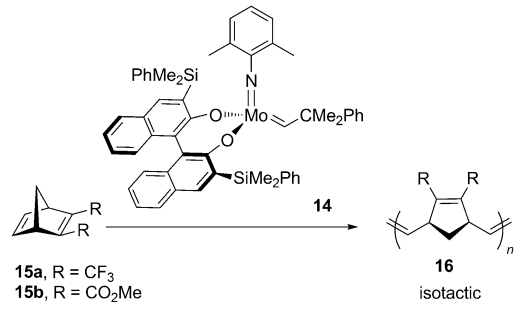
Guy Lloyd-Jones studied at Huddersfield Polytechnic (BSc. 1989) and Oxford University (D.Phil. with John M. Brown FRS, 1992) before tenure of a Royal Society western European postdoctoral fellowship, at the University of Basel, with Andreas Pfaltz. He joined the University of Bristol in 1996. His research interests center around organic and organometallic reaction mechanism and development; this being achieved by the strategic alliance of isotopic labelling with spectroscopy, spectrometry, kinetic analysis, and computation.

3. Prediction and Measurement

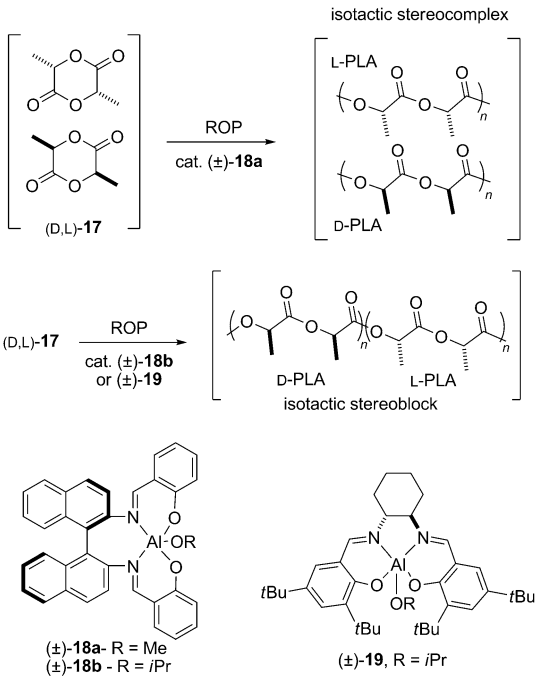
One of the least explored roles of racemic ligands/catalysts is in the evaluation of enantioselectivity and



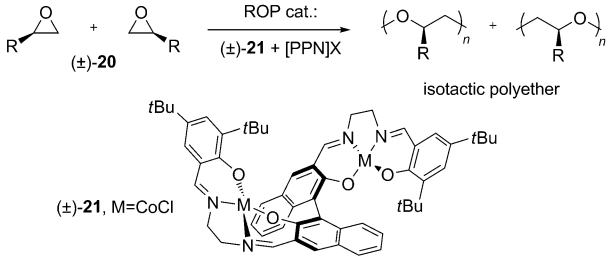
Scheme 2. Racemic (±)-*ansa*-metallocene complexes **4**,[8,9] **5**/**6**,[10] **7**/**8**,[12] **9**,[13,14] **10**/**11**,[15] and **12**/**13**,[16] in which the activity and polypropylene tacticity depend on the catalyst chirality. THF = tetrahydrofuran.



Scheme 3. Stereoselective ROMP of dienes **15** catalyzed by (±)-**14**.



Scheme 4. Ring-opening polymerization (ROP) of *rac*-lactide **17** to polylactic acid (PLA) by racemic aluminium alkoxide catalysts.



Scheme 5. Isospecific ROP of racemic epoxides **20** (R = Me, Et, vinyl, Ph, BnO, CF_3). [PPN]X = $[Ph_3P{=}N{-}PPh_3][tBuCH_2CO_2]$.[23]

enantiomeric purity. The underlying reason for this is probably that the basic concepts of enantioselective catalysis are deeply rooted in the use of enantiomerically pure single-catalyst systems, and thus graphically communicated in the form of single catalytic cycles. Racemic catalysts inherently present dual (mirror-image) cycles, with their relative turnover rates dependent on whether endogenous or exogenous chiral species can induce perturbation; this latter point provides us with opportunities for prediction and measurement.

3.1. Kinetic Resolution

The ability to evaluate the racemic form of a catalyst to predict the enantioselectivity potential of its single enantiomeric form prior to asymmetric synthesis or resolution would provide substantial opportunity to enhance the range of catalyst structures explored. In 2001, Lloyd-Jones and co-workers demonstrated that, under certain reaction conditions, racemic ligands could be evaluated to predict the selectivity obtained with their enantiopure form.[24] The method is specific to kinetic resolution processes; however, Pfaltz and co-workers have recently coupled this approach[25] to their mass spectrometric back-reaction analysis,[26] thus allowing far greater scope for potential application. The concept[24] is based on perturbation of a perfect parallel kinetic resolution, where enantiomeric substrates undergo turnover at identical rates by an enantiomer-selective dual catalyst, dual cycle, system. When the two cycles arise from a racemic catalyst, (+)-CAT and (−)-CAT (Figure 1), the following extremes can be envisaged: the catalyst is perfectly selective ($s = \infty$; Figure 1, left) for its matched enantiomer of substrate (**A**) or not selective at all ($s = 1$; Figure 1, right).

When $s = \infty$, the enantiomers enter mutually exclusive cycles, but when $s = 1$, they enter both cycles with equal efficiency. Thus, the greater the selectivity (s), the greater the partitioning between cycles, and the problem then becomes how to determine the extent of this partitioning. The solution to the problem came from study of systems where the catalyst

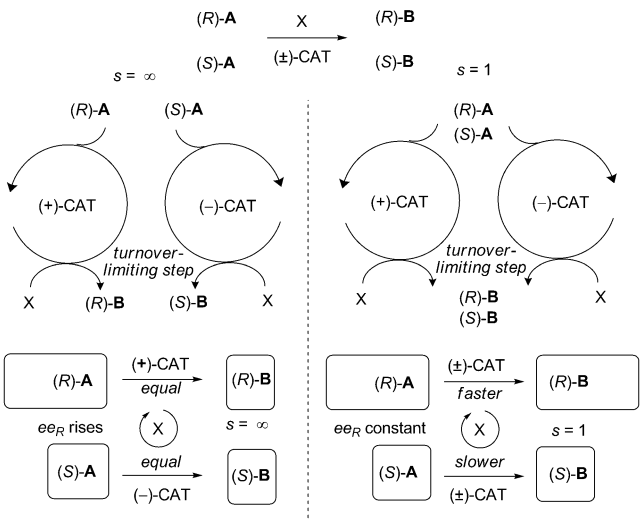


Figure 1. A generic racemic catalyst system converting scalemic substrate **A** (box size represents enantiomer proportion) into product **B**, under reaction conditions where [X] not [**A**] governs the turnover rates, at the extremes of kinetic resolution selectivity ($s=\infty$ versus $s=1$).[24]

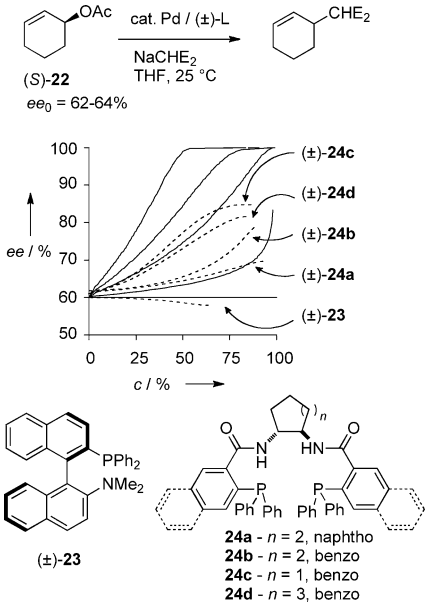


Figure 2. Change in *ee* value (*y* axis) of scalemic (*S*)-**22** as a function of its conversion in Pd-AAA (*c*, *x* axis) with *racemic* ligands **23** and **24a–d**. Dashed lines: data. Solid lines: ideal curves for $s=1$, 2, 5, 10, and 50. $E=CO_2Me$.

turnover rate is "governed" by another reactant, X, or on a mass transfer process.[27,28] Under these limiting reaction conditions, the turnover rates of the enantiomeric cycles no longer depend on the substrate concentration (or its enantiopurity) and the turnover rate of (+)-CAT is the same as that of (−)-CAT. By deployment of scalemic substrate ($0<ee_{\mathbf{A}}<100$), qualitative information on the magnitude of the *s* value can now be obtained (Figure 1).

When $s=\infty$, the partitioning is perfect and the catalyst removes (*R*)-**A** and (*S*)-**A** at an identical rate from the remaining scalemic pool, leading to a progressive increase in its *ee* value. In contrast when $s=1$, there is no partitioning and (*R*)-**A** and (*S*)-**A** compete for both cycles. They then react at rates proportional to their concentration and the *ee* value of the substrate (and product) remains constant. Kinetic simulations confirmed the feasibility of the strategy and revealed that an initial scalemic substrate of 60% *ee* was optimum for the qualitative distinction of the relative magnitude of *s* for a series of catalysts.[24] Evaluation of the kinetics[27] of a range of catalytic reactions[28] with potential for kinetic resolution and the requisite pseudo zeroth-order substrate dependency,[29] yielded two proof-of-concept experiments. The first was Pd-catalyzed asymmetric allylic alkylation (Pd-AAA), where nucleophilic attack of the π-allyl/Pd intermediate is frequently turnover limiting, with a pseudo zeroth-order dependency on the allyl ester concentration.[30]

The change in the *ee* value of cyclohexene acetate ((*S*)-**22;** $ee_0=62$–64%) on Pd-AAA with sodium dimethylmalonate using known ligands (±)-**23**, (±)-**24a**, and (±)-**24b** suggested (±)-**24b** to be superior (Figure 2). Although the shape of the Δee versus *c* curves indicated substantial deviation from ideality, use of the enantiomerically pure ligands confirmed that the predicted relative order of selectivity factors (*s*) were correct. Two new ligands, (±)-**24c** and (±)-**24d**, were then tested. Neither of the requisite diamines was commercially available, but both were readily prepared in racemic form. The results of the Δee versus *c* test performed with scalemic (*S*)-**22** suggested both ligands to be superior to **24b**. Resolution of 1,2-diaminocyclopentane and then evaluation of (*R*,*R*)-**24c** in the kinetic resolution of (±)-**22** yielded $s\geq100$, using the Kagan relationship,[31] this value is more than double that determined for (*R*,*R*)-**24b** under identical reaction conditions.[24]

The second proof-of-concept reaction was the Jacobsen–Katsuki epoxidation, for which a Mn/PhIO redox process was expected to be turnover limiting,[32] thus affording the requisite pseudo zeroth-order dependence in alkene substrate.[29] The results of the Δee versus *c* test performed with scalemic alkene (*R*)-**25** indicated that ligands **26a** and **26b** were both more selective than **26c** (Figure 3), just as would be expected from the well-established models in which the *t*Bu substituents on the salen ring block unselective alkene approach vectors.[33] Experiments with enantiopure catalysts confirmed that **26c** ($s=2$) had significantly lower selectivity than **26a** and **26b** ($s\geq6$). Although the system behaves closer to ideality than the Pd-AAA process,[34] the method did not allow conclusive distinction of **26a** ($s=9$) from **26b** ($s=6$). Further tests with the novel catalysts (±)-**26d** and (±)-**26e** had no detectable impact on the selectivity compared to (±)-**26a**,[27] a result later confirmed by Gilheaney and Daly in a conventional Jacobsen–Katsuki epoxidation.[35]

3.2. Prochiral Substrates

A different approach was taken in 2003 by Kagan and coworkers[36] who analyzed a two-stage sequential reduction by $BH_3{\cdot}SMe_2$ of diketone **27** to diol **28**, catalyzed by (±)-**29** (Scheme 6). Under limiting conditions, in which: i) the

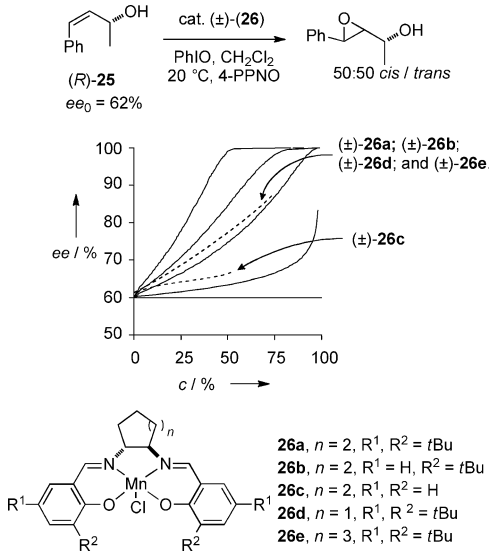
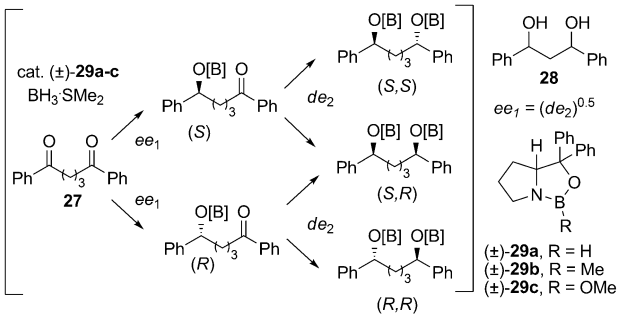


Figure 3. Change in *ee* value (*y* axis) of scalemic (*S*)-**25** as a function of its conversion in epoxidation (*c*, *x* axis) with racemic catalysts (±)-**26a–e**. Dashed lines: data. Solid lines: ideal curves for $s = 1$, 2, 5, 10, and 50. 4-PPNO = 4-phenylpyridine N-oxide.

stereoselectivity of both steps is identical, and ii) the catalyst does not dissociate from the substrate between step 1 and step 2, then the diastereoselectivity (de_2) can be used to calculate the enantioselectivity (ee_1) by the relationship $ee_1 = (de_2)^{0.5}$.

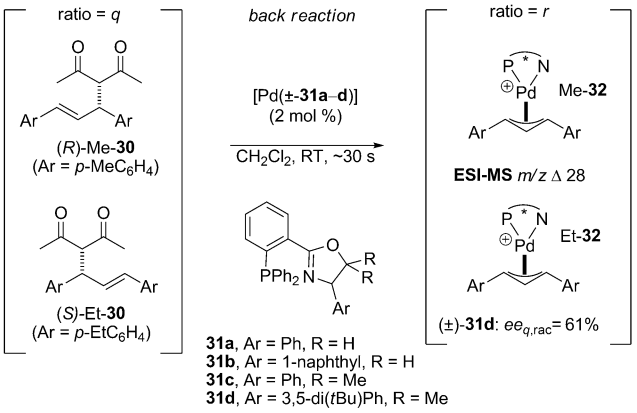


Scheme 6. Probing diastereoselectivity in the generation of diol **28** from the consecutive asymmetric reduction of diketone **27**, to predict the enantioselectivity induced by chiral oxazoborolidine catalysts **29**.

All three of the racemic catalysts (±)-**29a–c** reduced **27** to diol **28** with high diastereoselectivity (de_2). This result then predicts that all three induce high enantioselectivity (ee_1), a result that was in reasonable agreement with experiment (e.g. at 66 °C, $(de_2)^{0.5}$ with (±)-**29b** = 91 %; ee_{obs} with (*S*)-**29b** = 83 %). Although reactions meeting both conditions are only found in rare cases, this elegant study does demonstrate that enantioselectivity can be evaluated from a racemic catalyst,[36] without resort to kinetic resolution techniques.[24,25]

3.3. Back Reaction Analysis

More recently, the concept developed Lloyd-Jones and co-workers[24] was extended by Pfaltz and co-workers[25] into a practical mass-spectrometric (MS) method for screening racemic catalysts by use of mass-labeled quasienantiomeric products. The intrinsic enantioselectivity of the catalyst in the forward direction can be determined by ESI-MS monitoring[26] of the catalytic intermediates generated in the back reaction,[26a,d,e,f] provided that pseudo zeroth-order substrate dependency is engendered (Scheme 7). The verification for the method came again from Pd-AAA, in this case by



$s = (q^2\text{-}r + [(r\text{-}q^2)^2 - (rq\text{-}q)^2)]^{0.5})/(rq - q))$ and $ee_{q,rac}$ (%) = 100((*s*-1)/(*s*+1))

Scheme 7. The rapid ESI-MS back-reaction screening method of Pfaltz and co-workers[26] for the prediction of the enantioselectivity (ee_{corr}) that will be obtained in the forward direction for the Pd-AAA of 1,3-diarypropenyl esters with enantiopure phosphinooxazoline ligands **31a–d**.[25] corr = corrected, *q* = quasienantiomers, rac = racemic catalyst, obs = observed.

reaction of a 3:1 mixture of quasienantiomers (Me-**30** and Et-**30**; initial ratio = *q*). A series of racemic Pd complexes derived from ligands (±)-**31a–d** (Scheme 7) were assayed by reference to the relative intensities of the ESI-MS signal arising from the major isotopomer (^{108}Pd) of the cationic Pd/allyl intermediates Me-**32** and Et-**32**. Their ratio (*r*) was used to calculate the *s* value for the back reaction and thus predict the enantioselectivity ($ee_{q,rac}$) that should be observed in the forward direction. The predicted values for the forward reaction were then compared with those determined with enantiopure catalysts, thus confirming the proof of concept.

Importantly, although the observed and predicted selectivities deviated, they exhibited a simple linear relationship ($ee_{obs} = a\,ee_{q,rac} + b$), thus indicating that enantioselectivity can be reliably predicted from the racemic catalyst after

correction (ee_{corr}). The process was then employed for de novo evaluation. For example, ligand (±)-**31d** gave an $ee_{q,rac}$ value of 61% by MS screening, and thus $ee_{corr} = 81\%$, which is in excellent agreement with the $ee_{obs} = 82\%$ subsequently determined for Pd-AAA with enantiopure **31d**. A key feature is that the method is rapid: evaluation requires no work-up, purification or isolation, simply injection into the ESI-MS instrument. Moreover, as the ESI-MS back-reaction technique[26a,e–f] should be applicable to mixtures of racemic catalysts, provided that each has a unique mass signature, this method should allow substantially accelerated ligand screening.

3.4. High-Throughput Screening

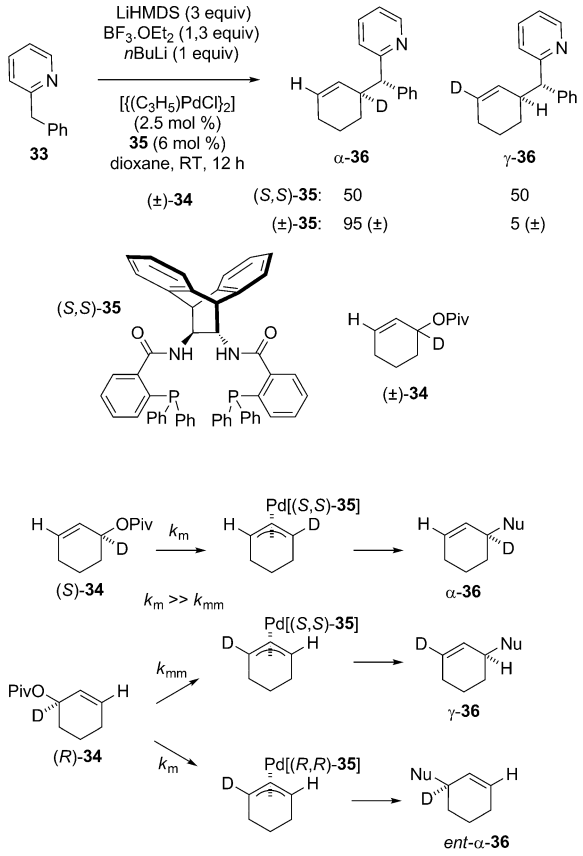
In a series of developments towards rapid and efficient assay of mixtures, Anslyn et al. has exploited metal-to-ligand charge transfer (MLCT) bands in circular dichroism (CD) spectroscopy with Cu and Pd complexes bearing racemic binap ligands (**1**) to quantify the *ee* value of the chiral reaction products.[37] The process works by way of indicator-displacement assays[37c] in combination with pattern recognition and an array of receptors. The sign of the Cotton effect allows enantiomer identification, and the identity and concentration of the diamine to be judged accurately by the intensity of a series of signals at selected wavelengths. Principal component analysis, in combination with training sets of data, provides real potential for high-throughput screening in asymmetric catalysis.

4. Mechanism

The application of racemic ligands and catalysts in mechanistic studies lies predominantly in situations where chiral but racemic substrates can undergo matched and mismatched reactions with the catalyst that lead to different regiochemical or stereochemical outcomes. The matched manifold can be selectively probed by parallel kinetic resolution with a racemic catalyst. Comparison of the outcome with the enantiomerically pure catalyst can then prove a valuable tool for the interrogation of the mechanism and in optimization of reaction conditions and thus selectivity.

4.1. Regioselectivity

Trost and Thaisrivongs recently reported Pd-AAA with lithiated picolines to selectively generate vicinal stereocenters.[38] The reaction of a racemic substrate with a single enantiomer of catalyst forces the generation of both diastereomeric η^3-cyclohexenyl/Pd intermediates, by matched and mismatched ionization events. These intermediates can interconvert, by π–σ–π processes, ligand conformation "flip"[40] and ion-pair relaxation,[41] and the outcome depends on whether equilibration is complete prior to nucleophilic attack.[42] This phenomenon was probed by the reaction of lithiated **33** with deuterated[39] cyclohexenyl ester (±)-**34** using [Pd(*S*,*S*)-**35**] as catalyst (Scheme 8). This gave equal proportions of regioisotopomeric products α-**36** and γ-**36**, both in good *de* (80%) and *ee* values (91%), indicative that equilibration is complete. However, when the racemic ligand (±)-**35** was employed, the α regioisotopomer (±)-α-**36** was obtained with very high selectivity (>95%), thus revealing a powerful matched/mismatch effect at the ionization stage.



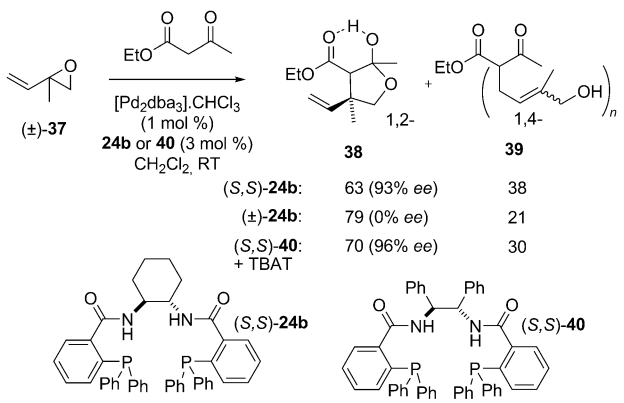
Scheme 8. Matched (k_m) and mismatched (k_{mm}) ionization of (±)-**34** by [Pd(**35**)].[38] HMDS = hexamethyldisilazane, piv = trimethylacetyl.

A similar approach was taken in a study of [(*S*,*S*)-**24b**Pd]-catalyzed addition of acetoacetate to isoprene monoxide (**37**), where 1,2-regioselectivity (**38**) is controlled by H bonding (Scheme 9).[43]

The possibility that the mismatched intermediate undergoes a greater proportion of 1,4-addition (**39**) was probed by the deployment of the racemic ligand (±)-**24b**, which led to increased 1,2-selectivity. This result then informed the use of a fluoride additive, in combination with (*S*,*S*)-**40**, to accelerate relaxation after mismatched ionization, thus leading to increased 1,2-selectivity and enantioselectivity;[43] other Pd-AAA reactions have been similarly analyzed.[44,45]

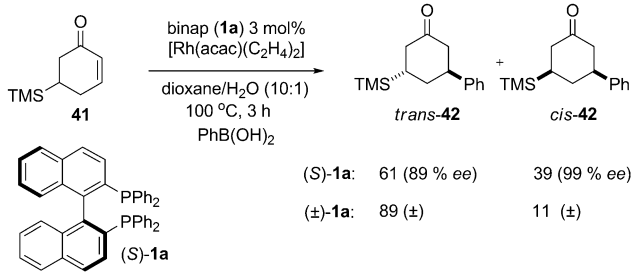
4.2. Diastereoselectivity

In the course of the mechanistic analysis of Rh-catalyzed phenylation of **41** to give **42**, Tomioka[46] considered Rh



Scheme 9. 1,2- versus 1,4-addition to isoprene monoxide (±)-**37** ($n = 1,2$). dba = dibenzylideneacetone, TBAT = tetra-*n*-butylammonium triphenyldifluorosilicate.[43]

addition to a quasichair cyclohexene, in which the TMS is pseudoequatorial. A *trans*-selective addition was proposed to direct the [PhRh(*S*-**1a**)] catalyst to the *Re* rather than *Si* face of the alkene in the mismatched substrate, thus leading to a lower *ee* value in the *trans* isomer, and conversely higher *ee* value in the *cis* isomer (Scheme 10). This hypothesis was tested with (±)-**1a**, thus leading to 89:11 *trans* selectivity, an outcome near identical to that obtained with the achiral ligand 1,4-bis(diphenylphosphano)butane.

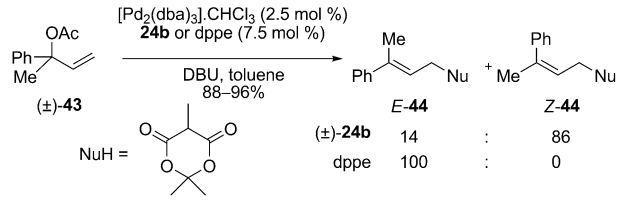


Scheme 10. Substrate- versus ligand-controlled phenylation of racemic (±)-**41**, explored with racemic binap ligand (±)-**1a**. acac = acetoacetonate, TMS = trimethylsilyl.

4.2. Achiral Products

One of the most enticing applications of racemic catalysis to date, outside of the well-explored area of polymerization, comes from the new paradigm for alkene geometry control of Trost and co-workers.[47] The Tsuji–Trost reaction of allylic acetate (±)-**43** using (*S*,*S*)-**24b** was found to afford an equal mixture of *E*- and *Z*-**44**, despite *E*-**44** being thermodynamically favored. *Z*-**44** was suspected to arise from a matched ionization event. Accordingly, deployment of (±)-**24b**, so that both enantiomers of **43** predominantly undergo matched ionization, gives useful *Z* selectivity (Scheme 11).

This intriguing example highlights how a chiral substrate and a chiral ligand can be of significant utility in the selective synthesis of an achiral product; the key feature being that the racemic catalyst allows both enantiomers of the racemic



Scheme 11. Racemic catalyst control of alkene geometry to favor the thermodynamically unfavorable product, *Z*-**44**. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, dppe = 1,2-bis(diphenylphospano)ethane.

substrate to react identically within the stereochemically controlling environment of the ligand.

5. Outlook

In contrast to the preferential discrimination approach, involving an exogeneous chiral modifier, we have focused on systems where the active catalyst is racemic. In this context, racemic chiral ligands and catalysts can be strategically applied to control or understand selectivity in cases where racemic substrates can undergo matched and mismatched reactions. In terms of generality of application, it should be noted that some caution must be exercised in systems where there is potential for catalyst aggregation,[40] or where there are multiple ligands coordinated to the metal. In these relatively rare cases, the catalytic behavior with the racemic, or indeed scalemic, form of the ligand can deviate substantially from the enantiopure. The strategic use of racemic catalysts was first developed in the area of polymerization, where there is often a need to control relative rather than absolute configuration. This has proven a fertile testing ground for selective facilitation of matched pathways; many of the concepts developed there are now ripe for translation and adoption in regular organic synthesis and catalyst discovery. We note in closing a salient point that emerges from the topics presented herein: all of the examples relate to main group, transition, and lanthanide metal catalysis. There have been very few reports on the strategic application of racemic organocatalysis.[48] This is an area of asymmetric catalysis that is currently dominated by the chiral pool, in terms of enantiomerically pure building blocks for catalyst synthesis. We anticipate that the techniques outlined herein may provide considerable scope for the accelerated discovery of new non-natural organocatalyst architectures, for example those based on helical, planar, or axial chirality, or with P or Si stereogenic centers.

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