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Note

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Outer-Sphere Control for Divergent Multicatalysis with Common Catalytic Moieties

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ABSTRACT: We herein report two examples of one pot, simultaneous reactions, mediated by multiple, orthogonal catalysts with the same catalytic motif. First, BINOL-derived chiral phosphoric acids (CPA) and phosphothreonine (pThr)-embedded peptides were found to be matched for two different steps in double reductions of bisquinolines. Next, two π-methylhistidine (Pmh)-containing peptides catalyzed enantio- and chemoselective acylations and phosphorylations of multiple substrates in one pot. The selectivity exhibited by common reactive moieties is adjusted solely by the appended chiral scaffold through outer-sphere interactions.

A remarkable feature of enzymes is their ability to catalyze highly selective transformations on specific substrates, often in tandem and simultaneous pathways and in the presence of competing, reactive analytes.[1] The tuning of active sites, which often employ a similar catalytic apparatus for bond-formation, to perform diverse molecular functions is a triumph of evolution.[2] However, by comparison, chemists struggle to mimic this level of control over the reactivities and selectivities of multiple catalysts in complex settings,[3] as cross-reactivity among diverse chemical species can intervene.[4–6] While approaches toward relay catalysis have recently seen a number of advances,[7] most of these studies (1) require either sequential addition of catalysts or intermediate purification steps, or (2) are combinations of two catalysts that are chemically distinct (i.e. hetero-combinations of metals, photocatalysts, and organocatalysts), such that both catalysts independently mediate orthogonal transformations.[8–10] While simultaneous operations of the same catalytic species is rare, a few reports of one pot multicatalytic reactions, such as with two ruthenium complexes (**Figure 1A**)[11] and a dual imidazolidinone/proline system (**Figure 1B**),[12] create an optimistic prognosis. These studies offer validation that a common, reactive moiety (Ru atom or

secondary amine) can be subtly modified to function divergently *in situ* (i.e. oxidations vs. reductions, and iminium vs. enamine catalysis).

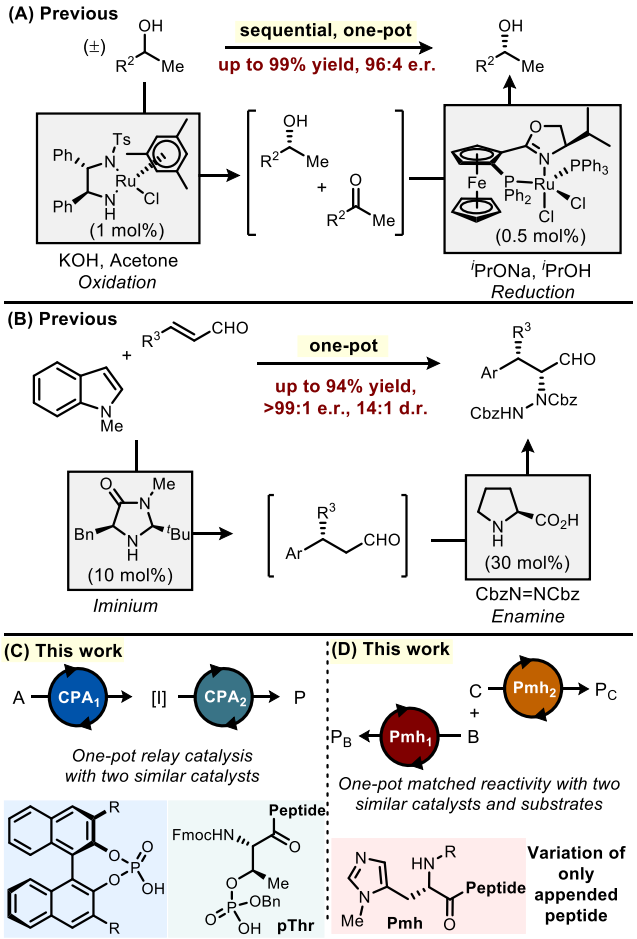


Figure 1. (A,B) Examples of organometallic and organocatalyst multicatalytic systems. **(C,D)** This work: multicatalysis with similar catalysts.

With these precedents in mind, we sought functional divergence with catalysts of even more closely related intrinsic reactivity. We chose to assess whether (1) two Brønsted acids or (2) two Lewis bases could function in the presence of one another to perform either a tandem reaction, or a parallel processing reaction scheme, simply through modification of the chiral scaffold appended to the catalytically competent group. The crafting of precise outer-sphere interactions between these catalysts and their targeted substrates would be essential in assigning specific catalytic functions, and discriminating between competing, but fully analogous types of bond formations.[13] The approach to assigning specific catalyst-substrate interactions described below uses peptide-based catalysts in a biomimetic manner, building on their analogy to enzymes.[14] Presented herein are reports involving two different families of catalysts: (1) phosphothreonine (pThr)-embedded peptides,[15–18] complementary

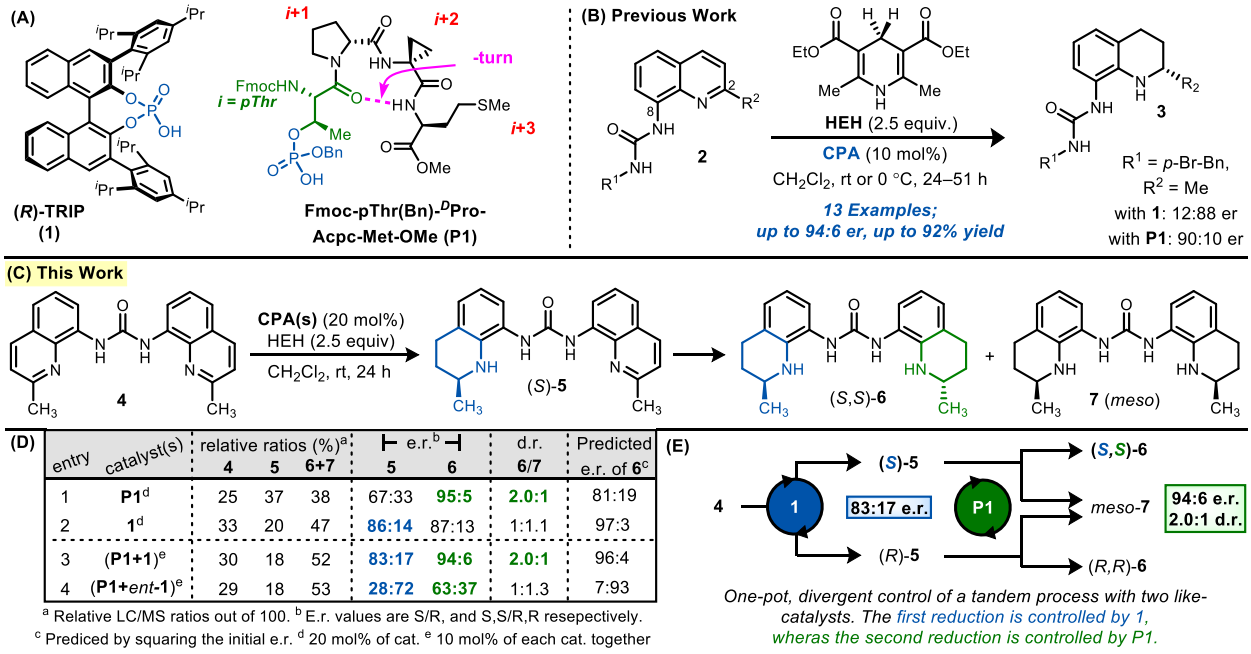
to BINOL-derived chiral phosphoric acid (CPA) catalysts,[19,20] are explored for multicatalytic transfer hydrogenation (**Figure 1C**); and (2) π-methylhistidine (Pmh)-containing peptides are explored for *in situ* parallel hydroxyl group transfer reactions (**Figure 1D**).[21]

Divergent, One Pot CPA Catalysis. While BINOL- and peptide-based CPA catalysts (like **P1** and **1**) maintain a common catalytic phosphoric acid, their overall chiral scaffolds are distinct (**Figure 2A**). In our previous studies of the transfer hydrogenation of 8-aminoquinolines (**2**), we reported that both catalyst **P1** and **1** were highly selective, affording tetrahydroquinoline **3** in up to 94:6 e.r. and with opposite absolute stereochemical configurations (**Figure 2B**).[15] Given the utility of reduced quinoline scaffolds, we chose to probe the possibility of sequential, high selectivity reductions with these catalysts on biologically relevant bisquinolines,[22,23] such as **4**, linked through the 8-substituted urea (**Figure 2C**). Upon initial formation of **5**, further reduction can produce a mixture of chiral (**6**) and *meso* (**7**) products. Initial reactions mediated by pThr-derived **P1** generated mono-reduced **5** with 67:33 e.r. (**Figure 2C–D**, entry 1), a lower level of selectivity than previously observed for the reduction of **2** to **3**. Yet, further reduction of **5** to **6**+**7** revealed a substantial amplification of product enantiopurity, producing **6** with 95:5 e.r..[24]

The combination of two subsequent chirality-generating reactions to enhance the e.r. of an asymmetric process is a manifestation of Horeau amplification (**Figure 2E**).[25–29] In this paradigm, e.r. may be enhanced at the expense of d.r., as the disfavored enantiomer in the first reduction is converted to *meso*-**7** through a second reduction. Under ideal conditions, assuming the catalyst reduces **4** and **5** with the same selectivity, the final e.r. of **6** can be predicted by squaring the initial selectivity.[30,31] Since catalyst **P1** produces mono-reduced **5** in 67:33 e.r. (s_1 = 2.0), the theoretical e.r. of **6** would be 81:19 (s_1^2 = 4.1); thus, **P1** substantially outperforms ideal Horeau amplification estimates (95:5 e.r., s_2 = 19), implying second order outer-sphere effects in the second reduction. In the case of **P1** mediated reductions of monoquinolines (2), secondary interactions between the peptide and the 8-aminoquinoline were essential for high selectivities; and these key outer-sphere interactions presumably operate in the reduction of these bisquinolines as well.[15]

Interestingly, BINOL-derived catalyst **1** produced mono-reduced **5** in higher initial e.r., 86:14 (s_1 = 6.1, **Figure 2D**, entry 2). Yet, upon second reduction, the e.r. of **6** minimally changes to 87:13 (s_2 = 6.7), much lower than the Horeau expectation (s_1^2 = 38, 97:3 e.r).[32] Thus, catalyst **1** is more selective in the first reduction, while **P1**

is more selective in the second. Furthermore, while **P1** and **1** previously gave the opposite sense of absolute stereochemistry in the reduction of monoquinoline (**2** to **3**; **Figure 2B**), both catalysts afford products with the same sense of stereochemistry with **4**.[31]



entry	catalyst(s)	relative ratios (%)[a] 4	5	6+7	e.r.[b] 5	6	d.r. 6/7	Predicted e.r. of 6[c]
1	**P1**[d]	25	37	38	67:33	**95:5**	**2.0:1**	81:19
2	**1**[d]	33	20	47	**86:14**	87:13	1:1.1	97:3
3	(**P1**+**1**)[e]	30	18	52	**83:17**	**94:6**	**2.0:1**	96:4
4	(**P1**+*ent*-**1**)[e]	29	18	53	**28:72**	**63:37**	1:1.3	7:93

[a] Relative LC/MS ratios out of 100. [b] E.r. values are S/R, and S,S/R,R resepectively. [c] Prediced by squaring the initial e.r. [d] 20 mol% of cat. [e] 10 mol% of each cat. together

Figure 2. (A) BINOL-derived and pThr-based CPAs. **(B)** Asymmetric transfer hydrogenation of 8-aminoquinolines with CPAs. **(C+D)** Scheme and catalyst screening for CPA-mediated reductions of bisquinoline **4**. **(E)** Kinetics diagram for this transformation.

Given the complementarity of catalysts **P1** and **1** for different steps of this bis-reduction, we wondered whether the catalysts could be combined in one pot to mediate their respective, matched reactions with high selectivity (**Figure 2E**). Indeed, reacting **4** in the presence of a 1:1 mixture of **1** and **P1** produced **5** in 83:17 e.r., and **6** in 94:6 e.r. and 2.0:1 d.r., constituting a synergistic effect for the combined catalysts in achieving better e.r. together than in individual screens (**Figure 2D**, entry 3). It appears that catalyst **1** predominantly controls its matched reduction of **4** to **5** (83:17 e.r. vs. 86:14 e.r. in individual screen). Alternatively, in the second reduction from **5** to **6**+**7**, the dual catalyst system outperforms individual reaction with only catalyst **1** (94:6 e.r. vs. 87:13 e.r.), indicating that **P1** affords rate enhancement in the second step (**1** also appears to compete to a low, but detectable extent). To further elucidate the level of control exhibited by **P1** on this second reduction, reactions were performed in the presence of both **P1** and *ent*-**1**. The first reduction was still controlled by *ent*-**1**, revealing **5** with the reversed (*R*)-stereochemistry (28:72 e.r., **Figure 2D**, entry 4). However, even though (*R*)-**5** was favored in the first step, the second reduction results in (*S*,*S*)-**6** as the major product (63:37 e.r.), revealing that **P1** competes ef-

fectively. Thus, this reversal of the stereochemical outcome between the first and second reductions elucidates the substantial control that *ent*-**1** and **P1** have in conducting their matched reductions in a tandem process. These results imply that, despite the shared identity of the catalytic phosphoric acid of **1** and **P1**, reactivity can be heavily tuned by appended chiral scaffold and specific, matched outer-sphere interactions (presumably **1** with **4** and **P1** with **5**).[33]

Control of Pmh-Catalysts through Peptide Variation. The divergent selectivity regimes of BINOL- and peptide-based CPAs described above allow for interpretable, catalyst-assigned outcomes in these multicatalytic parallel reactions, specifically due to the different, surrounding molecular architecture.[1] Complementary reactivity might not be unexpected for these two families, taking into account the dissimilar nature of the rigid BINOL framework in comparison to the functionalized and flexible nature of peptides. Yet, we are able to document related assignment of catalytic function based on outer-sphere tuning of common catalytic moieties with purely peptide-based systems as well,[14,34] specifically relying on Pmh-based catalysts for selective hydroxyl group transfers.

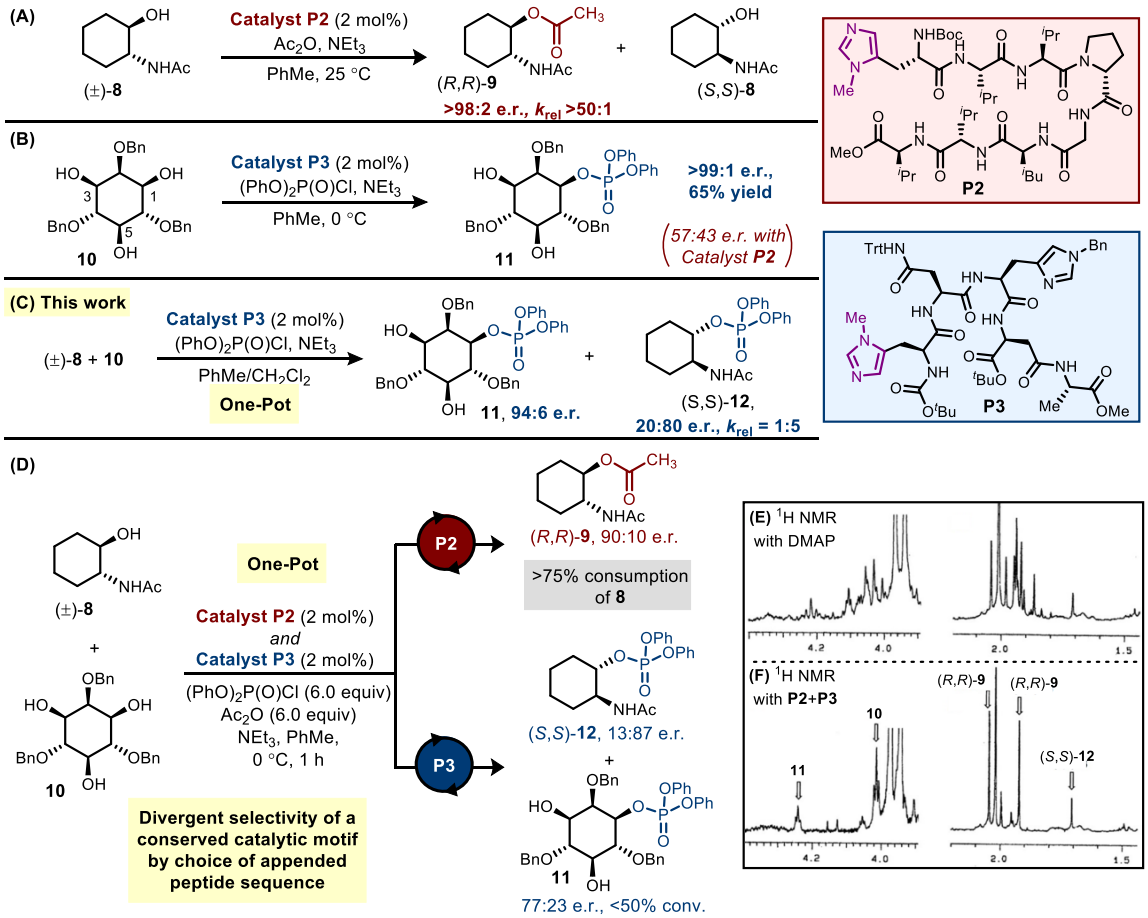


Figure 3. (A) Kinetic resolution of (±)-**8** with **P2** to yield acylated (*R,R*)-**9**. **(B)** Desymmetrizing phosphorylation of inositol derivative **10** with **P3**. **(C)** One pot phosphorylation of (±)-**8** and **10** revealed **P3** favors reaction with (*S*,*S*)-**8**, opposite to **P2**. **(D–F)** Scheme and NMR data for peptide-mediated one-pot reactions.

Some time ago, we showed that octameric Pmh catalyst **P2** facilitated the selective acylation of racemic *trans*-aminoalcohol **8** with a $k_{rel} > 50:1$ (**Figure 3A**).[35] With an alternative peptide backbone, Pmh peptide **P3** was reported to mediate the phosphorylation of an inositol derivative (**10**) with high levels of site- and enantioselectivity (>99:1 e.r.; **Figure 3B**).[36] However, catalysts **P2** and **P3** gave unspectacular, or even stereodivergent selectivity when applied to the reactions for which each was unoptimized. For example, when (±)-**8** and **10** were reacted in the presence of only $(PhO)_2P(O)Cl$ and **P3**, phosphorylated (*S*,*S*)-**12** was obtained with a k_{rel} of 1:5 (**Figure 3C**), the opposite stereochemistry shown with **P2** for acylation. These results indicated the crucial nature of the appended peptide sequences in tuning the selectivity of the shared Pmh residue through outer-sphere interactions.[35b] Furthermore, these divergent reactivities gave us hope that the two catalysts could exhibit specificity for their matched substrates in a one pot, parallel processing experiment wherein catalyst function was assigned by the independent studies of enantioselectivity.

Competition experiments were performed wherein substrates (±)-**8** and **10** were added together in one pot, along with both phosphorylating and acylating reagents(**Figure 3D**). DMAP provided a complex and intractable mixture of products by ^{1}H NMR (**Figure 3E**).[32] However, when equimolar amounts of the two Pmh-catalysts **P2** and **P3** were utilized, a vastly simplified product distribution is observed (**Figure 3F**). Racemic aminoalcohol **8** was mostly consumed (>75% conversion to products), and acylated (*R*,*R*)-**9** was obtained in 90:10 e.r., presumably under the control of **P2**. Additionally, **P3** was found to phosphorylate the unreacted enantiomer of **8**, affording (*S*,*S*)-**12** with 87:13 e.r.. In parallel and *in situ*, inositol derivative **10** was consumed more slowly (<50% conversion to products), and phosphate **11** could be isolated with still 77:23 e.r.. Hence, despite the complexity of this one pot reaction, and the conserved nature of the Pmh residue, the peptide sequences of **P2** and **P3** were indeed tuned to react preferentially with **8** and **10** as assigned. Since mostly acylation of (*R*,*R*)-**8** and *mono*-C1-phosphorylation of **10** was observed, with limited crossover reactivity seen, this example represents a striking simplification of the reaction mixture in comparison to the outcome with DMAP, most notably observed in the cleanliness of the crude NMR of the peptide catalytic system compared to that with DMAP (**Figure 3E–F**). Key

outer-sphere interactions between the peptides and specific, assigned substrates, which are absent for DMAP, are key to the observed selectivities.

Multicatalytic systems are a frontier for studies of synthetically-relevant catalysis, as a myriad of selectivity issues emerge, including the efficient performance of different catalysts for different bond-forming operations in one pot. When a common catalytic moiety is assigned aspirationally to perform a different function, the outer-sphere of the catalyst may be called upon to achieve some of the selectivity criteria associated with these complex reaction designs. In the examples explored above, these capabilities have been documented in two distinct reactivity paradigms of considerable generality—chiral phosphoric acid catalysis and chiral Lewis base catalysis. Much study remains to generalize these concepts for efficient process development. Yet, a basis for optimism seems firmly in place as examples of multicatalytic chemistry mount, and as rational control over the outer-sphere of powerful catalytic moieties develops further.

EXPERIMENTAL SECTION

General Information. Room temperature is defined as 21–25 °C. All reagents were purchased from commercial sources and used as received, unless otherwise noted. Solvents used for reactions, such as methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), and acetonitrile (MeCN) were either obtained from a Seca Solvent Purification System by Glass Countour, in which the solvents were dried over alumina and dispended under an atmosphere of argon, or distilled from appropriate drying agents prior to use. For all other purposes, solvents were used as received from commercial sources unless otherwise noted.

^{1}H NMR spectra were recorded on 300 MHz, 400 MHz, 500 MHz, or 600 MHz Varian or Agilent spectrometers at ambient temperature. Samples were prepared in chloroform-*d* ($CDCl_3$) and dimethyl sulfoxide-d_6 (d_6-DMSO). ^{1}H NMR data are reported as chemical shifts with multiplicity, coupling constants (*J*) in Hz, and integrations. Proton chemical shifts are reported in ppm (δ) and referenced to tetramethylsilane (TMS δ 0.00 ppm) or residual solvent ($CHCl_3$, δ 7.26 ppm, DMSO δ 2.50 ppm).[37] Multiplicity is reported as follows: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplets (dt), doublet of triplet of doublets (dtd), doubet of quartets (dq), triplet (t), quartet (q), quartet of doublets (qd), pentet (p), heptet (hept), multiplet (m), and overlapping multiplets (comp). ^{13}C NMR spectra with broadband proton decoupling were recorded on 500 (126) MHz or 600 (151) MHz Agilent spec-

trometers with complete proton decoupling at ambient temperature, unless otherwise noted. Carbon chemical shifts are reported in ppm (δ) and referenced to tetramethylsilane (TMS) or solvent ($CDCl_3$, δ 77.16 ppm, d_6-DMSO δ 39.52 ppm).[37] 31P NMR spectra were recorded on 500 (202) MHz Agilent spectrometers with complete proton decoupling at ambient temperature.

Low resolution mass spectrometry (MS) was acquired on a Waters SQD2 UPLC/MS equipped with an electrospray ionization (ESI) detector, with a Waters ACQUITY UPLC BEH C18 (1.7 μm, 2.1 x 50 mm) column. High resolution mass spectrometry (HRMS) was conducted by the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign using a Waters Synapt G2-Si instrument equipped with a QToF mass spectrometer and an ESI detector.

Infrared spectra were obtained using a Nicolet ATR/FT-IR spectrometer, and ν_{max} (cm^{-1}) were partially recorded in accordance with convention. Optical rotations were recorded on a Perkin Elmer Polarimeter 341 at the sodium D line (1.0 dm path length) at 20 °C. Analytical thin-layer chromatography (TLC) was performed using EMD Millipore silica gel 60 F_{254} precoated plates (0.25 mm thickness). The developed plates were visualized by a UV lamp and/or potassium permanganate ($KMnO_4$) stain.

Normal-phase column chromatography was performed with either silica gel 60 Å (32-63 microns) or with a Biotage Isolera One flash purification system equipped with 15 g, 30 g, 60 g, or 120 g SNAP Ultra HP-Sphere 25 μm columns using an appropriate linear gradient of EtOAc/Hexanes. Reversed-phase column chromatography as performed with a Biotage Isolera One flash purification system equipped with 30 g, 60 g, or 120 g SNAP KP-C18-HS or SNAP Ultra-C18 columns with an appropriate gradient of MeCN/H_2O. In some cases, 0.1% formic acid or trifluoroacetic acid buffers were utilized.

Enantiomeric ratio (e.r.) values were acquired using both HPLC and GC. Analytical HPLC was performed on both an Agilent 1100 series analytical chiral HPLC equipped with a photodiode array detector (210 nm, 230 nm, 250 nm, and 254 nm) and a Rainin SD-200 chromatograph, equipped with a single wavelength UV detector (214 nm), were used with a Chiralpak IB column (5 μm particle size, 4.5 x 250 mm) and a Chiralcel OD column (Alltech). Analytical GC was performed on a Hewlett-Packard 6890, employing a flame ionization detector and a Chiraldex G-TA column (Alltech).

Double Reductions of Unsymmetrical Bisquinolines with CPAs. See Supporting Information for **Figure S1.** Given this significant divergent selectivity displayed by catalysts **1** and **P1**, we sought to probe the effect further with unsymmetrical bisquinoline **13**, which presents the intriguing challenge of both enantio- and site-selectivity with respect to the first reduction (**14** vs. **15**, **Figure S2.A**). In this case, amplified enantioselectivities from this tandem process must come from either (1) a secondary kinetic resolution of the two enantiomers of **14** (**Figure S2.C**, blue),[38] or (2) a difference in selectivity for the reduction of **15** to **16** (**Figure S2.C**, red), as the Horeau-type correction of e.r. is no longer operative. Interestingly, with both catalysts **P1** and **1**, the initial reduction of **13** leads to mixtures of **14** and **15**, despite the quite different level of substitution on each ring (**Figure S2.B)**. Catalyst **1** gives a nearly equivalent ratio of **14** and **15**, while **P1** favors **14**.[39] Moreover, we observe that **P1** gives similar e.r. for the first reduction of either **4** and **13** (67:33 vs. 65:35), but also produces doubly reduced **15** with lower e.r. (76:24). Catalyst **1** yields substantially lower enantioselectivities than previously observed both at low and high conversion, and with the opposite senses of chirality as **P1** for product **15**. Taken together, the observations with substrate **13** unveil further the nuanced outer-sphere interactions of catalysts **1** and **P1** in the second reduction.

Previously Synthesized Compounds. Peptide **P1** was previously synthesized and characterized in a related publication.[15,16] Compound *trans*-2-acetamidocyclohexanol ((±)-**12**) was synthesized according to the method of Hawkins.[40] For the syntheses and characterizations of catalyst **P2** (Boc-Pmh-Val-Val-^{D}Pro-Leu-Val-Val-OMe) and acylated **13**, please see a related publication.[35] Compound 2,4,6-Tribenzyl-*myo*-inositol (**14**) was synthesized according to the method of Billington.[41] For the syntheses and characterizations of catalyst **P3** (Boc-Pmh-Asn(Trt)-His(πBn)-Asp(^{t}Bu)-Ala-OMe) and phosphorylated **15**, as well as methods for catalyst screening, please see a related publication.[36]

Compound Synthesis and Characterization. Reported yields are for the preparation of analytically pure standards. During purifications, mixed fractions were often excluded.

1,3-bis(2-methylquinolin-8-yl)urea (**4**). Modified from literature precedent,[42] a flame dried 100 mL round bottom flask was charged with 8-aminoquinaldine (2.00 g, 12.6 mmol, 2.10 equiv), 1,1′-Carbonyldiimidazole (CDI, 976 mg, 6.02 mmol, 1.00 equiv), and 32 mL THF. A condenser was added on the flask and was fit with a septum and placed under and Ar balloon. The solution was heated at 76 °C for 24 h, after which the reaction was

cooled to room temperature and concentrated. The crude mixture was purified via normal-phase chromatography, with a gradient eluent of 1 to 30% EtOAc/Hex. The isolated product was further crystallized from a solution of CH_2Cl_2/MeOH, resulting in pure product. Yield: 931 mg beige solid, 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 2.81 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.0, 152.4, 137.8, 136.7, 135.0, 126.7, 126.4, 122.5, 120.0, 115.3, 25.4. IR (cm^{-1}, neat): 3313, 1691, 1603, 1519, 1487, 1434, 1382, 1333, 1233, 1191, 1140, 1074, 827, 794, 761, 748, 714. HRMS (ESI-QToF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_4O$ 343.1559, found 343.1558. Mp: 177–178 °C. TLC: R_f (2:1 Hex/EtOAc) 0.64, visualized with UV light.

1-(2-methyl-1,2,3,4-tetrahydroquinolin-8-yl)-3-(2-methylquinolin-8-yl)urea (**5**). A flame dried 100 mL round bottom flask was charged with **4** (200 mg, 0.826 mmol, 1.00 equiv), Hantzsch ester (523 mg, 2.07 mmol, 2.50 equiv), diphenyl phosphate (103 mg, 0.410 mmol, 0.500 equiv), and 17 mL CH_2Cl_2. The flask was fit with a septum, placed under an N_2 atmosphere, and stirred for 24 h. The reaction was washed with $NaHCO_3$ (satd, aq, 20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product, which was predominantly **6**+**7**, was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 75% EtOAc/Hex to yield a mostly pure mixture of **5** with some **6**+**7**. The mixture was suspended in methanol, which dissolves all of **6**+**7** and some of **5**, and the suspended **5** was filtered to yield pure product. Yield: 12.8 mg beige solid, 4%. ^{1}H NMR (600 MHz, d_6-DMSO) δ 9.50 (s, 1H), 8.68 (s, 1H), 8.47 (dd, *J* = 6.1, 2.8 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.51–7.40 (comp, 3H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.3 Hz, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 4.96 (bs, 1H), 2.80 (ddd, *J* = 16.3, 11.1, 5.4 Hz, 1H), 2.75–2.67 (comp, 3H), 1.88 (dq, *J* = 11.9, 4.7 Hz, 1H), 1.52 – 1.41 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, d_6-DMSO) δ 156.7, 153.4, 137.1, 136.6, 135.5, 126.1, 126.0, 125.7, 123.5, 122.9, 122.6, 121.4, 119.2, 115.3, 114.2, 114.2, 46.6, 29.3, 26.3, 24.9, 22.3. IR (cm^{-1}, neat):3394, 1665, 1532, 1496, 1433, 1338, 1283, 1226, 1113, 830, 756, 731. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{23}N_4O$ 347.1872, found 347.1872. Mp: 200–201 °C. TLC: R_f (2:1 Hex/EtOAc) 0.48, visualized with UV light. Assay of enantiomeric purity: Enantiomers of product **5** were separated by a chiral IB column, eluting at a flow rate of 1.0 mL/min with 2.0% EtOH/Hex. R_t[(*S*)-**5**] = 27 min; R_t[(*R*)-**5**] = 30 min.

Cis- and trans-1,3-bis(2-methyl-1,2,3,4-tetrahydroquinolin-8-yl)urea (**6**+**7**). Two reactions were setup simultaneously: **(A)** A flame dried 100 mL round bottom flask was charged with **4** (75.0 mg, 0.219 mmol, 1.00 equiv), Hantzsch ester (117 mg, 0.460 mmol, 2.50 equiv), diphenyl phosphate (27.0 mg, 0.110 mmol, 0.500

equiv), and 40 mL $CHCl_3$. The flask was fit with a septum, placed under an Ar balloon, and stirred for 48 h. Upon consumption of all Hantzsch ester, the reaction was washed with $NaHCO_3$ (satd, aq, 40 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 75% EtOAc/Hex to yield a mostly pure mixture of **6**+**7**. **(B)** A flame dried 250 mL round bottom flask was charged with **4** (100 mg, 0.292 mmol, 1.00 equiv), Hantzsch ester (333 mg, 1.31 mmol, 4.50 equiv), diphenyl phosphate (37.0 mg, 0.146 mmol, 0.500 equiv), and 60 mL CH_2Cl_2. The flask was fit with a septum, placed under an Ar balloon, and stirred for 168 h. Upon consumption of all Hantzsch ester, the reaction was washed with $NaHCO_3$ (satd, aq, 60 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 75% EtOAc/Hex to yield a mostly pure mixture of **6**+**7**. **(A+B)** The crude products from both (A) and (B) were combined and further purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 60% EtOAc/Hex to yield pure product. **Yield:** 47.7 mg of **6**+**7** as a beige solid, 26%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 7.7 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.61 (t, J = 7.6 Hz, 1H), 6.07 (s, 1H), 3.44–3.33 (m, 1H), 2.92–2.69 (m, 2H), 1.93 (ddt, J = 12.6, 6.1, 3.5 Hz, 1H), 1.60–1.48 (m, 1H), 1.22 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.1, 140.7, 128.0, 125.1, 123.1, 121.8, 117.0, 47.3, 29.8, 26.8, 22.7. IR (cm^{-1}, neat): 3293, 2956, 2929, 1628, 1560, 1497, 1460, 1336, 1296, 1279, 1247, 1153, 1115, 1064, 961, 742. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{27}N_4O$ 351.2158, found 351.2188. TLC: R_f (2:1 Hex/EtOAc) 0.29, visualized with UV light. Assay of enantiomeric purity: Stereoisomers of products **6+7** were separated by a chiral IB column, eluting at a flow rate of 1.0 mL/min with 2.0% EtOH/Hex. R_t[(*S,S*)-**6**] = 33 min; R_t[*meso*-**7**] = 38 min; R_t[(*R,R*)-**6**] = 42 min.

(±)-2-acetamidocyclohexyl diphenyl phosphate [(±)-**12**]: A 100 mL round bottom flask was charged with (±)-**8** (200 mg, 1.27 mmol, 1.00 equiv), DMAP (8.0 mg, 0.070 mmol, 0.050 equiv), PhMe (25 mL), followed by sequential addition of triethylamine (distilled, 173 uL, 1.24 mmol, 1.30 equiv) and diphenylchlorophosphate (251 uL, 1.15 mmol, 1.20 equiv). CH_2Cl_2 (20 mL) was added to aid solubility. The reaction was stirred at RT for 12 h, followed by quenching by addition of MeOH (2 mL). The solution was concentrated and purified by flash chromatography, eluting with a gradient of 3% to 5% MeOH/CH_2Cl_2 to yield pure product. **Yield:** 130 mg light brown oil, 26%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (comp, 4H), 7.22–7.15 (comp, 6H), 6.34 (bd, J = 7.8 Hz, 1H), 4.38–4.28 (m, 1H), 3.93–3.83 (m, 1H), 2.13 (d, J = 12.4 Hz, 1H), 2.04–1.97 (m, 1H), 1.74 (d, J = 10.3

Hz, 1H), 1.69 (s, 3H), 1.62 (d, J = 13.1 Hz, 1H), 1.54 (qd, J = 12.7, 3.9 Hz, 1H), 1.35–1.16 (m, 2H), 1.09 (qd, J = 12.7, 3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, for analogous C–P splitting, see a related reference[43]) δ 170.2, 150.5 (d, J_{CP} = 7.5 Hz), 150.4 (d, J_{CP} = 7.5 Hz), 129.9, 125.7 (d, J_{CP} = 1.1 Hz), 125.6 (d, J_{CP} = 1.0 Hz), 120.3 (d, J_{CP} = 4.6 Hz), 120.2 (d, J_{CP} = 4.8 Hz), 81.0 (d, J_{CP} = 6.4 Hz), 53.6 (d, J_{CP} = 3.3 Hz), 32.61 (d, J_{CP} = 4.1 Hz), 32.1, 24.2, 24.0, 23.2. ^{31}P NMR (202 MHz, $CDCl_3$) δ –10.6. IR (cm^{-1}, thin film from $CHCl_3$): 3300, 2940, 2861, 1657, 1591, 1551, 1488, 1455, 1371, 1272, 1188, 1162, 1021, 952, 907, 726. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{24}NO_5PNa$ 412.1290, found 412.1292. TLC: R_f (9:1 CH_2Cl_2/MeOH) 0.33, visualized with UV light. Assay of enantiomeric purity: Enantiomers of product **12** were separated by a chiral OD column (Alltech), eluting at a flow rate of 0.5 mL/min with 1.5% EtOH/Hex. R_t[(*S*,*S*)-**12**] = 38 min; R_t[(*R*,*R*)-**12**] = 41 min.

1-(2-methylquinolin-8-yl)-3-(quinolin-8-yl)urea (**13**, see **Figure S2**). Modified from literature precedent,[43] a flame dried 100 mL round bottom flask was charged with 8-aminoquinoline (1.00 g, 6.93 mmol, 1.00 equiv), 1,1′-Carbonyldiimidazole (CDI, 675 mg, 4.16 mmol, 0.600 equiv), and 35 mL CH_2Cl_2. The solution was fitted with a septum and Ar balloon and stirred for 2 h. Then, 8-aminoquinaldine (1.10 g,6.92 mmol, 1.00 equiv) was added, and the reaction was stirred overnight for 22 h. The solution was concentrated, yielding a mixture of symmetrical urea products (including **4**) and the desired unsymmetrical product (**13**). The mixture was purified by automatic normal-phase chromatography, with a gradient eluent of 1 to 50% EtOAc/Hex. The isolated product was further purified with automatic reversed-phased chromatography, eluting with a gradient of 50% to 100% MeCN/H_2O to yield pure product. Yield: 409 mg white solid, 30%. ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 9.44 (s, 1H), 8.87 (dd, J = 4.2, 1.7 Hz, 1H), 8.70 (dd, J = 7.8, 1.3 Hz, 1H), 8.65 (dd, J = 7.7, 1.3 Hz, 1H), 8.19 (dd, J = 8.3, 1.7 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.53–7.45 (comp, 3H), 7.42 (dd, J = 8.2, 1.3 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 2.82 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.1, 152.4, 148.0, 138.5, 137.8, 136.7, 136.7, 135.7, 134.9, 128.3, 127.8, 126.66, 126.4, 122.6, 121.7, 120.3, 120.1, 115.4, 115.4, 25.4. IR (cm^{-1}, neat): 3249, 1667, 1518, 1489, 1434, 1380, 1324, 1254, 1191, 1079, 820, 787, 752, 731, 708. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}N_4O$ 329.1402, found 329.1401. Mp: 149–150 °C. TLC: R_f (2:1 Hex/EtOAc) 0.63, visualized with UV light.

1-(2-methyl-1,2,3,4-tetrahydroquinolin-8-yl)-3-(quinolin-8-yl)urea (**14**, see **Figure S2**). A flame dried 20 mL scintillation vial was charged with **13** (100 mg, 0.305 mol, 1.00 equiv), Hantzsch ester (193 mg, 0.762 mmol, 2.50 equiv), diphenyl phosphate (38.2 mg, 0.153, 0.500 equiv), and 6 mL CH_2Cl_2. The vial was flushed with Ar,

capped, and the reaction was stirred for 24 h. The solution was washed with $NaHCO_3$ (satd, aq, 6 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product, which included **13**, **14**, **15**, and **16**) was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex. The mostly pure product was further purified with automatic reversed-phase chromatography, eluting with a gradient of 25% to 100% MeCN/H_2O to yield pure product. Yield: 8.7 mg pale yellow solid, 9%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.66–8.59 (comp, 2H), 8.09 (d, J = 8.3 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.35 (dd, J = 8.3, 4.2 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.58 (bs, 1H), 4.28 (bs, 1H), 3.44–3.39 (m, 1H), 2.90 (ddd, J = 16.7, 11.4, 5.4 Hz, 1H), 2.81 (dt, J = 16.3, 4.5 Hz, 1H), 1.94 (ddt, J = 12.5, 6.1, 3.4 Hz, 1H), 1.60 (qd, J = 11.8, 4.9 Hz, 1H), 1.15 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.9, 148.0, 141.1, 138.7, 136.3, 135.6, 128.3, 128.1, 127.6, 125.6, 123.0, 121.4, 121.2, 120.2, 116.7, 115.4, 47.3, 29.8, 27.0, 22.6. IR (cm^{-1}, neat): 3270, 2923, 1644, 1542, 1488, 1423, 1382, 1327, 1284, 1252, 1221, 1115, 1102, 822, 787, 746. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}N_4O$ 333.1715, found 333.1715. Mp: 149–150 °C. TLC: R_f (2:1 Hex/EtOAc) 0.40, visualized with UV light. Assay of enantiomeric purity: Enantiomers of product **14** were separated by a chiral IB column, eluting at a flow rate of 1.0 mL/min with 10% EtOH/Hex. R_t[(*S*)-**14**] = 15 min; R_t[(*R*)-**14**] = 17 min.

1-(2-methylquinolin-8-yl)-3-(1,2,3,4-tetrahydroquinolin-8-yl)urea (**15**, see **Figure S2**). A flame dried 20 mL scintillation vial was charged with **13** (100 mg, 0.305 mol, 1.00 equiv), Hantzsch ester (193 mg, 0.762 mmol, 2.50 equiv), diphenyl phosphate (38.2 mg, 0.153, 0.500 equiv), and 6 mL CH_2Cl_2. The vial was flushed with Ar, capped, and the reaction was stirred for 24 h. The solution was washed with $NaHCO_3$ (satd, aq, 6 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product, which included **13**, **14**, **15**, and **16**) was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex. The mostly pure product was further purified with automatic reversed-phase chromatography, eluting with a gradient of 25% to 100% MeCN/H_2O, with a 0.1% formic acid buffer (aq), to yield mostly pure **15** as a colorless oil. Yield not reported. Compound **15** was a minor regioisomer of this reaction, and it was difficult to obtain and purify preparative amounts of material for characterization. The product was assigned for conversion measurements by UPLC/MS by a mostly pure NMR. ^{1}H NMR (400 MHz, $CDCl_3$, mostly pure) δ 9.49 (s, 1H), 8.49 (dd, J = 7.7, 1.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.32 (d, J = 6.9 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.97 (s, 1H), 4.41 (bs, 1H), 3.39–3.26 (m, 2H),

2.83 (t, J = 6.4 Hz, 2H), 2.49 (s, 3H), 2.01–1.83 (m, 2H). In particular, an observed singlet for the C2 methyl group helps to differentiate this compound from **14**. UPLC/MS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{21}N_4O$ 333.17, found 333.35.

1-(2-methyl-1,2,3,4-tetrahydroquinolin-8-yl)-3-(1,2,3,4-tetrahydroquinolin-8-yl)urea (**16**, see **Figure S2**). A flame dried 4 mL scintillation vial was charged with **13** (20.0 mg, 0.0600 mol, 1.00 equiv), Hantzsch ester (38.0 mg, 0.150 mmol, 2.50 equiv), diphenyl phosphate (7.50 mg, 0.0300, 0.500 equiv), and 1.25 mL CH_2Cl_2. The vial was flushed with Ar, capped, and the reaction was stirred for 24 h. The solution was washed with $NaHCO_3$ (satd, aq, 1.5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product, which included **13**, **14**, **15**, and **16**) was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex to yield pure product. Yield: 5.6 mg beige solid, 28%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–7.00 (comp, 2H), 6.92–6.84 (comp, 12H), 6.67–6.57 (comp, 2H), 6.23–6.15 (comp, 2H), 3.41–3.33 (m, 1H), 3.33–3.27 (m, 2H), 2.89–2.79 (m, 1H), 2.79–2.71 (comp, 2H), 1.98–1.94 (m, 1H), 1.94–1.86 (comp, 2H), 1.62–1.48 (m, 1H), 1.22 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.9, 140.5, 128.2, 125.1, 123.4, 123.4, 122.1, 121.8, 117.4, 117.0, 47.4, 42.1, 29.9, 27.2, 26.8, 22.6, 21.9. IR (cm^{-1}, neat): 3318, 2930, 1630, 1604, 1529, 1472, 1328, 1302, 1232, 1190, 1104, 1026, 744. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{25}N_4O$ 337.2028, found 337.2022. Mp: >200 °C. TLC: R_f (2:1 Hex/EtOAc) 0.22, visualized with UV light. Assay of enantiomeric purity: Enantiomers of product **16** were separated by a chiral IB column, eluting at a flow rate of 1.0 mL/min with 10% EtOH/Hex. R_t[(*S*)-**16**] = 11 min; R_t[(*R*)-**16**] = 12 min.

Determination of Absolute Stereochemistry of 5+6. In our previous study of the reduction of monoquinoline **2** to **3**, **P1** and **1** gave opposite absolute stereochemical configurations, yet generate the same enantiomers in the reduction of **4**. To probe this intriguing reversal, the absolute stereochemistry of enantioenriched **6** was sought. Unfortunately, numerous attempts to grow a single crystal of **5** or **6**, in addition to a number of related compounds, proved futile. However, the absolute stereochemistry of **3** had been determined in our previous study,[15] and we wondered whether this could be converted into a derivative of **6**. As such, (*R*)-TRIP (**1**) was utilized to facilitate the HEH-mediated reduction of **17** to (*R*)-**18** (**Figure S3A**). The secondary amine of (*R*)-**18** was next dimethylated, and the primary amine was deprotected and dimerized with CDI to yield a mixture of (*R*,*R*)-**19** and *meso*-**20**. Intriguingly, the observed e.r. and dr (98:2 e.r., 4.26:1 dr) are similar to the predicted values from squaring the selectivity of the initial reduction (89:11 e.r., s = 8.1), which would give s^2 = 65, 98:2 e.r., 4.10 d.r.,

representing ideal Horeau kinetics for asymmetric amplification. Upon dimethylation of enantioenriched **6**, from reduction of **4** with (*R*)-TRIP (**1**), *chiral*-**19** proved to have *bis*-(*S*) stereochemistry (**Figure S2B**). Hence, while **P1** processes both monoquinoline **2** and bisquinoline **4** with the same absolute stereochemistry of reduction, **1** shows enantiodivergence, representing another intriguing complementary feature of these two catalyst systems.

Benzyl (2-methylquinolin-8-yl)carbamate (**17**, see **Figure S3A**). A flame dried 100 mL round bottom flask was charged with 8-aminoquinaldine (1.00 g, 6.23 mmol, 1.00 equiv), 25 mL THF, and 6.3 mL $NaHCO_3$ (satd, aq). The vessel was cooled to 0 °C, followed by addition of benzyl chloroformate dropwise (948 μL, 6.64 mmol, 1.05 equiv). The reaction was allowed to warm to rt slowly, and stirred overnight for 18 h. Upon completion of the reaction, the reaction was concentrated, redissolved in CH_2Cl_2 (20 mL), and washed with $NaHCO_3$ (satd, aq, 20 mL). The organics were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex to yield pure product. Yield: 1.454 g beige solid, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.42 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.54–7.33 (m, 7H), 7.29 (d, J = 8.4 Hz, 1H), 5.31 (s, 2H), 2.71 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.2, 153.5, 137.5, 136.3, 136.3, 134.0, 128.7, 128.5, 128.4, 126.2, 126.1, 122.5, 120.5, 114.6, 67.0, 25.2. IR (cm^{-1}, neat): 3357, 1723, 1604, 1573, 1521, 1492, 1455, 1434, 1383, 1339, 1311, 1237, 1192, 1109, 1023, 978, 862, 797, 748. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2$ 293.1290, found 293.1288. Mp: 79–80 °C. TLC: R_f (4:1 Hex/EtOAc) 0.50, visualized with UV light.

(R)-Benzyl (2-methyl-1,2,3,4-tetrahydroquinolin-8-yl)carbamate (**18**). The (*R*)-stereochemistry was assigned in analogy to a similar substrate from a previous study.[15] A flame dried 20 mL scintillation vial was charged with **17** (121 mg, 0.413 mmol, 1.00 equiv), Hantzsch ester (261 mg, 1.03 mmol, 2.50 equiv), and catalyst [**(A)** diphenyl phosphate (52.0 mg, 0.250 mmol, 0.500 equiv); **(B)** (*R*)-TRIP (**1**, 12.0 mg, 0.0159 mmol, 4 mol%)]. The vial was flushed with argon, charged with 8.5 mL CH_2Cl_2, capped, and stirred for 48 h. Upon completion, the reaction was washed with $NaHCO_3$ (satd, aq, 10 mL), with the aqueous layer being reextracted with CH_2Cl_2 (10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex to yield a mixture of **18** and oxidized HEH byproduct (HEox). For reaction **(B)**, the crude material was used in the next step without further purification assuming full yield. For reaction **(A)**, the crude material was further purified by two automatic

reversed-phase chromatography columns, eluting with a gradient of 30% to 100% MeCN/H_2O and 50% to 85% MeCN/H_2O, both with a 0.1% formic acid buffer (aq). The protonated product was dissolved in 2 mL CH_2Cl_2 (2 mL) and washed with 2 mL $NaHCO_3$ (satd, aq), dried over Na_2SO_4, filtered, and concentrated to yield pure **18** as a colorless oil. Yield not reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.31 (comp, 5H), 7.16 (bs, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.34 (bs, 1H), 3.41–3.31 (m, 1H), 2.90–2.71 (m, 2H), 1.93 (ddt, J = 11.9, 5.6, 3.1 Hz, 1H), 1.54 (ddt, J = 16.7, 12.0, 5.2 Hz, 1H), 1.23 (d, J = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO, 60 °C) δ 154.2, 137.8, 136.7, 128.1, 127.5, 125.4, 122.5, 122.4, 121.3, 115.2, 65.5, 46.4, 28.9, 26.0, 21.7. IR (cm^{-1}, thin film from $CHCl_3$): 3315, 2930, 1697, 1608, 1498, 1453, 1330, 1218, 1065, 1020, 982, 909, 728. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_2$ 297.1603, found 297.1603. TLC: R_f (4:1 Hex/EtOAc) 0.32, visualized with UV light. Assay of enantiomeric purity: Enantiomers of product **18** were separated by a chiral IB column, eluting at a flow rate of 1.0 mL/min with 15% EtOH/Hex. R_t[(*S*)-**18**] = 6.0 min; R_t[(*R*)-**18**] = 6.5 min.

Cis- and trans-1,3-bis(1,2-dimethyl-1,2,3,4-tetrahydroquinolin-8-yl)urea (**19+20**). *Preparation from **6***: Modified from literature precedent,[44] a flame dried 4 mL scintillation vial was charged with **6** (16.7 mg, 0.0476 mmol, 1.00 equiv), 0.75 mL MeCN, and formaldehyde (37% aq soln, 29.0 μL, 0.357 mmol, 7.50 equiv). Sodium cyanoborohydride (22.0 mg, 0.357 mmol, 7.50 equiv), handled entirely in a well ventilated fume hood or capped vials, was added quickly to the reaction. The vessel was fitted with a septum, pierced with a cannula leading to a solution of $NaHCO_3$ (satd, aq) to neutralize any HCN. Glacial acetic acid (10 μL) was added, and the reaction was allowed to stir for 1 h, after which more glacial acetic acid (10 μL) was added. The reaction was stirred overnight for 18 h, after which the mixture was slowly added to a solution of $NaHCO_3$ (satd, aq, 20 mL). This mixture was extracted with CH_2Cl_2 (20 mL x 2), and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex, followed by automatic reversed-phase chromatography, with a gradient eluent of 30% to 100% MeCN/H_2O, finally followed by normal-phase chromatography with a gradient eluent of 1% to 40% EtOAc/Hex to yield 10.8 mg of **19**+**20** as a white solid (60% yield). *Preparation from **17***: Modified from literature precedent,[44,45] a 100 mL round bottom flask containing crude **18**+HEox (assumed 0.413 mmol of **18**, 1.00 equiv) was charged with 3.0 mL MeCN and formaldehyde (37% aq soln, 168 μL, 2.07 mmol, 5.00 equiv). Sodi-

um cyanoborohydride (130 mg, 130 mmol, 5.00 equiv), handled entirely in a well ventilated fume hood or capped vials, was added quickly to the reaction. The vessel was fitted with a septum, pierced with a cannula leading to a solution of $NaHCO_3$ (satd, aq) to neutralize any HCN. Glacial acetic acid (123 μL) was added, and the reaction was allowed to stir for 15 min. A thick sludge formed; as such 2.0 mL of additional MeCN was added. The reaction was stirred overnight for 18 h, after which the mixture was slowly added to a solution of $NaHCO_3$ (satd, aq, 100 mL). This mixture was extracted with CH_2Cl_2 (100 mL x 2), and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 100% EtOAc/Hex, followed by automatic reversed-phase chromatography, with a gradient eluent of 25% to 100% MeCN/H_2O, with a 0.1% formic acid buffer (aq). The protonated product was dissolved in 2 mL CH_2Cl_2 (2 mL) and washed with 2 mL $NaHCO_3$ (satd, aq), dried over Na_2SO_4, filtered, and concentrated to yield 25.0 mg of mostly pure **21**, which was taken forward to the next step without further purification. A 10 mL round bottom containing **21** was charged with 0.75 mL MeOH and 0.75 mL THF. The vessel was fitted with a septum, which was pierced by a balloon of H_2, connected to a needle; and H_2 was bubbled through the solution. The reaction was stirred at rt overnight for 20 h, after which the crude mixture was filtered through a plug of celite, eluting with MeCN and MeOH. The solution was concentrated to yield 14 mg of mostly pure **22**, which was taken forward to the next step without further purification. A 4 mL scintillation vial containing **22** (14.0 mg, 0.0805 mmol, 1.00 equiv) was charged with 0.5 mL THF, followed by 1,1′-Carbonyldiimidazole (CDI, 31.0 mg, 0.191 mmol, 2.4 equiv), which was added portionwise over the course of 1 day. The vial was capped and heated at 70 °C for 96 h. Upon completion, the reaction was concentrated and purified by automatic normal phase chromatography, with a gradient eluent of 1% to 40% EtOAc/Hex, yielding pure product. Yield: 7.0 mg of **19**+**20** as a white solid, 4% yield from **17**, 4 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, J = 6.8 Hz, 1H), 7.29–7.23 (m, 1H), 6.95 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 3.09 (qd, J = 6.7, 3.5 Hz, 1H), 2.78–2.72 (m, 2H), 2.54 (d, J = 3.3 Hz, 3H), 2.04–1.88 (m, 1H), 1.69–1.50 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 153.6, 138.9, 138.7, 132.7, 129.9, 124.1, 123.0, 123.0, 118.4, 54.1, 54.0, 41.2, 40.6, 24.5, 24.3, 22.0, 19.2. IR (cm^{-1}, thin film from CH_2Cl_2): 3272, 2966, 2928, 1654, 1602, 1535, 1468, 1411, 1379, 1315, 1220, 1191, 771. HRMS (ESI-QToF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{31}N_4O$ 379.2498, found 379.2497. TLC: R_f (4:1 Hex/EtOAc) 0.17, visualized with UV light. Assay of enantiomeric purity: Enantiomers of products **19**+**20**

were separated by a chiral IB column, eluting at a flow rate of 1.0 mL/min with 2.0% EtOH/Hex. R_t[(*S,S*)-**19**] =14 min; R_t[**20**] =15 min; R_t[(*R,R*)-**19**] = 16 min.

General Procedures for Catalyst Screening. *Bisquinoline reduction.* A flame dried 5 mL scintillation vial was charged with substrate (**4** or **13**; 0.0600 mmol, 1.00 equiv), Hantzsch ester (38.0 mg, 0.150 mmol, 2.50 equiv), catalyst (**DPP**, **P1**, or **1**; 0.0120 mmol, 0.200 equiv), and 1.25 mL CH_2Cl_2. The vial was flushed with Ar, capped, and stirred for 24 h. After conclusion of the reaction, the conversion was measured by LC/MS. The reaction was washed with $NaHCO_3$ (satd, aq, 1.0 mL), the aqueous layer was reextracted with 2 mL CH_2Cl_2, and the combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product, which was purified by automatic normal-phase chromatography, with a gradient eluent of 5% to 75% EtOAc/Hex to yield *mono*-reduced products (**5**, **14**, or **15**), plus *di*-reduced products (**6**+**7** that were inseparable, or **16**). The e.r. and dr of both isolates were measured by HPLC. All reported results are the average of ≥ 2 trials.

Monoquinoline reduction (from literature precedent[15]): An oven dried 4 mL vial equipped with a stir bar was charged with catalyst (0.00600 mmol, 0.100 equiv), quinoline **17** (17.6 mg, 0.0600 mmol, 1.00 equiv), and Hantzsch ester (38.0 mg, 0.150 mmol, 2.5 equiv.). The vial was flushed with Ar, charged with 1.25 mL CH_2Cl_2, capped, and stirred for 24 h. The reaction was quenched by addition of $NaHCO_3$ (1 mL), with the aqueous layer being reextracted with CH_2Cl_2 (2 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated to yield crude product. This was taken up in $CDCl_3$ to determine conversion via ^{1}H NMR and e.r. by HPLC. Reported values are the average of 2 trials. With **P1** as catalyst, **18** was produced in 92% conv., 59:41 e.r.; with **1** as catalyst, **18** was produced in 99% conv., 11:89 e.r..

One-pot site- and enantioselective acylations and phosphorylations. Substrates **10** (14.3 mg, 0.0318 mmol, 1.00 equiv) and (±)-**8** (5.0 mg, 0.032 mmol, 1.0 equiv) were dissolved in PhMe (3 mL). Solutions of catalyst **P3** (0.7 mg, $6*10^{-4}$ mmol, 2 mol%) and **P2** (0.6 mg, $6*10^{-4}$ mmol, 2 mol%) were added, followed by triethylamine (distilled, 56 μL, 0.40 mmol, 13 equiv). Acetic anhydride (18 μL, 0.19 mmol, 6.0 equiv) and diphenylchlorophosphate (40 μL, 0.19 mmol, 6.0 equiv) were then added in rapid succession. After 1 h, an aliquot (1.5 mL) of the reaction was quenched with methanol (0.75 mL) and the solvent was removed *in vacuo*. Product distribution was monitored by ^{1}H and ^{31}P NMR spectroscopy (see **Figure 3**). Products were separated and analyzed by HPLC and GC as detailed below. *Separation of reaction products*: Reaction products **9**, **11**, and **12** were separated by

normal phase HPLC employing a YMC PVA-Sil column (Waters), eluting at a flow rate of 10 mL/min with the following gradient ramp from Hex to 6.5% ^{i}PrOH/Hex over 40 min. R_t(**9**+**12**) = 27 min; R_t(**11**) = 30 min. *Assay of enantiomeric purity (**11**)*: Enantiomers of product **11** were separated by chiral HPLC employing a Chiralcel OD column (Alltech), eluting at a flow rate of 0.5 mL/min with 30% EtOH/Hex. R_t[**11**(3-P)] = 11.5 min; R_t[**11**(1-P)] = 12.5 min.[46] *Separation of reaction products*: Reaction products **9** and **12** were separated by chiral HPLC employing an L-Leucine column (Regis), eluting at a flow rate of 0.5 mL/min with 15% EtOH/Hex. R_t(**12**) = 16.8 min; R_t(**9**) = 20.3 min. *Assay of enantiomeric purity (**9**)*: Enantiomers of product **9** were separated by chiral GC employing a 30m Chiraldex G-TA column (Alltech). Conditions: temperature = 135 °C; flow rate = 60 psi. R_t[(*R*,*R*)-**9**] = 12.0 min; R_t[(*S*,*S*)-**9**] = 12.8 min.[35] *Assay of enantiomeric purity (**12**)*: Enantiomers of product **12** were separated by a chiral OD column (Alltech), eluting at a flow rate of 0.5 mL/min with 1.5% EtOH/Hex. R_t[(*S*,*S*)-**12**] = 38 min; R_t[(*R*,*R*)-**12**] = 41 min.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Further commentary on Horeau amplification.
Study of CPA-mediated reduction of an unsymmetric bisquinoline
Schemes for substrate synthesis and testing
Tables for conversion dependence of enantioselectivities reduction of bisquinolines
HPLC and UPLC/MS traces for catalytic reductions
X-ray crystallographic data for compounds (±)-**5** and (±)-**14**

Crystallographic data are deposited with the Cambridge Crystallographic Data Centre under the accession numbers CCDC 1882216 and 1882217.

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Notes

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The authors declare no competing financial interests.

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for both **3** and **6**, while catalyst 1 produces (*R*)-**3** and (*S*)-**6** with opposite chirality. For assignment of the absolute stereochemistry of the products, see the **Supporting Information**.

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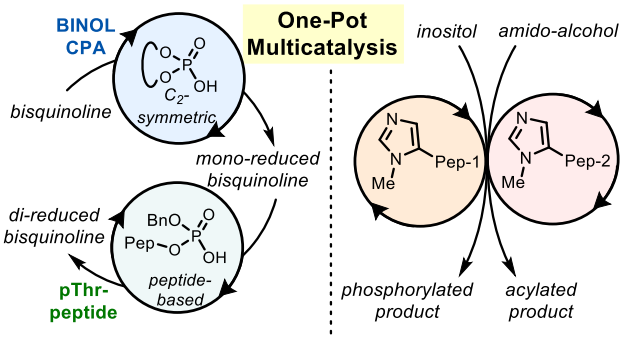
TOC Graphic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