Haptophilicity and Substrate Direction in Diastereoselective Heterogeneous Hydrogenation

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ABSTRACT. Stereoselectivity in heterogeneous hydrogenation of olefins and arenes is typically dictated by the steric properties of the organic substrate, and the inherent steric preference is difficult to alter through modification of catalyst or experimental parameters. One strategy to access counter-steric selectivity is to incorporate a stereochemically-defined functional group into the substrate that can adsorb to the catalyst surface and "direct" hydrogen addition from the same face. This perspective provides an overview of heterogeneous directed hydrogenation and elucidates a few design rules about directing group identity, substrate structure, and catalyst composition that lead to diastereoselective reactivity. Monometallic heterogeneous catalysts are capable of diastereoselective directed hydrogenation only with a limited set of substrate scaffolds and directing functional groups. In a given substrate, a complex interplay between directing group conformation, steric bulk, and adsorption strength makes it difficult to predict whether steric or electronic factors will dominate the diastereoselectivity. We then discuss more recent examples of

bimetallic catalysts for this reaction and look toward opportunities for bimetallic structures to yield more tunable and general heterogeneous directed hydrogenation catalysts.

Introduction

Supported metal nanoparticles are among the most important hydrogenation catalysts in the synthesis of complex organic molecules.¹⁻¹⁰ Because natural products and pharmaceutically-relevant compounds frequently contain multiple stereocenters, any hydrogenation steps in their synthetic routes will require differentiation of diastereotopic faces of the organic molecule.¹¹⁻¹⁸ Heterogeneous catalysts typically favor hydrogenation from the less-hindered face of the organic compound due to the steric constraints of substrate adsorption onto the metal nanoparticle surface.¹⁹⁻²³ This inherent steric preference comes from the substrate structure itself and is difficult to alter through either catalyst or experimental parameters. In order to access counter-steric selectivity, one strategy is to incorporate a stereochemically-defined functional group into the molecule that can coordinate to the catalyst surface and thereby "direct" hydrogen addition from the same face.



Figure 1: Steric vs. haptophilic facial selectivity preferences in heterogeneous catalysis.

The first observations of counter-steric selectivity in heterogeneous hydrogenation that are attributable to a directing group effect were made in the 1950s.²⁴⁻³⁰ These observations prompted a systematic exploration of the structural origin of counter-steric facial selectivity in a series of

papers by Thompson and coworkers in the 1970s.³¹⁻³⁶ Thompson postulated that a heterogeneous catalyst could be modelled as a nominally flat surface, and in the presence of a relatively flat polycyclic substrate, hydrogenation would always exhibit a steric preference to occur from the opposite face of a stereochemically-defined functional group (**Figure 1a**). However, if that functional group has a strong enough attractive interaction with the catalyst surface to overcome the inherent steric preference, the opposite stereoselectivity would be observed (**Figure 1b**). The term "haptophilicity" was coined to describe the interplay between functional group steric bulk and surface adsorption strength in dictating directed diastereoselectivity.

Monometallic Catalysts: Olefin Substrates

Thompson demonstrated these concepts in the hydrogenation of fluorene and phenanthrene derivatives using Pd/C and Pt/C catalysts. In the hydrogenation of a fluorene core (1), the identity of the functional group in the allylic position had a strong influence on the diastereoselectivity of the hydrogenation (**Table 1**).³⁵ An alcohol or aldehyde substituent (entry 1 and 2) resulted in a >90:10 ratio of hydrogen addition *cis* to the R group to generate the directed product **2a** while a carboxylic acid, ester, or ketone (entry 6-8) reversed the selectivity to ~20:80 in favor of *trans* addition (**2b**). The authors then correlated the observed *2a:2b* diastereomeric ratio to physical parameters of the functional group including electronegativity (X), basicity (pK_a), and molar refractivity (M_D), which serves as a proxy for volume. The authors hypothesized that steric bulk and electron density of the R group work at cross-purposes to dictate the facial selectivity of hydrogen addition. Comparison of R groups with similar size, CH₂OH vs. COOH, illustrates that the more electronegative and Lewis-basic alcohol functionality yields higher ratios of the directed *cis* product (entry 1, 6). Deprotonating the carboxylic acid to generate the Li and Na carboxylates increases their adsorption strength to the surface with the looser Na⁺ ion pair showing stronger

direction (entry 4, 5). In contrast, steric bulk of the functional group plays a major role in inhibiting directed diastereoselectivity. In a comparison of two R groups with similar electronic properties, CHO vs. COMe, the larger steric bulk of the ketone relative to the aldehyde flips the selectivity to 14:86 in favor of the sterically-preferred *trans* product (entry 2, 8). Unfortunately, it is not possible to define a unified parameter for group haptophilicity or directing ability because of the convoluted steric and electronic parameters of each functional group.

Table 1: Influence of functional group on directed diastereoselectivity and correlation to

 electronegativity, basicity, and molar refractivity.

	R	Pd/C H ₂ , MeO(CH ₂) ₂ C 1 atm, RT	→ → → → → → → → → → → → → → → → → → →	R directed	2b =	R
Entry	R	yield (%)	dr (2a:2b)	Х	pKa	M _D
1	CH,OH	>97	95:5	3.65	-2.2	7.24
2	CHO	°65	93:7	2.90	-8	5.73
3	CN	>97	75:25	3.20	-10	6.46
4	COONa	>90	55:45	2.95	+4.8	-
5	COOLi	>90	23:77	2.95	+4.8	-
6	COOH	>97	18:82	2.85	-6.1	7.25
7	COOMe	>97	15:85	2.75	-6.3	12.0
8	COMe	>97	14:86	2.70	-7.2	10.4

^aSide product is primarily the fully hydrogenated alcohol.

Thompson and coworkers subsequently showed that the choice of solvent was also critical in dictating the directing ability of an OH group in the hydrogenation of a phenanthrene scaffold (3) using both Pd/C and Pt/C (**Table 2**).³³ Solvents with high dielectric constants, typically containing Lewis basic functional groups, can competitively adsorb to the catalyst surface, inhibiting adsorption of the substrate via its OH directing group and preferentially producing the steric product **4b** (entry 2-5). The solvent-covered surface also presents a modified steric and dipolar environment as the substrate approaches the catalyst, which may alter the inherent preference of

the substrate-surface interaction. Non-polar and non-interacting solvents such as hexanes resulted in the highest diastereoselectivity toward the directed product **4a** (entry 1).

	CH ₂ OH	catalyst H ₂ , solvent 1 atm, RT	t 4a	CH ₂ OH	+ + + 4b	CH ₂ OH
		Dielectric	Pd/C		Pt/C	
Entry	Solvent	constant	yield (%)	dr (4a:4b)	yield (%)	dr (4a:4b)
1	Hexane	1.9	89	61:39	90	81:19
2	Bu ₂ O	3.1	94	27:73	90	51:49
3	DŃE	7.2	94	20:80	96	36:64
4	THF	7.6	93	18:82	90	30:70
5	DMF	36.7	99	6:94	90	9:91

 Table 2. Influence of solvent on directed diastereoselectivity.

Efforts to expand and generalize the concept of directed diastereoselective hydrogenation yielded mixed results in studies of monocyclic terpene-based scaffolds by Mitsui and Seghal.³⁷⁻³⁹ With OH as the directing functional group, Raney Ni showed modestly higher directed selectivity than Pt and other noble metal catalysts across most substrate scaffolds, but the maximum selectivity achievable ranged widely from 50:50 to 96:4 dr (a:b) depending on the steric properties of the substrate (**Table 3**). In considering a range of substrate structural motifs—homoallylic or allylic alcohols, 5- or 6-membered rings, endocyclic or exocyclic olefins—no obvious structural parameters could be correlated to higher directed diastereoselectivity. The greater conformational flexibility of the monocyclic structures compared to the fluorene and phenanthrene scaffolds make it more challenging to rationalize and predict how steric bulk and directing group adsorption interact in these substrates.

Table 3: Influence of metal catalyst and substrate structure on directed diastereoselectivity.

Substrate -	catalyst	OH	OH	
	H₂, EtOH	5-7 R +	5-7 JuR	
	1-60 atm, RT	a = directed	b	
Substrate	dr (a:b)	Substrate	dr (a:b)	
	Ni: 75:25	OH	Ni: 70:30	
	Pt: 30:70	Me	Pt: 31:69	
	Ni: 96:4	OH	Ni: 81:19	
	_r Pt: 55:45	Me	Pt: 33:67	
OH	Ni: 61:39	OH	Ni: 50:50	
n-F	Pr Pt: 53:47	Me	Pt: 33:67	
OH	Pr Ni: 74:26	Me	Ni: 52:48	
n-	Pt: 48:52		Pt: 24:76	

Nonetheless, due to the excellent reactivity of supported metal catalysts, numerous natural product total syntheses have taken advantage of a haptophilic effect to achieve highly diastereoselective heterogeneous hydrogenation. In the synthesis of (–)-englerin A by Ma and coworkers, hydrogenation of compound **5** was found to proceed selectively to the directed product **6** in the presence of Raney Ni at 90 atm of H₂ pressure (**Figure 2a**).⁴⁰ A previous racemic synthesis by Nicolau and coworkers utilized Crabtree's catalyst, an established molecular catalyst for OH-directed hydrogenation, to set the same stereocenter, which confirmed the role of the alcohol in directing facially-selective hydrogen addition.⁴¹ In the synthesis of fasicularin by Kibayashi and coworkers, an alcohol directing group was also thought to be critical in diastereoselective hydrogenation of an iminium intermediate, formed in-situ after deprotection of amine **7** in the presence of Pd/C and 1 atm H₂ (**Figure 2b**).⁴² A striking solvent effect was observed in this transformation where nonpolar solvents such as cyclohexane favored the directed product **8** (5.2:1)

while the reaction in EtOH produced a 1:1.7 mixture of diastereomers, consistent with an adsorptive interaction between the OH group and the Pd nanoparticle surface. Amines have also been utilized as directing groups in the diastereoselective directed hydrogenation of **9** toward the synthesis of (-)-hispidospermidin by Overman and coworkers.⁴³ Using Rh/C as the catalyst under 90 atm of H₂, the directed hydrogenation product **10** was obtained as a single diastereomer (**Figure 2c**). In this reaction, the Lewis basicity and small steric bulk of the primary amine were crucial toward obtaining strong directing group adsorption to the Rh surface. Tosyl-protected or alkyl-functionalized analogs of amine **9** resulted in significantly lower diastereoselectivity.^{44,45}



Figure 2. Synthetic examples of heterogeneous directed hydrogenation.

Around the same time that the haptophilic effect was first being explored in heterogeneous systems, Brown, Crabtree, Evans, and others demonstrated that molecular Ir and Rh complexes were effective catalysts for the directed hydrogenation of olefins with allylic and homoallylic

oxygen-containing directing groups.⁴⁶⁻⁵⁴ High diastereoselectivity was accessible across a broad substrate scope of cyclic and acyclic olefins, and introduction of chiral ligands into the catalyst complex could impart enantioselectivity to achiral substrates.⁵⁵ In a seminal review on substrate-directed chemical reactivity by Hoveyda, Evans, and Fu in 1993, the authors concluded that heterogeneous catalysts were inferior to their homogeneous counterparts for substrate-directed hydrogenation for the following reasons:

"Although heteroatom functional groups can influence the stereochemical course of heterogeneous reductions, a number of variables, such as the nature of the directing group, solvent, catalyst, support, and hydrogen pressure are important and often must be optimized to achieve useful levels of selectivity. These changes in reaction conditions cannot be effected predictably; poisoning is often a problem, and different catalyst batches seldom show identical reactivity. It is for these reasons that heterogeneous catalysis does not offer a general and reliable solution to the notion of heteroatom-directed hydrogenation reactions."⁵⁶

For these reasons and the excellent selectivity and generality of the molecular catalysts, relatively little work has been done in the intervening years on substrate-directed heterogeneous hydrogenation of olefins.

Monometallic Catalysts: Arenes

One area in which some effort has persisted in achieving stereoselective heterogeneous hydrogenation is in arene hydrogenation. The low reactivity of arenes necessitates high catalyst loading, hydrogen pressure, and temperature in order to achieve reasonable reactivity, and very few molecular catalysts are stable under these conditions.^{57,58} As a result, heterogeneous noble metal catalysts remain the dominant catalysts in arene hydrogenation.^{18,59-61}

Table 4: Influence of functional group in directed arene hydrogenation.

Ć	R	Rh/C or AI_2O_3 H ₂ , EtOH 49 atm, 25 °C	•	
	11		12a = di	rected 12b = steric
	Entry	R	yield (%)	dr (12a:12b)
	1	NH ₂ ª	100	98:2
	2	CH ₃	92	36:64
	3	OH	88	35:65
	4	OPr	88	8:92
	5	CO,H	>92	16:84
	6	COĴMe	>92	15:85
	7		>92	19:81
	8	OH ^Ē	89	85:15
	9	NH ₂ •HCI	90	68:32

^areaction at 70 °C ^bwith additional 6 mol% KOH

Systematic studies of Rh-catalyzed hydrogenation of indane derivatives (11) in ethanol clearly illustrated the intertwined roles of steric bulk and functional group Lewis basicity in the stereoselectivity of arene hydrogenation (**Table 4**).⁶²⁻⁶⁴ Interestingly, the only functional group that showed a significant preference for the directed product 12a was the primary amine (entry 1). The OH group, while capable of modest direction in the olefin examples described previously, showed the same selectivity as the Me substituent, indicating a predominantly steric preference (entry 2, 3). Bulkier groups (CO₂H, CO₂Me, CO₂NH₂, and OPr) shifted the selectivity further in favor of the steric product 12b (entry 4-7).

The need for stronger Lewis basicity in arene hydrogenation relative to olefins likely stems from the fact that the arene itself has a stronger π -adsorption interaction with the Rh surface, which must be partially disrupted in order for the substrate to adsorb from the same face as the directing group.^{65,66} The importance of strong Lewis basicity is further highlighted in the presence of acidic or basic additives. Upon addition of 6 mol% KOH to 1-indanol, a significant enhancement of the directed product was observed due to deprotonation of the OH group and its subsequent increase in basicity (entry 8). Correspondingly, protonation of the primary amine with HCl resulted in significant erosion of its directed stereoselectivity (entry 9). When strong Lewis bases like amines and alkoxides are required for adsorption to the catalyst surface, poisoning of the surface through irreversible coordination becomes a major issue.⁶⁷⁻⁷¹ In 1-indamine (entry 1), higher temperatures are required during hydrogenation in order to drive product desorption and catalyst turnover.



Figure 3. Chiral auxiliaries exert a predominantly steric influence in heterogeneous arene hydrogenation.

Due to the inherent planarity of arene substrates, significant effort has been invested in generating diastereotopic faces through covalent attachment of chiral auxiliaries. Chiral proline derivatives have been utilized as an auxiliary to enhance steric selectivity in heterogeneous arene hydrogenation (**Figure 3**).^{16,72-79} For example, hydrogenation of pyroglutamic acid covalently linked to o-toluic acid (**16**) resulted in 5:95 *dr* favoring the steric product over a Rh/Al₂O₃ catalyst (**Figure 3**).⁷⁹ Both the rigidity of the lactam and steric bulk of the CO₂Me substituent played important roles in dictating the high diastereoselectivity in this substrate. The less rigid proline

methyl ester (15) and less bulky prolinol (14) auxiliaries resulted in lower steric diastereoselectivities.^{80,81}

In contrast to sterically-governed chiral auxiliaries, Prins and coworkers utilized an anilide scaffold in order to introduce a proline moiety with a free secondary amine.⁸²⁻⁸⁴ As with the 1-indamine hydrogenation described above, the secondary amine **13** would likely have sufficient Lewis basicity to coordinate to the Rh surface. Indeed, moderate diastereoselectivity toward the directed product (78:22 *dr*) was observed, likely through amine coordination to the Rh surface and minimization of steric repulsion between the ortho-methyl group and the proline moiety.





Relatively few synthetic examples exist of directed arene hydrogenation in complex natural product synthesis. Daich and coworkers utilized a diastereoselective hydrogenation of a furan moiety (17, 19) as a key step to generate several members of the tricyclic furoindolizidinol family (18, 20).⁸⁵ In this work, the highly oxophilic Raney Ni catalyst showed superior

diastereoselectivity toward the OH-directed product (**18a**, **20a**) compared to the noble metal Pd, Rh, and Ru catalysts (**Table 5**). However, complex steric and electronic effects were still at play given the dramatic changes in absolute diastereomeric ratio depending on the orientation of the furan ring.

Based on the literature discussed thus far, some general trends on haptophilicity as a driving force for diastereoselective heterogeneous hydrogenation can be elucidated. Raney Ni consistently shows higher directed diastereoselectivity for oxygen-based directing groups compared to noble metal catalysts such as Pt, Pd, Rh, and Ru. However, Raney Ni is the least reactive hydrogenation catalyst and requires high catalyst loadings and harsh conditions, typically high H₂ pressure and long reaction times, in order to drive reactivity. Amine directing groups show stronger adsorptive interactions with noble metal catalysts compared to alcohols and are capable of inducing diastereoselective hydrogenation of arenes. However, product inhibition and catalyst turnover become a challenge due to the strong binding of the amine to the surface. Across all examples, the substrate scope of heterogeneous directed hydrogenation is limited, and product diastereoselectivity is difficult to predict based on substrate structure and directing functional group. In light of these observations, monometallic catalysts do not provide a general solution toward the directed hydrogenation of olefins and arenes.

Bimetallic Catalysts



Figure 4. (a) Bimetallic catalyst design for directed hydrogenation compared to **(b)** molecular Crabtree's catalyst. **(c)** Comparison of directed diastereoselectivity using pseudo-axial and pseudo-equatorial directing groups.

Recently, our group hypothesized that bimetallic catalysts with two distinct binding sites may provide a more general solution to achieving high diastereoselectivity in the OH-directed heterogeneous hydrogenation reaction. Using bimetallic alloys containing a noble metal and a firstrow transition metal, we envisioned that the OH directing group would preferentially bind to the more oxophilic first-row transition metal while the noble metal would still be available to activate H_2 and bind the olefin (**Figure 4a**).⁸⁶ We showed that careful control over surface composition in a Pd-Cu bimetallic nanoparticle enabled high diastereoselectivity in the hydrogenation of a range of cyclic homoallylic and allylic alcohols, achieving comparable diastereoselectivities in some cases to Crabtree's catalyst, [Ir(COD)(py)(PCy₃)]PF₆ (**Figure 4b**). While the conformation of the substrate still had an impact on the inherent steric preferences of the hydrogenation, we were able to elucidate a general principle for directed substrate design in heterogeneous systems. Substrates with a pseudo-axial OH directing group (21) were capable of strong haptophilic interaction with the Pd-Cu surface, resulting in diastereoselectivities >92:8 across a range of structures, while equatorial OH groups (22) led to much lower diastereoinduction (Figure 4c).



Table 6. Large-scale heterogeneous hydrogenation of a chiral imine using a bimetallic catalyst.

To our knowledge, only one other example has used the formation of a bimetallic structure to enhance hydrogenation diastereoselectivity compared to its monometallic counterpart, which in this case relies primarily on steric control. In the process optimization for pilot-scale synthesis of peliglitizar, a candidate drug for type II diabetes, Muslehiddinoglu, Li, and coworkers developed a diastereoselective hydrogenation of imine **23** containing an alpha-phenylethylamine chiral auxiliary (**Table 6**).⁸⁷ In this example, addition of Cu or Na to Pd/C enhanced the inherent selectivity preference of the substrate (86:14 *dr* on pure Pd, entry 3) to achieve 97:3 *dr* over the bimetallic catalyst (entry 5, 6). The addition of chiral organic modifiers to Pd/C was also effective in enhancing diastereoselectivity to some degree (entry 4), a strategy that creates a chiral steric environment at the catalyst surface.⁸⁸⁻⁹² While the steric properties of the chiral auxiliary dictate

hydrogenation diastereoselectivity regardless of the catalyst composition, enhanced imine adsorption to the Pd-Cu bimetallic surface may help reduce formation of the undesired product.

New Catalyst Designs

In order to design more selective bimetallic catalysts for directed heterogeneous hydrogenation, we draw inspiration from a large body of literature on noble metal bimetallic nanoparticles that have demonstrated excellent hydrogenation selectivity and reactivity compared to their noble metal-only counterparts.⁹³⁻⁹⁷ While we will not exhaustively review this body of literature, we hope to highlight a few examples that illustrate the versatility of bimetallic structures in altering substrate adsorption, reaction chemoselectivity, and catalytic rates. The observed catalytic changes typically stem from three possible modifications to surface properties upon formation of the bimetallic structure—electronic hybridization with the second metal, a change in surface ensemble geometry, and the creation of heterobimetallic adsorption sites (**Figure 5**). We anticipate that all of these bimetallic mechanisms will be relevant for heterogeneous directed hydrogenation.





Electronic modification of the noble metal through hybridization with the second metal in a coreshell or alloy structure will have a major impact on the adsorption strength of any heteroatom directing group as well as the arene or olefin to be hydrogenated. Core-shell structures exemplify a purely electronic effect, wherein the ensemble geometry of the surface remains nearly identical to that of the monometallic structure, but the electronic and redox properties of the surface are strongly influenced by the underlying core metal.⁹⁸⁻¹⁰⁰ This concept has been utilized most frequently in electrocatalysis, but surface science and DFT studies on single crystal model systems have shown that gaseous adsorbates bind very differently on supported monolayer films compared to thicker slabs.¹⁰¹⁻¹⁰⁹ For example, Chen and coworkers showed that ethylene adsorbs as a di- σ -bonded intermediate on bulk Pt(111) single crystals but exhibits much weaker binding as a π -coordinated species on Pt epitaxial monolayers grown on Ni(111).^{110,111} For directed hydrogenation, we anticipate that weakening surface binding of the olefin or arene while retaining or strengthening directing group coordination will be a key strategy toward increasing selectivity for the directed reaction.

Another common bimetallic design is known as a single-atom alloy, in which the noble metal is sufficiently dilute in the surface so as to have no other noble metal nearest neighbors. Site isolation of the noble metal combined with its electronic modification through alloy formation is crucial towards achieving reaction selectivity.¹¹²⁻¹¹⁴ Dilute alloys of active noble metals (Pd, Pt, Rh) embedded within a more inert matrix (Cu, Ag, Au) have shown excellent chemoselectivity for the semihydrogenation of alkynes and dienes.¹¹⁵⁻¹¹⁹ In most cases, the selectivity stems from a significantly weaker adsorption of the semihydrogenated product on the isolated atom site compared to a larger ensemble, leading to fast product desorption and suppression of over-hydrogenation. Intermetallic alloy surfaces have also been leveraged to a similar effect to enforce site isolation of an active metal within a more inert matrix.¹²⁰⁻¹²⁴

In addition to unsaturated C-C bonds, bimetallic alloys have also proven effective in the selective hydrogenation of carbonyls in the presence of olefins.¹²⁵⁻¹³¹ Similar to the alkyne

semihydrogenation examples, weakening of olefin adsorption to the noble metal likely plays an important role in achieving chemoselectivity.^{132,133} However, bifunctional binding to both metal atoms in the bimetallic may also be critical. Using alloys of an active metal (Ru, Rh, Ir, Pd, Pt) with a more oxophilic partner (Re, Fe, Co, Zn, Sn), selective carbonyl hydrogenation is illustrative of a reaction that relies upon electronic modification, ensemble geometry reduction, and bifunctional reactivity to achieve high chemoselectivity (**Figure 6a**).¹³⁴⁻¹⁴¹ Adsorption of the aldehyde moiety on the base metal species and activation of H₂ on the noble metal contributes to preferential carbonyl hydrogenation, but suppression of the native reactivity of the noble metal through electronic and ensemble geometry perturbation is also required.



Figure 6. Heterogeneous reactions that utilize bifunctional substrate adsorption to influence catalytic reactivity or chemoselectivity.

Catalytic reactions that rely on bifunctional binding of reactants typically feature substrates containing both carbon and oxygen functionality and catalysts containing both an active metal and an oxophilic component.¹⁴²⁻¹⁴⁴ The oxophilic component can take the form of a base metal in a bimetallic alloy or a metal oxide support material. In phenolic hydrodeoxygenation reactions catalyzed by noble metals supported on reducible oxides, bifunctional adsorption occurs at the

metal-support interface (**Figure 6b**).^{143,145,146} Hydrogen and the aromatic ring of phenol are activated on the noble metal nanoparticle while the OH group binds strongly to the reduced metal oxide, facilitating the cleavage of the C–O bond at the interface and dramatically increasing turnover frequency (TOF) relative to the noble metal nanoparticle alone.¹⁴⁷⁻¹⁴⁹ CO₂ hydrogenation over Cu/ZnO/Al₂O₃ is likewise thought to be an interfacial reaction, where bifunctional binding of CO₂ across the Cu/ZnO interface enhances reactivity and alters product selectivity from CO to methanol (**Figure 6c**).¹⁵⁰⁻¹⁵⁵

The ideal catalyst for heterogeneous directed hydrogenation will likely contain elements from each of these bimetallic examples. Some of the key design principles include 1) limiting the size of large noble metal ensembles to weaken olefin or arene adsorption and minimize undirected reactivity, 2) creating an atomic-level mixture of the two metals for bifunctional substrate adsorption, either in the form of a bimetallic alloy or metal/metal oxide interface, and 3) tuning the electronic properties of the bimetallic surface for efficient H₂ activation, directing group coordination, and product desorption. In addition, the precise composition and ratio of the bimetallic surface will need to be tailored to the organic substrate and directing functionality. We anticipate that the Lewis acidity of the second metal must be matched to the Lewis basicity of the directing group in order to achieve optimal directing group binding and turnover. The electronic and geometric properties of the noble metal will likewise require tuning to achieve moderatestrength olefin or arene adsorption, sufficient to drive hydrogenation reactivity but not so strong that the undirected reaction dominates.

Given the advances in atomically-precise materials synthesis and characterization over the last three decades, we believe that many of the challenges associated with heterogeneous directed hydrogenation can now be addressed through the synthesis of well-defined bimetallic catalysts. In particular, batch-to-batch reproducibility is much improved across the entire field of heterogeneous catalysis due to improved control over materials synthesis coupled to detailed structural characterization for every batch. Poisoning of the surface by the directing group can be alleviated in bimetallic catalysts because the identity and concentration of the alloying metal can be modified in order to weaken (or strengthen) directing group surface coordination. Finally, understanding how substrate structure, directing group identity, and experimental parameters influence the stereochemical outcome of heterogeneous reactions remains an open question. With the synthetic tools now available, we can systematically study these parameters and tailor the bimetallic surface appropriately to maximize reactivity and selectivity for any class of organic compound. In doing so, we aim to elucidate design principles for the catalyst and organic substrate that will enable predictable, general, and reliable heterogeneous directed hydrogenation.

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REFERENCES

- (1) Sabatier, P. *La catalyse en chimie organique*; C. Béranger: France, 1920.
- (2) Raney, M. Catalysts from alloys Nickel catalysts. *Ind. Eng. Chem.*, **1940**, *32*, 1199-1203.
- (3) Lindlar, H. Ein Neuer Katalysator Fur Selektive Hydrierungen. *Helv. Chim. Acta*, **1952**, *35*, 446-456.

- (4) Bond, G. C.; Webb, G.; Wells, P. B.; Winterbottom, J. M. Patterns of Behavior in Catalysis by Metals. *J. Catal.*, **1962**, *1*, 74-84.
- (5) Freifelder, M. Catalytic hydrogenation in organic synthesis; Wiley, 1978.
- (6) Rylander, P. N. *Catalytic hydrogenation in organic syntheses*; Academic Press: San Diego, 1979.
- (7) Augustine, R. L. *Heterogeneous catalysis for the synthetic chemist*; M. Dekker: New York, 1996.
- (8) Augustine, R. L. Selective heterogeneously catalyzed hydrogenations. *Catal. Today*, **1997**, *37*, 419-440.
- (9) Nishimura, S. *Handbook of heterogeneous catalytic hydrogenation for organic synthesis*; Wiley New York, 2001.
- (10) Augustine, R. L. Whither Goest Thou, Catalysis. Catal. Lett., 2016, 146, 2393-2416.
- (11) Fujimoto, R.; Kishi, Y.; Blount, J. F. Total synthesis of (±)-gephyrotoxin. J. Am. Chem. Soc., **1980**, 102, 7154-7156.
- (12) Lu, Z.; Li, Y.; Deng, J.; Li, A. Total synthesis of the Daphniphyllum alkaloid daphenylline. *Nat. Chem.*, **2013**, *5*, 679-684.
- (13) Shi, H. Y.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J. Total Synthesis of (-)-Himalensine A. J. Am. Chem. Soc., 2017, 139, 17755-17758.
- (14) Zhang, Y. D.; Danishefsky, S. J. Total Synthesis of (±)-Aplykurodinone-1: Traceless Stereochemical Guidance. J. Am. Chem. Soc., 2010, 132, 9567-9569.
- (15) Zhao, N.; Yin, S. Q.; Xie, S. L.; Yan, H.; Ren, P.; Chen, G.; Chen, F.; Xu, J. Total Synthesis of Astellatol. *Angew Chem Int Edit*, **2018**, *57*, 3386-3390.
- (16) Kukula, P.; Prins, R. Diastereoselective hydrogenation in the preparation of fine chemicals. *Top. Catal.*, **2003**, *25*, 29-42.
- (17) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J. C.; Huang, A.; Rivera, N. R.; Njolito, E.; Hsiao, Y.; McWilliams, J. C.; Williams, J. M.; Armstrong, J. D.; Sun, Y. K.; Mathre, D. J.; Grabowski, E. J. J.; Tillyer, R. D. Highly diastereoselective heterogeneously catalyzed hydrogenation of enamines for the synthesis of chiral beta-amino acid derivatives. J. Am. Chem. Soc., 2004, 126, 3048-3049.
- (18) Gualandi, A.; Savoia, D. Substrate induced diastereoselective hydrogenation/reduction of arenes and heteroarenes. *RSC Adv.*, **2016**, *6*, 18419-18451.
- (19) Burwell, R. L. Stereochemistry and Heterogeneous Catalysis. *Chem. Rev.*, **1957**, *57*, 895-934.
- (20) Cocker, W.; Shannon, P. V. R.; Staniland, P. A. The chemistry of terpenes. Part I. Hydrogenation of the pinenes and the carenes. J. Chem. Soc. C, **1966**, 41-47.
- (21) Bartók, M. Stereochemistry of heterogeneous metal catalysis; Wiley: Chichester, New York, 1985.
- (22) Glorius, F. Asymmetric hydrogenation of aromatic compounds. *Org. Biomol. Chem.*, **2005**, *3*, 4171-4175.
- (23) Moock, D.; Wagener, T.; Hu, T.; Gallagher, T.; Glorius, F. Enantio- and Diastereoselective, Complete Hydrogenation of Benzofurans by Cascade Catalysis. *Angew. Chem. Int. Ed.*, **2021**, *60*, 13677-13681.
- (24) Minckler, L. S.; Hussey, A. S.; Baker, R. H. The Stereoisomers of 10-Hydroxymethyl-2decalol. J. Am. Chem. Soc., 1956, 78, 1009-1012.

- (25) Haynes, N. B.; Timmons, C. J. The Hydrogenation of Some Hexahydronaphthalene Derivatives as a Step in Terpene Syntheses. *Proc. Chem. Soc. Lond.*, **1958**, 345-346.
- (26) Dart, M. C.; Henbest, H. B. 714. Aspects of stereochemistry. Part XV. Catalytic hydrogenation of cyclic allylic alcohols in the presence of sodium nitrite. J. Chem. Soc., 1960, 3563-3570.
- Halsall, T. G.; Rodewald, W. J.; Willis, D. Studies in the Synthesis of Terpenes. Part IV. The Synthesis of (±)-6-Beta-Hydroxy-5 : 5 : 9-Beta-Trimethyl-Trans-Decal-2-One. J. Chem. Soc., 1959, 2798-2804.
- (28) Howard, T. J. Competition between steric and non-steric directive effects in catalytic hydrogenation: Preliminary communication. *Recl. Trav. Chim. Pays-Bas*, **1964**, *83*, 992-994.
- (29) Nishimura, S.; Mori, K. Hydrogenation and Hydrogenolysis. VI. The Stereochemistry of the Catalytic Hydrogenation of Some Allylic Alcohols Related to Cholest-4-ene. *Bull. Chem. Soc. Jpn.*, **1963**, *36*, 318-320.
- (30) Mcmurry, J. E. Total Synthesis of Copacamphene. *Tetrahedron Lett.*, **1970**, 3731-&.
- (31) Thompson, H. W.; Wong, J. K. Stereochemical control of reductions. 8. Exploration of the inner limits of the haptophilic effect with 2-exo-substituted 7-methylenenorbornanes. *J. Org. Chem.*, **1985**, *50*, 4270-4276.
- (32) Thompson, H. W.; McPherson, E. Stereochemical control of reductions. 6. The hydroxymethyl group as a hinge for internal reagent delivery. *J. Org. Chem.*, **1977**, *42*, 3350-3353.
- (33) Thompson, H. W.; McPherson, E.; Lences, B. L. Stereochemical control of reductions. 5. Effects of electron density and solvent on group haptophilicity. *J. Org. Chem.*, **1976**, *41*, 2903-2906.
- (34) Thompson, H. W.; McPherson, E. Stereochemical control of reductions. IV. Control of hydrogenation stereochemistry by intramolecular anionic coordination to homogeneous catalysts. *J. Am. Chem. Soc.*, **1974**, *96*, 6232-6233.
- (35) Thompson, H. W.; Naipawer, R. E. Stereochemical control of reductions. III. Approach to group haptophilicities. *J. Am. Chem. Soc.*, **1973**, *95*, 6379-6386.
- (36) Thompson, H. W. Stereochemical control of reductions. Directive effect of carbomethoxy vs. hydroxymethyl groups in catalytic hydrogenation. J. Org. Chem., **1971**, *36*, 2577-2581.
- (37) Mitsui, S.; Ito, M.; Nanbu, A.; Senda, Y. Stereochemistry and mechanism of the catalytic hydrogenation of methylcyclohexenols. *J. Catal.*, **1975**, *36*, 119-124.
- (38) Mitsui, S.; Senda, Y.; Saito, H. The Stereoselectivity of Catalysts in Hydrogenation. I. The Catalytic Hydrogenation of 2-Cyclopentylidenecyclopentanol and 2-Benzylidene-1-tetralol. *Bull. Chem. Soc. Jpn.*, **1966**, *39*, 694-697.
- (39) Sehgal, R. K.; Koenigsberger, R. U.; Howard, T. J. Effect of ring size on hydrogenation of cyclic allylic alcohols. *J. Org. Chem.*, **1975**, *40*, 3073-3078.
- (40) Zhou, Q.; Chen, X.; Ma, D. Asymmetric, Protecting-Group-Free Total Synthesis of (-)-Englerin A. Angew. Chem. Int. Ed., 2010, 49, 3513-3516.
- (41) Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. Total Synthesis of Englerin A. J. Am. Chem. Soc., **2010**, 132, 8219-8222.
- (42) Abe, H.; Aoyagi, S.; Kibayashi, C. First Total Synthesis of the Marine Alkaloids (±)-Fasicularin and (±)-Lepadiformine Based on Stereocontrolled Intramolecular Acylnitroso-Diels–Alder Reaction. J. Am. Chem. Soc., 2000, 122, 4583-4592.

- (43) Overman, L. E.; Tomasi, A. L. Enantioselective Total Synthesis of Hispidospermidin. J. Am. Chem. Soc., **1998**, 120, 4039-4040.
- (44) Tamiya, J.; Sorensen, E. J. A spontaneous bicyclization facilitates a synthesis of (-)hispidospermidin. *Tetrahedron*, **2003**, *59*, 6921-6932.
- (45) Tamiya, J.; Sorensen, E. J. A Concise Synthesis of (-)-Hispidospermidin Guided by a Postulated Biogenesis. J. Am. Chem. Soc., 2000, 122, 9556-9557.
- (46) Brown, J. M. Directed Homogeneous Hydrogenation [New Synthetic Methods (65)]. *Angewandte Chemie International Edition in English*, **1987**, *26*, 190-203.
- (47) Brown, J. M.; Hall, S. A. Scope and limitations of the stereoselective homogeneous hydrogenation of methylenecyclohexanols by cationic rhodium complexes. *Tetrahedron Lett.*, **1984**, *25*, 1393-1396.
- (48) Crabtree, R. H.; Davis, M. W. Directing Effects in Homogeneous Hydrogenation with [Ir(cod)(PCy₃)(py)]PF₆. J. Org. Chem., **1986**, 51, 2655-2661.
- (49) Crabtree, R. H.; Davis, M. W. Occurrence and Origin of a Pronounced Directing Effect of a Hydroxyl Group in Hydrogenation with [Ir(cod)P-C-Hx₃(Py)]PF₆. Organometallics, 1983, 2, 681-682.
- (50) Crabtree, R. H.; Felkin, H.; Fillebeenkhan, T.; Morris, G. E. Dihydridoiridium Diolefin Complexes as Intermediates in Homogeneous Hydrogenation. *J. Organomet. Chem.*, **1979**, *168*, 183-195.
- (51) Crabtree, R. H.; Felkin, H.; Morris, G. E. Cationic Iridium Diolefin Complexes as Alkene Hydrogenation Catalysts and Isolation of Some Related Hydrido Complexes. J. Organomet. Chem., 1977, 141, 205-215.
- (52) Evans, D. A.; Morrissey, M. M.; Dow, R. L. Hydroxyl-Directed Hydrogenation of Homoallylic Alcohols Effects of Achiral and Chiral Rhodium Catalysts on 1,3 Stereocontrol. *Tetrahedron Lett.*, **1985**, *26*, 6005-6008.
- (53) Evans, D. A.; Morrissey, M. M. Rhodium(I)-Catalyzed Hydrogenation of Olefins the Documentation of Hydroxyl-Directed Stereochemical Control in Cyclic and Acyclic Systems. J. Am. Chem. Soc., **1984**, 106, 3866-3868.
- (54) Stork, G.; Kahne, D. E. Stereocontrol in Homogeneous Catalytic Hydrogenation via Hydroxyl Group Coordination. J. Am. Chem. Soc., **1983**, 105, 1072-1073.
- (55) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. Asymmetric Hydrogenation of Olefins Using Chiral Crabtree-type Catalysts: Scope and Limitations. *Chem. Rev.*, **2014**, *114*, 2130-2169.
- (56) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-directable chemical reactions. *Chem. Rev.*, **1993**, *93*, 1307-1370.
- (57) Widegren, J. A.; Finke, R. G. A review of the problem of distinguishing true homogeneous catalysis from soluble or other metal-particle heterogeneous catalysis under reducing conditions. *J. Mol. Catal. A: Chem.*, **2003**, *198*, 317-341.
- (58) Tran, B. L.; Fulton, J. L.; Linehan, J. C.; Lercher, J. A.; Bullock, R. M. Rh(CAAC)-Catalyzed Arene Hydrogenation: Evidence for Nanocatalysis and Sterically Controlled Site-Selective Hydrogenation. *ACS Catal.*, **2018**, *8*, 8441-8449.
- (59) Wiesenfeldt, M. P.; Nairoukh, Z.; Dalton, T.; Glorius, F. Selective Arene Hydrogenation for Direct Access to Saturated Carbo- and Heterocycles. *Angew. Chem. Int. Ed.*, **2019**, *58*, 10460-10476.

- Maegawa, T.; Akashi, A.; Yaguchi, K.; Iwasaki, Y.; Shigetsura, M.; Monguchi, Y.; Sajiki, H. Efficient and Practical Arene Hydrogenation by Heterogeneous Catalysts under Mild Conditions. *Chem. Eur. J.*, 2009, *15*, 6953-6963.
- (61) Augustine, R. L. *Heterogeneous catalysis for the synthetic chemist*; CRC Press, 2020.
- (62) Ranade, V. S.; Consiglio, G.; Prins, R. Functional-Group-Directed Diastereoselective Hydrogenation of Aromatic Compounds. 2. J. Org. Chem., **2000**, 65, 1132-1138.
- (63) Ranade, V. S.; Consiglio, G.; Prins, R. Functional-Group-Directed Diastereoselective Hydrogenation of Aromatic Compounds. 1. J. Org. Chem., **1999**, *64*, 8862-8867.
- (64) Borszeky, K.; Mallat, T.; Baiker, A. Diastereoselective Hydrogenation of Indenols: Evidence for Sterically and Electronically Unfavorable Adsorption on Palladium. J. Catal., 1999, 188, 413-416.
- (65) He, H. R.; Dasgupta, A.; Rioux, R. M.; Meyer, R. J.; Janik, M. J. Competitive Hydrogenation between Linear Alkenes and Aromatics on Close-Packed Late Transition Metal Surfaces. *J. Phys. Chem. C*, **2019**, *123*, 8370-8378.
- (66) Jenkins, S. J. Aromatic adsorption on metals via first-principles density functional theory. *Proc. Math. Phys. Eng. Sci.*, **2009**, *465*, 2949-2976.
- (67) Kunz, S. Supported, Ligand-Functionalized Nanoparticles: An Attempt to Rationalize the Application and Potential of Ligands in Heterogeneous Catalysis. *Top. Catal.*, **2016**, *59*, 1671-1685.
- (68) Chen, T. Y.; Rodionov, V. O. Controllable Catalysis with Nanoparticles: Bimetallic Alloy Systems and Surface Adsorbates. *ACS Catal.*, **2016**, *6*, 4025-4033.
- (69) Niu, Z. Q.; Li, Y. D. Removal and Utilization of Capping Agents in Nanocatalysis. *Chem. Mater.*, **2014**, *26*, 72-83.
- (70) Schoenbaum, C. A.; Schwartz, D. K.; Medlin, J. W. Controlling the Surface Environment of Heterogeneous Catalysts Using Self-Assembled Monolayers. Acc. Chem. Res., 2014, 47, 1438-1445.
- (71) Vile, G.; Albani, D.; Almora-Barrios, N.; Lopez, N.; Perez-Ramirez, J. Advances in the Design of Nanostructured Catalysts for Selective Hydrogenation. *ChemCatChem*, 2016, 8, 21-33.
- (72) Tungler, A.; Fodor, K. Synthesis of chiral amino acids and amines over solid catalysts. *Catal. Today*, **1997**, *37*, 191-208.
- (73) Besson, M.; Pinel, C. Diastereoselective catalytic hydrogenation on heterogeneous metal catalysts. *Top. Catal.*, **1998**, *5*, 25.
- (74) Douja, N.; Besson, M.; Gallezot, P.; Pinel, C. Diastereoselective hydrogenation of 2-methylnicotinic acid derivatives with supported metallic catalysts. J. Mol. Catal. A: Chem., 2002, 186, 145-151.
- (75) Douja, N.; Malacea, R.; Besson, M.; Pinel, C. Heterogeneous diastereoselective hydrogenation of pyridine and corresponding enamine covalently bound to pantolactone. *J. Mol. Catal. A: Chem.*, **2004**, *210*, 205-209.
- (76) Háda, V.; Tungler, A.; Szepesy, L. Diastereoselective heterogeneous catalytic hydrogenation of N-heterocycles: Part II. Hydrogenation of pyrroles. *Appl. Catal., A*, **2001**, *210*, 165-171.
- (77) Hegedűs, L.; Háda, V.; Tungler, A.; Máthé, T.; Szepesy, L. Diastereoselective heterogeneous catalytic hydrogenation of N-heterocycles. Part I. Hydrogenation of pyridines. *Appl. Catal.*, *A*, **2000**, *201*, 107-114.

- (78) Besson, M.; Gallezot, P.; Neto, S.; Pinel, C. Diastereoselective hydrogenation of o-toluic acid derivatives over supported rhodium and ruthenium heterogeneous catalysts. *Chem. Commun.*, **1998**, 1431-1432.
- (79) Besson, M.; Delbecq, F.; Gallezot, P.; Neto, S.; Pinel, C. Asymmetric Synthesis of 2-Methyl Cyclohexane Carboxylic Acids by Heterogeneous Catalysis: Mechanistic Aspects. *Chem. Eur. J.*, **2000**, *6*, 949-958.
- (80) Besson, M.; Gallezot, P.; Neto, S.; Pinel, C. Influence of the nature of chiral auxiliaries on the diastereoselective hydrogenation of ortho-substituted benzoic acid derivatives. *Tetrahedron Asymmetry*, **2000**, *11*, 1809-1818.
- (81) Besson, M.; Blanc, B.; Champelet, M.; Gallezot, P.; Nasar, K.; Pinel, C. Diastereoselective Hydrogenation of Substituted Aromatics on Supported Metal Catalysts. *J. Catal.*, **1997**, *170*, 254-264.
- (82) Kukula, P.; Prins, R. Diastereoselective hydrogenation of pyrazine derivatives: An alternative method of preparing piperazine-(2S)-carboxylic acid. J. Catal., **2002**, 208, 404-411.
- (83) Ranade, V. S.; Consiglio, G.; Prins, R. Catalytic diastereoselective hydrogenation of (S)-proline-modified anthranilic acid. *Catal. Lett.*, **1999**, *58*, 71-74.
- (84) Ranade, V. S.; Prins, R. Diastereoselective Hydrogenation of (S)-Proline-2-methylanilide. *J. Catal.*, **1999**, *185*, 479-486.
- (85) Šafář, P.; Žúžiová, J.; Marchalín, Š.; Tóthová, E.; Prónayová, N.; Švorc, Ľ.; Vrábel, V.; Daïch, A. Highly diastereoselective approach to novel phenylindolizidinols via benzothieno analogues of tylophorine based on reductive desulfurization of benzo[b]thiophene. *Tetrahedron Asymmetry*, **2009**, *20*, 626-634.
- (86) Shumski, A. J.; Swann, W. A.; Escorcia, N. J.; Li, C. W. Heterogeneous Hydroxyl-Directed Hydrogenation: Control of Diastereoselectivity through Bimetallic Surface Composition. ACS Catal., 2021, 11, 6128-6134.
- (87) Müslehiddinoğlu, J.; Li, J.; Tummala, S.; Deshpande, R. Highly Diastereoselective Hydrogenation of Imines by a Bimetallic Pd–Cu Heterogeneous Catalyst. *Org. Process Res. Dev.*, **2010**, *14*, 890-894.
- (88) Bartók, M. Unexpected Inversions in Asymmetric Reactions: Reactions with Chiral Metal Complexes, Chiral Organocatalysts, and Heterogeneous Chiral Catalysts. *Chem. Rev.*, 2010, 110, 1663-1705.
- (89) Baiker, A. Crucial aspects in the design of chirally modified noble metal catalysts for asymmetric hydrogenation of activated ketones. *Chem. Soc. Rev.*, **2015**, *44*, 7449-7464.
- (90) Meemken, F.; Baiker, A. Recent Progress in Heterogeneous Asymmetric Hydrogenation of C=O and C=C Bonds on Supported Noble Metal Catalysts. *Chem. Rev.*, **2017**, *117*, 11522-11569.
- (91) Dong, Y.; Goubert, G.; Groves, M. N.; Lemay, J. C.; Hammer, B.; McBreen, P. H. Structure and Dynamics of Individual Diastereomeric Complexes on Platinum: Surface Studies Related to Heterogeneous Enantioselective Catalysis. Acc. Chem. Res., 2017, 50, 1163-1170.
- (92) Gellman, A. J.; Tysoe, W. T.; Zaera, F. Surface Chemistry for Enantioselective Catalysis. *Catal. Lett.*, **2015**, *145*, 220-232.
- (93) Yu, W.; Porosoff, M. D.; Chen, J. G. Review of Pt-Based Bimetallic Catalysis: From Model Surfaces to Supported Catalysts. *Chem. Rev.*, **2012**, *112*, 5780-5817.

- (94) Wu, J.; Li, P.; Pan, Y.-T.; Warren, S.; Yin, X.; Yang, H. Surface lattice-engineered bimetallic nanoparticles and their catalytic properties. *Chem. Soc. Rev.*, **2012**, *41*, 8066-8074.
- (95) Liu, K.; Qin, R.; Zheng, N. Insights into the Interfacial Effects in Heterogeneous Metal Nanocatalysts toward Selective Hydrogenation. J. Am. Chem. Soc., **2021**, 143, 4483-4499.
- (96) Alonso, D. M.; Wettstein, S. G.; Dumesic, J. A. Bimetallic catalysts for upgrading of biomass to fuels and chemicals. *Chem. Soc. Rev.*, **2012**, *41*, 8075-8098.
- (97) Zhang, L.; Zhou, M.; Wang, A.; Zhang, T. Selective Hydrogenation over Supported Metal Catalysts: From Nanoparticles to Single Atoms. *Chem. Rev.*, **2020**, *120*, 683-733.
- (98) Gawande, M. B.; Goswami, A.; Asefa, T.; Guo, H.; Biradar, A. V.; Peng, D.-L.; Zboril, R.; Varma, R. S. Core–shell nanoparticles: synthesis and applications in catalysis and electrocatalysis. *Chem. Soc. Rev.*, **2015**, *44*, 7540-7590.
- (99) Das, S.; Pérez-Ramírez, J.; Gong, J.; Dewangan, N.; Hidajat, K.; Gates, B. C.; Kawi, S. Core–shell structured catalysts for thermocatalytic, photocatalytic, and electrocatalytic conversion of CO₂. *Chem. Soc. Rev.*, **2020**, *49*, 2937-3004.
- (100) Long, N. V.; Yang, Y.; Minh Thi, C.; Minh, N. V.; Cao, Y.; Nogami, M. The development of mixture, alloy, and core-shell nanocatalysts with nanomaterial supports for energy conversion in low-temperature fuel cells. *Nano Energy*, **2013**, *2*, 636-676.
- (101) Stamenkovic, V.; Mun, B. S.; Mayrhofer, K. J. J.; Ross, P. N.; Markovic, N. M.; Rossmeisl, J.; Greeley, J.; Norskov, J. K. Changing the activity of electrocatalysts for oxygen reduction by tuning the surface electronic structure. *Angew Chem Int Edit*, **2006**, *45*, 2897-2901.
- (102) Stamenkovic, V. R.; Mun, B. S.; Arenz, M.; Mayrhofer, K. J. J.; Lucas, C. A.; Wang, G. F.; Ross, P. N.; Markovic, N. M. Trends in electrocatalysis on extended and nanoscale Pt-bimetallic alloy surfaces. *Nat. Mater.*, **2007**, *6*, 241-247.
- (103) Goodman, D. W. Chemistry on Monolayer Metallic-Films. *Ultramicroscopy*, 1990, 34, 1-9.
- (104) Fruhberger, B.; Eng, J.; Chen, J. G. Observation of anomalous reactivities of Ni/Pt(111) bimetallic surfaces. *Catal. Lett.*, **1997**, *45*, 85-92.
- (105) Murillo, L. E.; Goda, A. M.; Chen, J. G. Selective hydrogenation of the CO bond in acrolein through the architecture of bimetallic surface structures. *J. Am. Chem. Soc.*, **2007**, *129*, 7101-7105.
- (106) Greeley, J.; Mavrikakis, M. Surface and subsurface hydrogen: Adsorption properties on transition metals and near-surface alloys. *J. Phys. Chem. B*, **2005**, *109*, 3460-3471.
- (107) Menning, C. A.; Hwu, H. H.; Chen, J. G. G. Experimental and theoretical investigation of the stability of Pt-3d-Pt(111) bimetallic surfaces under oxygen environment. *J. Phys. Chem. B*, **2006**, *110*, 15471-15477.
- (108) Hwu, H. H.; Eng, J.; Chen, J. G. G. Ni/Pt(111) bimetallic surfaces: Unique chemistry at monolayer Ni coverage. J. Am. Chem. Soc., 2002, 124, 702-709.
- (109) Chen, J. G.; Menning, C. A.; Zellner, M. B. Monolayer bimetallic surfaces: Experimental and theoretical studies of trends in electronic and chemical properties. *Surface Science Reports*, **2008**, *63*, 201-254.
- (110) Khan, N. A.; Zellner, M. B.; Chen, J. G. Cyclohexene as a chemical probe of the low-temperature hydrogenation activity of Pt/Ni(111) bimetallic surfaces. *Surf. Sci.*, 2004, 556, 87-100.

- (111) Khan, N. A.; Zellner, M. B.; Murillo, L. E.; Chen, J. G. A Comparison of Similarities and Differences in the Activities of Pt/Ni(111) and Ni/Pt(111) Surfaces. *Catal. Lett.*, 2004, 95, 1-6.
- (112) Zhang, T. J.; Walsh, A. G.; Yu, J. H.; Zhang, P. Single-atom alloy catalysts: structural analysis, electronic properties and catalytic activities. *Chem. Soc. Rev.*, **2021**, *50*, 569-588.
- (113) Hannagan, R. T.; Giannakakis, G.; Flytzani-Stephanopoulos, M.; Sykes, E. C. H. Single-Atom Alloy Catalysis. *Chem. Rev.*, **2020**, *120*, 12044-12088.
- (114) Mao, J. J.; Yin, J. S.; Pei, J. J.; Wang, D. S.; Li, Y. D. Single atom alloy: An emerging atomic site material for catalytic applications. *Nano Today*, **2020**, *34*.
- (115) Kyriakou, G.; Boucher, M. B.; Jewell, A. D.; Lewis, E. A.; Lawton, T. J.; Baber, A. E.; Tierney, H. L.; Flytzani-Stephanopoulos, M.; Sykes, E. C. H. Isolated Metal Atom Geometries as a Strategy for Selective Heterogeneous Hydrogenations. *Science*, 2012, 335, 1209-1212.
- (116) Boucher, M. B.; Zugic, B.; Cladaras, G.; Kammert, J.; Marcinkowski, M. D.; Lawton, T. J.; Sykes, E. C. H.; Flytzani-Stephanopoulos, M. Single atom alloy surface analogs in Pd_{0.18}Cu₁₅ nanoparticles for selective hydrogenation reactions. *Phys. Chem. Chem. Phys.*, 2013, 15, 12187-12196.
- (117) Pei, G. X.; Liu, X. Y.; Yang, X. F.; Zhang, L. L.; Wang, A. Q.; Li, L.; Wang, H.; Wang, X. D.; Zhang, T. Performance of Cu-Alloyed Pd Single-Atom Catalyst for Semihydrogenation of Acetylene under Simulated Front-End Conditions. *ACS Catal.*, 2017, 7, 1491-1500.
- (118) Pei, G. X.; Liu, X. Y.; Wang, A. Q.; Lee, A. F.; Isaacs, M. A.; Li, L.; Pan, X. L.; Yang, X. F.; Wang, X. D.; Tai, Z. J.; Wilson, K.; Zhang, T. Ag Alloyed Pd Single-Atom Catalysts for Efficient Selective Hydrogenation of Acetylene to Ethylene in Excess Ethylene. ACS Catal., 2015, 5, 3717-3725.
- (119) Lucci, F. R.; Liu, J. L.; Marcinkowski, M. D.; Yang, M.; Allard, L. F.; Flytzani-Stephanopoulos, M.; Sykes, E. C. H. Selective hydrogenation of 1,3-butadiene on platinum-copper alloys at the single-atom limit. *Nat. Commun.*, **2015**, *6*.
- (120) Dasgupta, A.; He, H.; Gong, R.; Shang, S.-L.; Zimmerer, E. K.; Meyer, R. J.; Liu, Z.-K.; Janik, M. J.; Rioux, R. M. Atomic control of active-site ensembles in ordered alloys to enhance hydrogenation selectivity. *Nat. Chem.*, **2022**.
- (121) Han, A. J.; Zhang, J.; Sun, W. M.; Chen, W. X.; Zhang, S. L.; Hang, Y. H.; Feng, Q. C.; Zheng, L. R.; Gu, L.; Chen, C.; Peng, Q.; Wang, D. S.; Li, Y. D. Isolating contiguous Pt atoms and forming Pt-Zn intermetallic nanoparticles to regulate selectivity in 4nitrophenylacetylene hydrogenation. *Nat. Commun.*, 2019, 10.
- (122) Armbruster, M.; Kovnir, K.; Behrens, M.; Teschner, D.; Grin, Y.; Schlogl, R. Pd-Ga Intermetallic Compounds as Highly Selective Semihydrogenation Catalysts. J. Am. Chem. Soc., 2010, 132, 14745-14747.
- (123) Dasgupta, A.; Rioux, R. M. Intermetallics in catalysis: An exciting subset of multimetallic catalysts. *Catal. Today*, **2019**, *330*, 2-15.
- (124) Wang, Z. S.; Garg, A.; Wang, L. X.; He, H. R.; Dasgupta, A.; Zanchet, D.; Janik, M. J.; Rioux, R. M.; Roman-Leshkov, Y. Enhancement of Alkyne Semi-Hydrogenation Selectivity by Electronic Modification of Platinum. ACS Catal., 2020, 10, 6763-6770.
- (125) Carothers, W. H.; Adams, R. Platinum oxide as a catalyst in the reduction of organic compounds. V. The preparation of primary alcohols by the catalytic hydrogenation of aldehydes. J. Am. Chem. Soc., **1924**, *46*, 1675-1683.

- (126) Tuley, W.; Adams, R. The reduction of cinnamic aldehyde to cinnamyl alcohol in the presence of platinum-oxide platinum black and promoters. XI. J. Am. Chem. Soc., 1925, 47, 3061-3068.
- (127) Adams, R.; Garvey, B. S. Selective reduction of citral by means of platinum-oxide platinum black and a promoter. XII. J. Am. Chem. Soc., **1926**, 48, 477-482.
- (128) Ponec, V. On the role of promoters in hydrogenations on metals; α,β-unsaturated aldehydes and ketones. *Appl. Catal., A*, **1997**, *149*, 27-48.
- (129) Gallezot, P.; Richard, D. Selective Hydrogenation of α,β -Unsaturated Aldehydes. *Catal. Rev.*, **1998**, *40*, 81-126.
- (130) Maki-Arvela, P.; Hajek, J.; Salmi, T.; Murzin, D. Y. Chemoselective hydrogenation of carbonyl compounds over heterogeneous catalysts. *Appl. Catal., A*, **2005**, *292*, 1-49.
- (131) Luneau, M.; Lim, J. S.; Patel, D. A.; Sykes, E. C. H.; Friend, C. M.; Sautet, P. Guidelines to Achieving High Selectivity for the Hydrogenation of α,β-Unsaturated Aldehydes with Bimetallic and Dilute Alloy Catalysts: A Review. *Chem. Rev.*, **2020**, *120*, 12834-12872.
- (132) Murillo, L. E.; Menning, C. A.; Chen, J. G. Trend in the C=C and C=O bond hydrogenation of acrolein on Pt-M (M = Ni, Co, Cu) bimetallic surfaces. *J. Catal.*, **2009**, *268*, 335-342.
- (133) Haubrich, J.; Loffreda, D.; Delbecq, F.; Sautet, P.; Krupski, A.; Becker, C.; Wandeltt, K. Adsorption of alpha, beta-Unsaturated Aldehydes on Pt(111) and Pt-Sn Alloys: II. Crotonaldehyde. J. Phys. Chem. C, 2009, 113, 13947-13967.
- (134) Chen, B. F.; Li, F. B.; Huang, Z. J.; Yuan, G. Q. Tuning catalytic selectivity of liquid-phase hydrogenation of furfural via synergistic effects of supported bimetallic catalysts. *Appl. Catal., A*, **2015**, *500*, 23-29.
- (135) Bidaoui, M.; Especel, C.; Sabour, S.; Benatallah, L.; Saib-Bouchenafa, N.; Royer, S.; Mohammedi, O. Toward the improvement in unsaturated alcohol selectivity during alpha,beta-unsaturated aldehyde selective hydrogenation, using Zn as promoter of Pt. J. Mol. Catal. A: Chem., 2015, 399, 97-105.
- (136) Mahata, N.; Goncalves, F.; Pereira, M. F. R.; Figueiredo, J. L. Selective hydrogenation of cinnamaldehyde to cinnamyl alcohol over mesoporous carbon supported Fe and Zn promoted Pt catalyst. *Appl. Catal., A*, **2008**, *339*, 159-168.
- (137) Merlo, A. B.; Vetere, V.; Ramallo-Lopez, J. M.; Requejo, F. G.; Casella, M. L. Liquidphase furfural hydrogenation employing silica-supported PtSn and PtGe catalysts prepared using surface organometallic chemistry on metals techniques. *React. Kinet. Mech. Catal.*, 2011, 104, 467-482.
- (138) Delbecq, F.; Sautet, P. Influence of Sn additives on the selectivity of hydrogenation of alpha-beta-unsaturated aldehydes with Pt catalysts: a density functional study of molecular adsorption. *J. Catal.*, **2003**, *220*, 115-126.
- (139) Musci, J. J.; Merlo, A. B.; Casella, M. L. Aqueous phase hydrogenation of furfural using carbon-supported Ru and RuSn catalysts. *Catal. Today*, **2017**, *296*, 43-50.
- (140) Ning, X.; Xu, Y. M.; Wu, A. Q.; Tang, C.; Jia, A. P.; Luo, M. F.; Di, J. Q. Kinetic study of selective hydrogenation of crotonaldehyde over Fe-promoted Ir/BN catalysts. *Appl. Surf. Sci.*, 2019, 463, 463-473.
- (141) Tamura, M.; Tokonami, K.; Nakagawa, Y.; Tomishige, K. Rapid synthesis of unsaturated alcohols under mild conditions by highly selective hydrogenation. *Chem. Commun.*, 2013, 49, 7034-7036.

- (142) Barbaro, P.; Liguori, F.; Linares, N.; Marrodan, C. M. Heterogeneous Bifunctional Metal/Acid Catalysts for Selective Chemical Processes. *Eur. J. Inorg. Chem.*, 2012, 2012, 3807-3823.
- (143) Robinson, A. M.; Hensley, J. E.; Medlin, J. W. Bifunctional Catalysts for Upgrading of Biomass-Derived Oxygenates: A Review. *ACS Catal.*, **2016**, *6*, 5026-5043.
- (144) Ye, R. P.; Ding, J.; Gong, W. B.; Argyle, M. D.; Zhong, Q.; Wang, Y. J.; Russell, C. K.; Xu, Z. H.; Russell, A. G.; Li, Q. H.; Fan, M. H.; Yao, Y. G. CO₂ hydrogenation to highvalue products via heterogeneous catalysis. *Nat. Commun.*, **2019**, *10*.
- (145) Robinson, A.; Ferguson, G. A.; Gallagher, J. R.; Cheah, S.; Beckham, G. T.; Schaidle, J. A.; Hensley, J. E.; Medlin, J. W. Enhanced Hydrodeoxygenation of m-Cresol over Bimetallic Pt–Mo Catalysts through an Oxophilic Metal-Induced Tautomerization Pathway. ACS Catal., 2016, 6, 4356-4368.
- (146) Robinson, A. M.; Mark, L.; Rasmussen, M. J.; Hensley, J. E.; Medlin, J. W. Surface Chemistry of Aromatic Reactants on Pt- and Mo-Modified Pt Catalysts. J. Phys. Chem. C, 2016, 120, 26824-26833.
- (147) Nelson, R. C.; Baek, B.; Ruiz, P.; Goundie, B.; Brooks, A.; Wheeler, M. C.; Frederick, B. G.; Grabow, L. C.; Austin, R. N. Experimental and Theoretical Insights into the Hydrogen-Efficient Direct Hydrodeoxygenation Mechanism of Phenol over Ru/TiO₂. *ACS Catal.*, 2015, *5*, 6509-6523.
- (148) Hernandez-Mejia, C.; Gnanakumar, E. S.; Olivos-Suarez, A.; Gascon, J.; Greer, H. F.; Zhou, W. Z.; Rothenberg, G.; Shiju, N. R. Ru/TiO₂-catalysed hydrogenation of xylose: the role of the crystal structure of the support. *Catal. Sci. Technol.*, **2016**, *6*, 577-582.
- (149) Griffin, M. B.; Ferguson, G. A.; Ruddy, D. A.; Biddy, M. J.; Beckham, G. T.; Schaidle, J. A. Role of the Support and Reaction Conditions on the Vapor-Phase Deoxygenation of m-Cresol over Pt/C and Pt/TiO₂ Catalysts. ACS Catal., **2016**, *6*, 2715-2727.
- (150) Álvarez, A.; Bansode, A.; Urakawa, A.; Bavykina, A. V.; Wezendonk, T. A.; Makkee, M.; Gascon, J.; Kapteijn, F. Challenges in the Greener Production of Formates/Formic Acid, Methanol, and DME by Heterogeneously Catalyzed CO₂ Hydrogenation Processes. *Chem. Rev.*, **2017**, *117*, 9804-9838.
- (151) Jung, K. T.; Bell, A. T. Effects of Zirconia Phase on the Synthesis of Methanol over Zirconia-Supported Copper. *Catal. Lett.*, **2002**, *80*, 63-68.
- (152) Lam, E.; Corral-Pérez, J. J.; Larmier, K.; Noh, G.; Wolf, P.; Comas-Vives, A.; Urakawa, A.; Copéret, C. CO₂ Hydrogenation on Cu/Al₂O₃: Role of the Metal/Support Interface in Driving Activity and Selectivity of a Bifunctional Catalyst. *Angew. Chem. Int. Ed.*, **2019**, 58, 13989-13996.
- (153) Larmier, K.; Liao, W.-C.; Tada, S.; Lam, E.; Verel, R.; Bansode, A.; Urakawa, A.; Comas-Vives, A.; Copéret, C. CO₂-to-Methanol Hydrogenation on Zirconia-Supported Copper Nanoparticles: Reaction Intermediates and the Role of the Metal–Support Interface. *Angew. Chem. Int. Ed.*, **2017**, *56*, 2318-2323.
- (154) Lam, E.; Larmier, K.; Wolf, P.; Tada, S.; Safonova, O. V.; Copéret, C. Isolated Zr Surface Sites on Silica Promote Hydrogenation of CO₂ to CH₃OH in Supported Cu Catalysts. J. Am. Chem. Soc., 2018, 140, 10530-10535.
- (155) Roy, S.; Cherevotan, A.; Peter, S. C. Thermochemical CO₂ Hydrogenation to Single Carbon Products: Scientific and Technological Challenges. ACS Energy Lett., 2018, 3, 1938-1966.

TOC Graphic



Bimetallic catalysts tune X group adsorption strength