Catalytic Directing Groups

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A New Direction in Enantioselective Catalysis: Scaffolding Ligands in Olefin Hydroformylation

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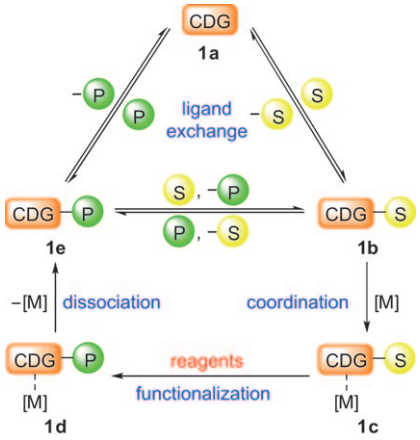
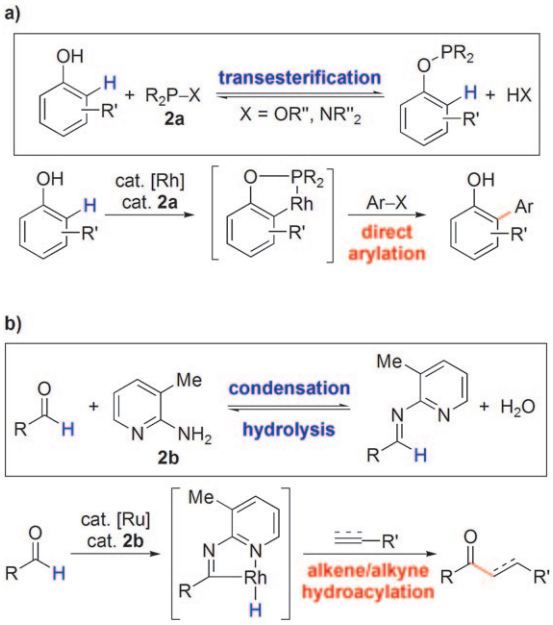
asymmetric catalysis · directing groups · hydroformylation · regioselectivity · scaffolding ligands

The combination of transition metals and organocatalysts is an exciting synthetic strategy that has resulted in new transformations and mechanisms.[1] Within this context, metal–organic cooperative catalysis, a term defined by Jun and co-workers, specifies a type of tandem catalysis that was previously most relevant to C–H bond functionalization.[2] However, this term aptly describes any catalytic process that features an organocatalyst capable of forming covalent bonds to a substrate and dative bonds to a transition-metal catalyst simultaneously (Scheme 1). The term "catalytic catalyst-directing groups" was coined for these organocatalysts because of their ability to direct metal-catalyzed transformations.[3] The more general term "scaffolding ligands"[4] has also been used by analogy with scaffolding proteins, which promote various biological processes by bringing multiple proteins together.[4b,5] Overall, scaffolding organocatalysts function by bringing a metal catalyst and substrate into close proximity; they ideally promote subsequent transformations with enhanced reactivity[6] and selectivity.[7] Herein, we present a brief overview of metal–organic cooperative catalysis to ultimately highlight a seminal breakthrough by Tan and co-workers in asymmetric catalysis.[8]



Scheme 1. Transition-metal-catalyzed reactions promoted by catalytic directing groups (CDG; M is the transition metal). Substrate (S) and product (P) readily exchange under the reaction conditions.

The ruthenium- and rhodium-catalyzed *ortho* arylation of simple phenols is one of the earliest examples of metal–organic cooperative catalysis (Scheme 2a).[9] In these transformations, there is a rapid equilibrium process in which an unprotected phenol (S in Scheme 1) exchanges with an alkoxy substituent on phosphite **2a**, the scaffolding organocatalyst or catalytic directing group (CDG, **1a** in Scheme 1), to generate the ligand–substrate complex (CDG–S, **1b**). The resulting phosphite coordinates to the catalytically active Ru or Rh species and undergoes *ortho* arylation. The final product is released upon a second ligand-exchange process between the ligand–product complex (CDG–P, **1e**) and another substrate



Scheme 2. Examples of transition-metal-catalyzed reactions promoted by catalytic directing groups:[7,8] a) Phosphite/phosphinite/phosphoramidite transesterification; b) Schiff base condensation.

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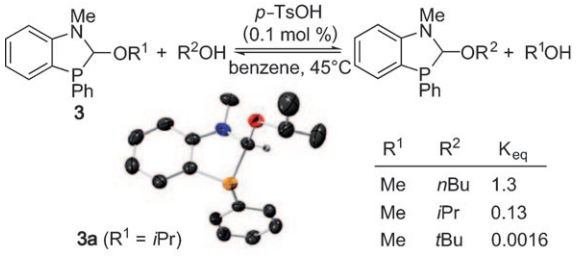
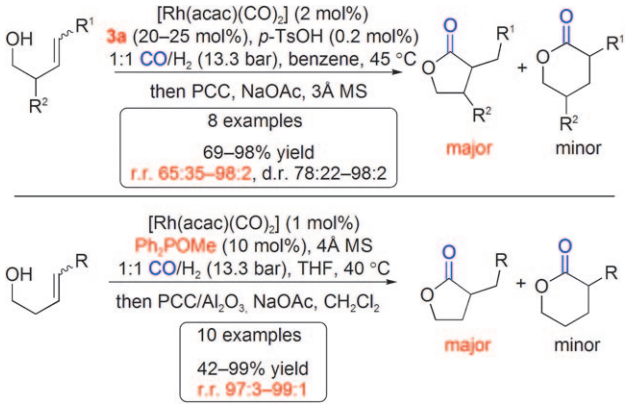
molecule. In place of phosphites, phosphinites can also be used, as can phosphoramidites, because rapid equilibration occurs between the alkoxide (or aryl oxide) and alkyl amide (or aryl amide) groups at the P^{III} center. C–H bond activation is inefficient without the catalytic directing group because such cyclometalation reactions would result in a strained four-membered metallaoxetane. The organocatalyst serves to promote arylation by enabling catalysis through a more favorable five-membered metallacycle.

This concept has been used in the rhodium-catalyzed hydroacylation of alkenes and alkynes promoted by 2-amino-3-picoline as a scaffolding ligand (Scheme 2b). In this process, a Schiff condensation forms an imine bearing a pyridine directing group (CDG–S). The Lewis basic pyridine then directs selective C–H bond activation and functionalization.[10] Competitive decarbonylation occurs in the absence of this scaffolding organocatalyst. Catalytic directing groups have been applied to the industrially relevant alkene hydroformylation.[11] In this atom-economical reaction, alkenes are converted into aldehydes with syngas (i.e., a mixture of CO and H_2) through the formation of new C–C and C–H bonds. Terminal alkenes typically undergo hydroformylation with linear selectivity (i.e., anti-Markovnikov). Branch-selective hydroformylation of internal alkenes, however, is challenging.[12]

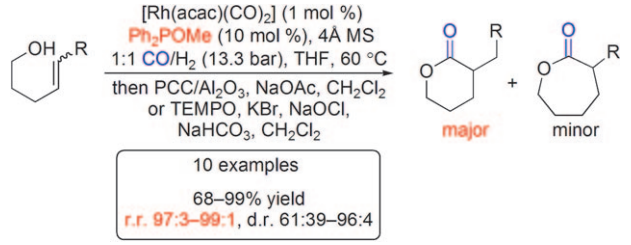
In 2008, the Tan and Breit groups independently reported the highly regioselective catalytic hydroformylation of homoallylic alcohols.[3,4] Tan and co-workers designed an alkoxy benzoazaphosphole ligand **3** derived from *N*-methylaniline that was capable of undergoing facile exchange with alcohols (Schemes 3 and 4).[4] The Breit research group demonstrated that Ph_2POMe was a suitable catalytic directing group for hydroformylation (Scheme 4).[3] Notably, the functionalization of 1,2-disubstituted olefins and other substrates containing stereocenters proceeded with excellent regio- and stereoselectivity. Additionally, the chemoselective hydroformylation of homoallylic alcohols over unactivated alkenes was observed. In all cases, regioselectivity levels were drastically degraded when PPh_3 was used as the ligand.[3,4] The analogous homoallylic methyl ether displayed low reactivity and regioselectivity.[3] The Breit research group established that bishomoallylic alcohols could also undergo regioselective hydroformylation to yield δ-lactones preferentially over ε-lactones (Scheme 5).[13]



Scheme 3. The alkoxy benzoazaphosphole catalytic directing group described by Tan and co-workers.[4] An ORTEP plot of the scaffolding ligand was created from the coordinates obtained from Ref. [4] (C black, O red, N blue, P orange, H white).



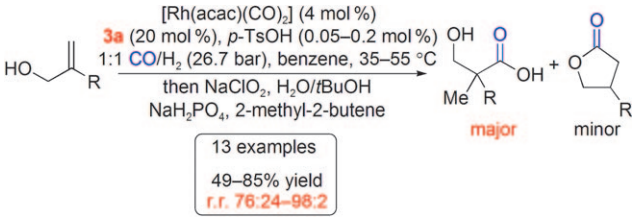
Scheme 4. Regio- and diastereoselective rhodium-catalyzed hydroformylation of homoallylic alcohols.[3,4] acac = acetylacetonate, MS = molecular sieves, PCC = pyridinium chlorochromate, d.r. = diastereomeric ratio, r.r. = regioisomeric ratio (γ-lactone/δ-lactone).



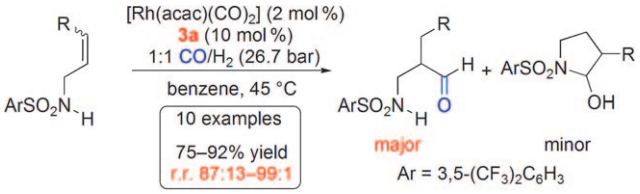
Scheme 5. Regio- and diastereoselective rhodium-catalyzed hydroformylation of bishomoallylic alcohols.[13] TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl, r.r. = regioisomeric ratio (δ-lactone/ε-lactone).

As mentioned previously, catalytic directing groups not only have the ability to improve selectivities but can also enable transformations that are otherwise difficult. For example, the formation of quaternary centers by hydroformylation has been described as a formidable challenge.[14] However, by using an alkoxy benzoazaphosphole scaffolding ligand, Tan and co-workers successfully applied the rhodium-catalyzed hydroformylation of allylic alcohols to the construction of quaternary carbon centers (Scheme 6).[15]

Allylic amines are also excellent candidates for hydroformylation promoted by catalytic directing groups. Because the alkoxy benzoazaphosphole described by Tan and co-workers exchanges readily with allylic sulfonamides, regioselective hydroformylation at the β position is possible



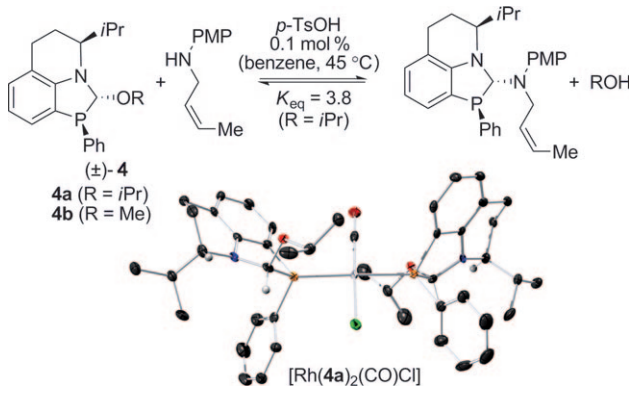
Scheme 6. Regioselective rhodium-catalyzed hydroformylation of allylic alcohols for the construction of quaternary carbon centers.[15] r.r. = regioisomeric ratio (branched/linear).



Scheme 7. Regioselective rhodium-catalyzed hydroformylation of allylic sulfonamides.[16] r.r. = regioisomeric ratio (branched/linear).

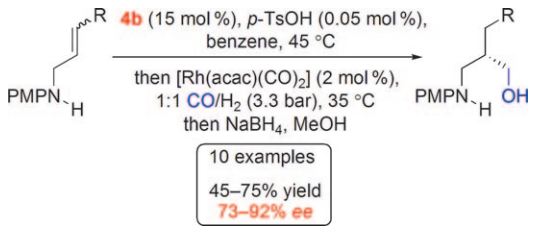
(Scheme 7).[16] Importantly, the equilibration between alkoxy and sulfonamide substrates depends strongly on the pK_a value of the N–H hydrogen atom, whereby electron-deficient sulfonamides are optimal.

Finally, Tan and co-workers have now demonstrated that asymmetric catalysis is possible with scaffolding ligands. By introducing a tetrahydroisoquinoline group on the alkoxy benzoazaphosphole, the synthesis of a chiral scaffolding ligand (**4a**) was achieved (Scheme 8).[8] Using **4b**, allylic anilines underwent efficient hydroformylation to afford chiral



Scheme 8. Chiral alkoxy benzoazaphosphole catalytic directing groups.[8] An ORTEP plot of the rhodium–scaffolding ligand complex [Rh(**4a**)$_2$(CO)Cl] was created from the coordinates obtained from Ref. [8] (C black, O red, N blue, P orange, Rh silver, Cl green). PMP = *p*-methoxyphenyl.

1,3-aminoalcohols with up to 92% *ee* (Scheme 9). More importantly, this reaction showcases a distinct strategy for asymmetric induction and demonstrates the potential of using chiral catalytic directing groups to promote enantioselective reactions.



Scheme 9. Enantioselective rhodium-catalyzed hydroformylation of allylic anilines.[8]

Although we have focused herein on scaffolding through covalent interactions, site-selective functionalization can also be directed by supramolecular interactions.[17] We anticipate that new developments in catalysis will include the design of novel scaffolding organocatalysts and their application to other transformations. Further understanding of the reaction mechanism, including the importance of preassociation and rapid equilibration, will advance this emerging area of catalysis.

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