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Asymmetric Catalysis

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Dual Catalysis Becomes Diastereodivergent**

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asymmetric catalysis · diastereodivergence · dual catalysis · enantioselectivity · match–mismatch effects

Despite all the advances in the field of asymmetric synthesis, a considerable challenge arises when multiple chiral centers are created in a single chemical transformation, thus potentially leading to the formation of mixtures of diastereomers. Diastereoselective asymmetric reactions have been established, but are commonly limited to the synthesis of one of the possible relative configurations.[1]

The development of diastereodivergent processes would be highly desirable to overcome these restrictions and open up larger sections of chemical space. The term "diastereodivergent" implies the uncommon ability to generate each and every one of the possible product diastereoisomers from the same starting materials. The series of opposite enantiomers can then be easily accessed by employing the enantiomer of the chiral catalyst(s) involved.

The selected examples depicted in Scheme 1 represent the state of the art in this field. The Deng group[2] reported the generation of two nonadjacent stereocenters through a tandem conjugate addition of β-cyanoketones to α-chloroacrylonitriles followed by protonation (Scheme 1a). Remarkably, cinchona derivatives **A** and **B** led to different diastereomers (*syn*-**3** and *anti*-**4**, respectively) whereas the quasi-enantiomeric series of catalysts (not shown) enabled access to the opposite enantiomers. Melchiorre and co-workers reported an elegant thio-Michael reaction (Scheme 1b),[3] wherein evaluation of the influence of solvents and additives ultimately led to the development of conditions that allow access to each stereoisomer. Interestingly, the same chiral catalyst can be employed to access complementary diastereomers, highlighting the dramatic change in catalyst conformation induced by the additives and the solvent. In a third example, Maulide and co-workers reported an unprecedented switch in diastereoselectivity in their studies on the palladium-mediated asymmetric allylic alkylation of lactone **8** (Scheme 1c).[4] The authors developed two catalytic systems involving different chiral ligands (phosphoramidite L1 and PHOX L2) leading to both *cis* and *trans* cyclobutene products in excellent selectivities. Once again, the opposite enantiomers of the products were obtained simply by employing the enantiomeric series of chiral ligands.

In all the aforementioned diastereodivergent processes the chiral information encoded in the catalyst is transferred to multiple stereocenters, setting up the relative and absolute configuration of the desired product.[5] Each diastereoisomer thus requires the development of an ad hoc set of reaction conditions that must be carefully identified and optimized.

A conceptually different and perhaps more rational approach to selectively access all the stereoisomers of a given compound bearing multiple stereocenters would be the design of a process in which several chiral catalysts are simultaneously present in the reaction environment, each of which would dictate the absolute stereochemistry of a single stereocenter. Ideally, this implies that any possible permutation of the absolute stereochemistry of the stereocenters of the desired product could be obtained simply by choosing the appropriate absolute configuration of each individual chiral catalyst. Though strikingly "modular", the challenges that this approach entails are impressive: in such a system, multiple chiral catalysts should coexist without interfering with each other, and each chiral catalyst must be able to operate without suffering match–mismatch effects due to the presence of other chiral catalysts.

A first step towards this goal has been taken by MacMillan et al. in their elegant hydrohalogenation of enals (Scheme 2).[6] As shown, enal **10** is presumably activated by imidazolidinone **D** as an iminium species, which then undergoes reduction by Hantzsch ester to deliver the chiral reduced aldehyde **11**. This aldehyde is directly treated with an electrophilic source of halogen in the presence of a new imidazolidinone catalyst **E** to deliver the final product *syn*-**12** in excellent selectivities (Scheme 2). The authors showed that employing the enantiomer of **E** (*ent*-**E**) in the second catalytic step resulted in the formation of the diastereomeric product *anti*-**12** with only minor erosion of stereochemical purity. As the outcome of the second catalytic step does not seem to be affected by the absolute configuration of the first stereocenter installed, in principle all four possible stereoisomers can be accessed simply by selecting the appropriate absolute configuration of the two catalysts.[6]

This elegant report inevitably raises the question of whether it is possible to realize a transformation in which two chiral centers are created simultaneously by independent

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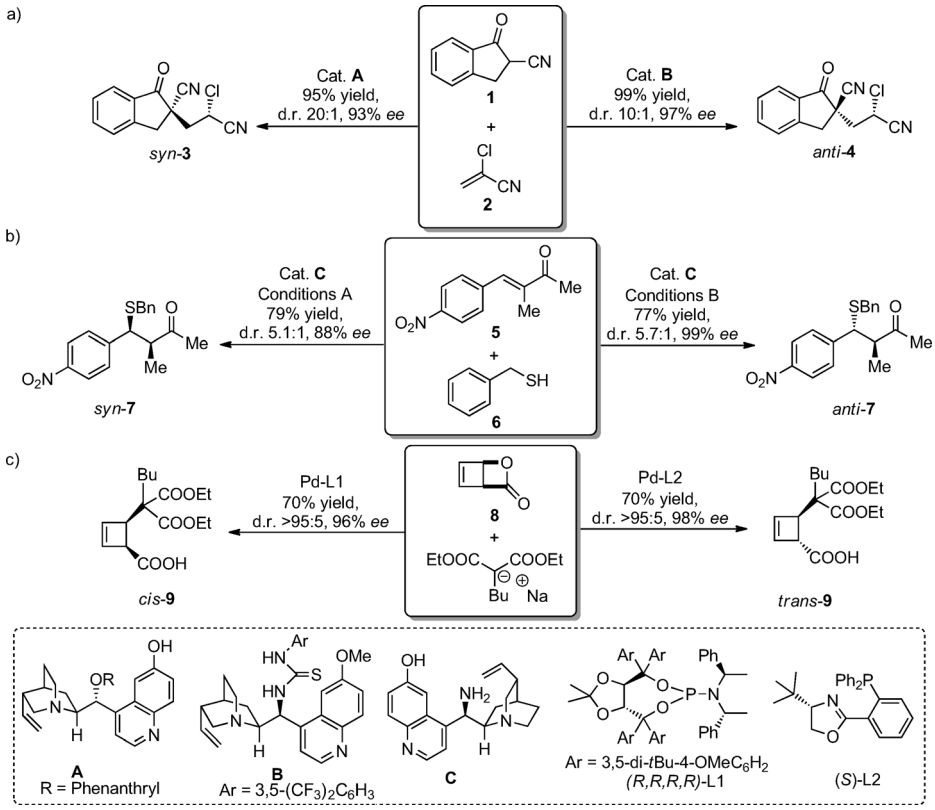
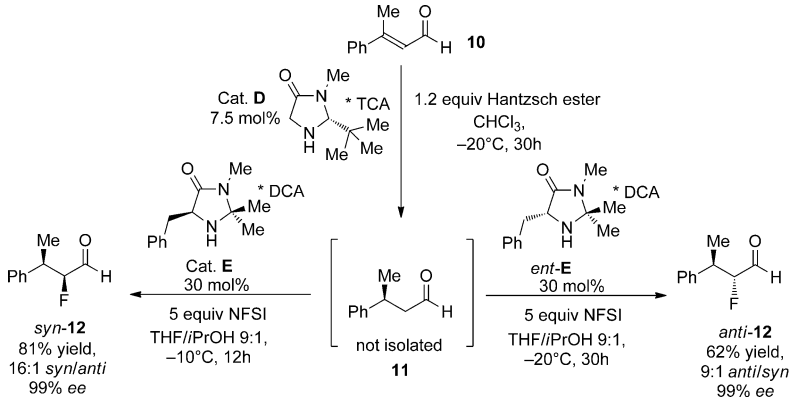


Scheme 1. Representative examples of the state of the art in diastereodivergent catalytic transformations. Bn = benzyl.

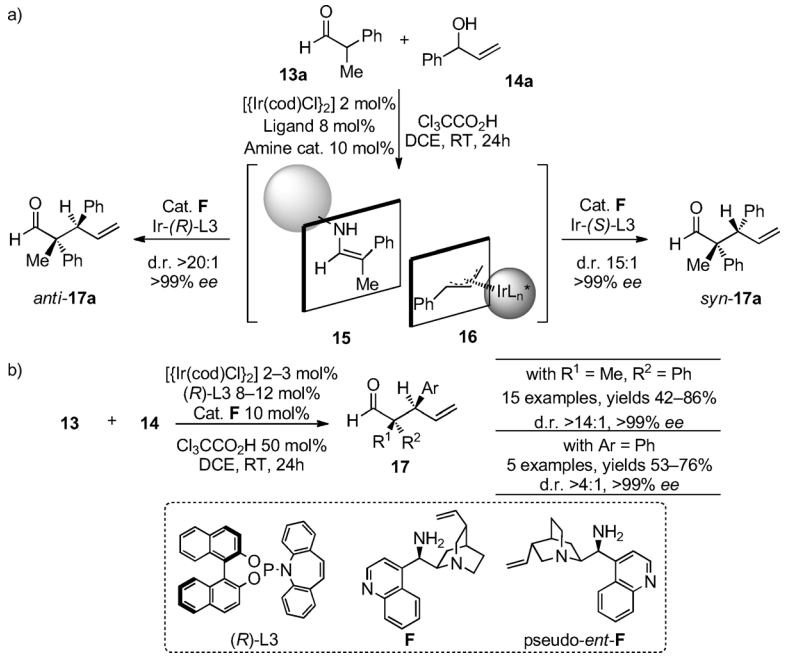


Scheme 2. MacMillan's sequential use of two chiral catalysts for the generation of diastereomeric pairs of products. DCA = dichloroacetic acid, TCA = trichloroacetic acid, NFSI = *N*-fluorobenzenesulfonimide.

control from two chiral catalysts co-existing in the same reaction vessel.

In a recent report, Carreira et al. provided an answer to this question.[7] Their work focuses on the conceptually simple α-alkylation of a racemic α-branched aldehyde (Scheme 3). Suitable modes of catalytic asymmetric activation were identified for each one of the two reaction partners; namely, the generation of a chiral enamine (upon interaction of aldehyde **13** with chiral amine **F**) would set the stage for stereoselective α-functionalization[8] by a chiral electrophilic allyliridium complex (generated from a racemic allylic alcohol substrate).[9] This reaction would thus entail two reacting partners, each activated by a chiral catalyst. The newly formed C–C bond would connect two emerging stereocenters, the stereochemical orientation of each dictated by the absolute configuration of the respective catalyst (Scheme 3a).

In initial experiments performed with achiral catalysts and in the presence of one chiral and one achiral catalyst the intrinsic bias of the system was evaluated. It was found that the amine catalyst does not control the formation of the β-stereocenter (1.3:1 d.r. for the model reaction when the metal catalyst is achiral), whereas the iridium catalyst has a moderate intrinsic preference for one diastereomer (3:1 d.r. for the

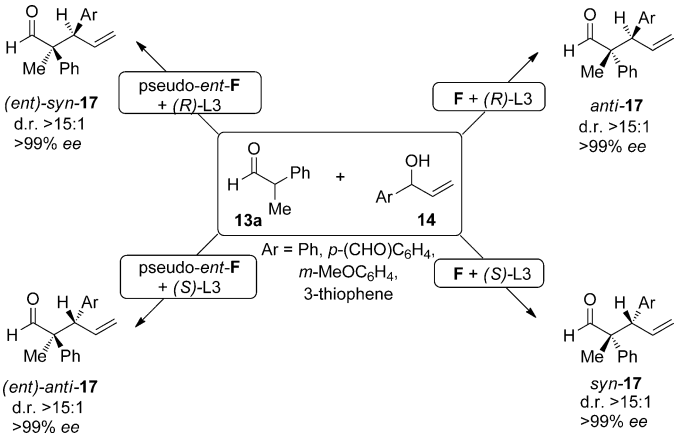


Scheme 3. Asymmetric stereodivergent iridium-catalyzed allylic alkylation of chiral enamine nucleophiles and substrate scope. cod = 1,5-cyclooctadienyl, DCE = 1,2-dichlorethane.

model reaction when the amine catalyst is achiral). When the two enantiopure catalysts Ir-L3 and **F** were combined, a single stereoisomer was observed with excellent selectivity (> 20:1 d.r., > 99 % *ee*; Scheme 3a). Each catalyst therefore remarkably exerts nearly absolute control over the stereocenter derived from the fragment it activates. The reaction can be successfully applied to differently substituted α-branched aldehydes and aromatic allylic alcohols, both symmetrical and unsymmetrical, achieving excellent enantioselectivities although with some erosion of the diastereoselection when compared to the model substrate (Scheme 3b).

The authors then hypothesized that a switch in the absolute configuration of one of the chiral catalysts could lead to a different stereoisomer of the product, provided no match–mismatch effects were at play. Indeed, subjection of the starting materials to every possible permutation of the catalysts led to each of the four possible product stereoisomers in outstanding selectivities (Scheme 4). Arguably, planarization of both partners' reactive sites minimizes any match–mismatch effects at the transition state, allowing each catalyst to control one stereocenter independently from the other. Carreira's work is a prime example of synergistic dual catalysis, as both reaction partners are independently and simultaneously activated by two catalysts.[10,11]

The work summarized in this Highlight represents a breakthrough in the areas of diastereodivergent processes and dual catalysis. For the first time, two chiral catalysts have been proven to simultaneously but independently control the formation of two stereocenters, such that the permutation of the enantiomers of these catalysts allow near perfect control over the final stereochemistry of the product. As mentioned previously, a significant advantage is that the complementary diastereomer of a given product series becomes easily



Scheme 4. Accessing all possible diastereoisomers of product **17** by chiral catalyst permutations.

accessible by simply employing the opposite enantiomer of one of the catalysts, rather than by developing of a new set of conditions. Minimal match–mismatch effects in the coupling of the two chiral intermediates are a stringent, key prerequisite.

A final comment should be made on the fact that there are possibly several examples of dual catalysis already reported which might, upon revisiting, be amenable to diastereodivergent behavior. Further ingenious developments in this area are, thus, highly anticipated.

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