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Abstract This article highlights the recent conceptual advances in stereodivergent catalytic asymmetric allylic alkylation (AAA). Since an earlier breakthrough by Carreira and co-workers, the field of stereodivergent AAA has been dominated by synergistic dual catalysis, i.e., switching the absolute configuration of two distinct chiral catalysts (metal/organo or heterobimetallic) to access all four stereoisomeric products. In this context, the most recent examples of this methodology have been highlighted, including a dynamic kinetic asymmetric transformation (DyKAT) reported by Liao and Zhang and co-workers in 2020. Significantly, the use of a single-chiral metal catalyst for the AAA, coupled with a stoichiometric α-fluorination in a sequence-dependent diastereodivergent strategy, has been disclosed by You and co-workers in 2020. Most recently, the same group have uncovered an intriguing time-dependent enantiodivergent asymmetric allylic amination to give each enantiomeric product using a single-enantiomeric metal catalyst; *via* two sequential kinetic resolutions.

Keywords asymmetric allylic alkylation (AAA) C–C/C–X bond formation dynamic kinetic asymmetric transformation (DyKAT) kinetic resolution stereodivergent synergistic

Chirality or handedness, i.e., the non-superimposability of a structure (lacking a plane or center of symmetry) with its mirror-image, strongly impacts various Chemistry/Biology areas, and plays an important role e.g. in Materials Chemistry [1]. In Medicinal Chemistry it is critical to evaluate the therapeutic and toxicological properties of all stereoisomers of a drug molecule because diastereoisomers and enantiomers may exhibit distinct biological and pharmacological activities [2]. From an asymmetric synthesis perspective, enantiomers are readily available by using catalysts with opposite absolute configuration, while the access to all diastereoisomers of a molecule has remained a significant challenge. In turn, stereodivergent asymmetric catalysis, i.e., the catalytic generation of all stereoisomeric products, is of significant importance [3]; an "ideal" synthesis would use the same substrates under identical conditions in a single stereodivergent operation; by simple permutation of the chiral catalysts used. Notably, stereodivergent synthesis has been also developed with artificial molecular machines, and thus has proved significant in Supramolecular Catalysis [4]. In Organic Chemistry, the transition metal-catalyzed asymmetric allylic alkylation (AAA) of nucleophiles using allylic electrophiles has been amongst the most important C–C and C–X bond formations [5]; palladium and iridium catalysts have been most commonly used to control both regioselectivity and enantioselectivity (use of chiral ligands). In contrast, the control of diastereoselectivity in case of using prochiral or racemic nucleophiles has proved challenging; e.g. due to potential match–mismatch effects in the diastereo-determining transition states. Therefore, a general fully stereodivergent AAA methodology has been a long-standing goal, and a breakthrough has been achieved only recently.

The concept of diastereo- and enantiodivergent catalytic AAA using an allylic substrate, with a suitable leaving group (LG), and a prochiral or racemic carbonyl substrate can be represented with two distinct simultaneous activations (Fig. 1a). In principle, a chiral low-oxidation state metal catalyst (M*) is required to convert the allylic substrate into a chiral π-allyl–metal species (electrophile). Concurrently, another chiral catalyst (Y*; *N*-centered species or metal) is needed to generate a chiral enamine or enolate (nucleophile) from the carbonyl substrate. The activated chiral intermediates would react regioselectively in a C–C bond formation (AAA) to give the corresponding branched α-allylated carbonyl product; bearing two contiguous stereogenic centers (α/β). Ideally, all four stereoisomers would be accessible in a fully stereodivergent process if each chiral catalyst independently exerts complete inherent stereocontrol, i.e., each catalyst would block the opposite diastereoface of the respective planar intermediate during the construction of the corresponding stereocenter. To date, according to this synergistic concept (Fig 1a), two distinct chiral dual catalyst systems have been reported in the diastereo- and enantiodivergent AAA (C–C bond formation): synergistic dual catalysis using a metal/organo system (Fig. 1b) or a heterobimetallic system (Fig. 1c). More recently, a two-step strategy has been uncovered where a single-chiral metal catalyst has been exploited in the AAA (C–C bond formation) coupled with a stoichiometric C–F bond formation; relying on a sequence-dependent diastereo-switch (Fig. 1d). Most recently, a single-enantiomeric metal catalyst has been found to trigger a time-dependent enantiodivergent AAA (dearomatizing C–N bond formation) *via* two sequential kinetic resolutions (Fig 1e).

In 2013, Carreira and co-workers have reported a proof-of-principle for the fully stereodivergent AAA using racemic allylic alcohols and racemic α-branched aldehydes, in the presence of a metal/organo system containing two distinct chiral catalysts (Ir*/N*) and a Brønsted acid (trichloroacetic acid, sub-stoichiometric; Fig. 1b) [6]. They used the combination of a chiral Ir(I) complex, derived from phosphoramidite/alkene ligand (*R*)-**1** [or (*S*)-**1**], and chiral cinchona alkaloid-derived primary amine **N-2** (or its pseudo-enantiomer **N-2'**). By switching the absolute configuration of the two chiral catalysts, all four stereoisomeric α-branched γ,δ-unsaturated aldehydes (bearing adjacent quaternary/tertiary stereocenters) were formed in 71–80% yield with 15:1 ~ >20:1 *dr* and >99% *ee*. The diastereocontrol in this dynamic kinetic asymmetric transformation (DyKAT) *via* a metal/organo strategy was proposed to originate from an outer-sphere nucleophilic addition of the *in situ*-formed chiral enamine to the *in situ*-generated chiral π-allyl–Ir(III) species. Density functional theory (DFT) modeling of stabilizing non-covalent interactions in the diastereo-determining transition states by Sunoj and co-workers have revealed critical quinolone•••phenyl π-stacking (enamine/π-allyl–Ir) and several C–H•••π interactions for the Ir–(*R*)-**1**/**N-2** and Ir–(*R*)-**1**/**N-2'** combinations, respectively [7]. In 2014, Carreira and co-workers have disclosed a related synergistic Ir*/N* catalyst system for the stereodivergent AAA between racemic allylic alcohols and linear aldehydes [8]. Here, the same chiral Ir(I) complex [derived from (*R*)-**1** or (*S*)-**1**] and a chiral *O*-silyl prolinol ether (i.e., a secondary amine instead of primary amine **N-2** or **N-2'**) were used as a dual catalyst system; in the presence of a Brønsted acid (dimethyl hydrogenphosphate, sub-stoichiometric) [7]. This modification addressed the main issue regarding the use of linear aldehydes, i.e., an epimerization of the tertiary α-stereocenter in the product. In 2017, Hartwig and co-workers have reported a distinct Ir*/N* dual catalyst system for the stereodivergent AAA between allylic carbonates and α-aryl perfluorophenyl esters [9]. Here, a similar chiral Ir(I) complex

(metallacyclic) and an enantioenriched cyclic isothiourea Lewis base (benzotetramisole) were used in cooperativity; in the presence of a Brønsted base (EtN^iPr_2, stoichiometric). In contrast to Carreira's work involving *in situ*-formed chiral enamines [6,8], Hartwig's system relies on the *in situ*-generation of chiral zwitterionic ammonium enolates. A key to both stereocontrol and catalyst turnover was shown to be the presence of the poorly nucleophilic perfluorophenolate in low concentration.

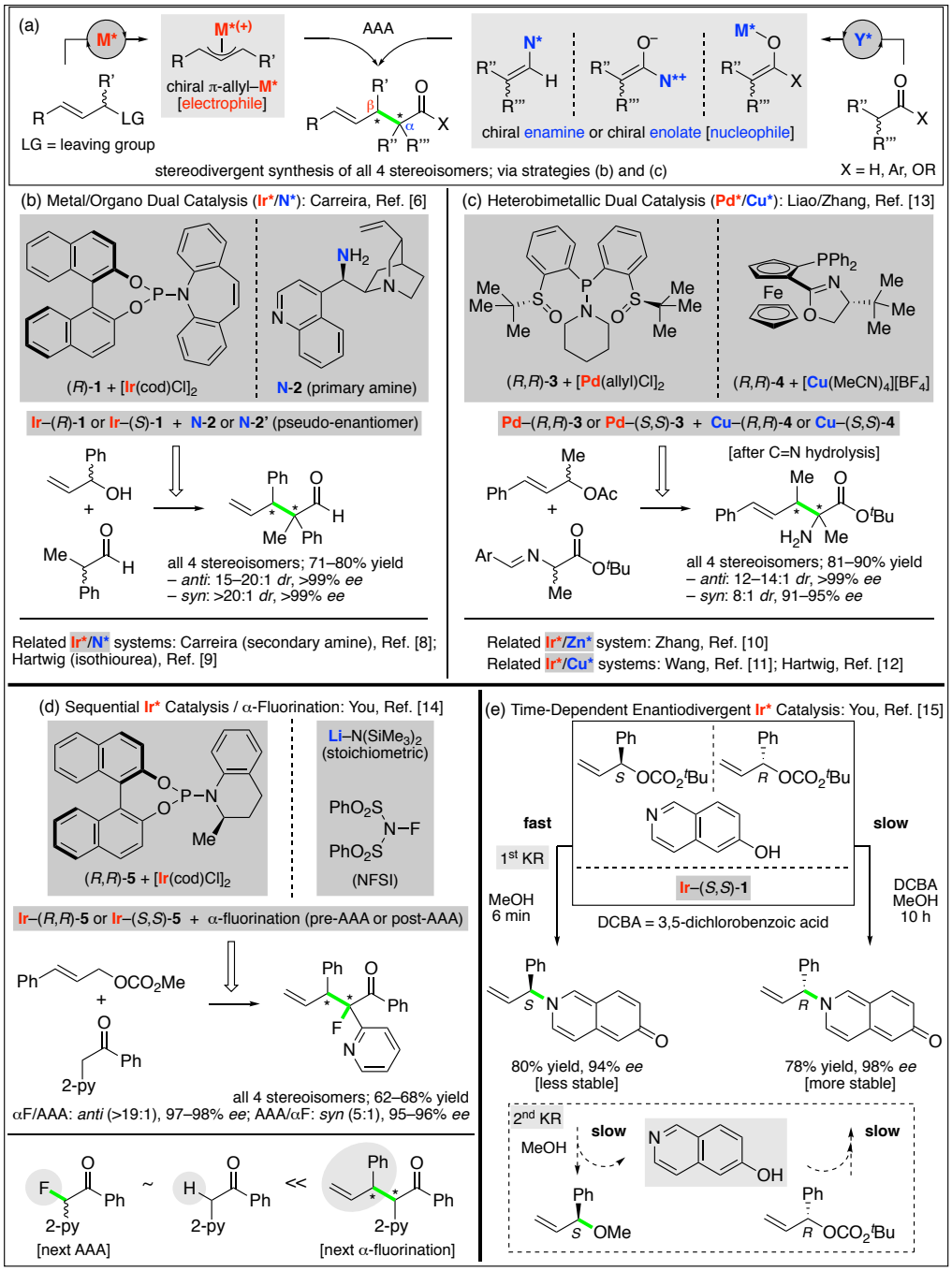

Fig. 1. Stereodivergent catalytic asymmetric allylic alkylation (AAA). **(a)** concept of synergistic dual catalysis in diastereo- and enantiodivergent AAA (C–C bond formation); for strategies (b) and (c). **(b)** Metal/organo dual catalysis (Ir*/N*). **(c)** Heterobimetallic dual catalysis (Pd*/Cu*; Ir*/Zn*; Ir*/Cu*). **(d)** Catalysis with a single-chiral metal species (Ir*) in an overall diastereo- and enantiodivergent AAA (C–C bond formation) coupled with a C–F bond formation (sequence-dependent diastereo-switch). **(e)** Catalysis with a single-enantiomeric metal species (Ir*) in a time-dependent enantiodivergent AAA (dearomatizing C–N bond formation); *via* two sequential kinetic resolutions (KRs).

As a second strategy, synergistic heterobimetallic catalysis –involving *in situ*-generated chiral metal enolates– has been investigated recently by several groups (Fig. 1c) [10,11,12,13]. Here, a combination of two chiral transition metal catalysts has been used, and by varying their absolute configuration all four stereoisomeric products were obtained in high yields with excellent relative and absolute stereocontrol. In 2016, Zhang and co-workers have uncovered the first example of synergistic heterobimetallic catalysis (Ir*/Zn*) for the stereodivergent AAA between allylic carbonates and α-hydroxy ketones [10]. They used chiral Ir(I)–phosphoramidite and Zn(II)–semi-crown complexes; in the presence of molecular sieves 4 Å. In 2018, Wang and co-workers have reported a related Ir*/Cu* system for the stereodivergent AAA between allylic carbonates and α-aldimine α-methyl esters [11]. The same chiral Ir(I) complex was used in combination with a chiral Cu(I)–phosphine/oxazoline complex; in the presence of a Brønsted base (Cs_2CO_3, stoichiometric). In 2019, Hartwig and co-workers have disclosed another Ir*/Cu* system for the stereodivergent AAA between allylic carbonates and α-(2-pyridyl) α-fluoro esters by using chiral Ir(I) metallacycle and Cu(I)–bis(phosphine) complexes; in the presence of a Brønsted base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, catalytic) [12,7]. In 2020, Liao and Zhang and co-workers have reported another type of synergistic heterobimetallic catalyst system (Pd*/Cu*) for the stereodivergent AAA between racemic 1,3-disubstituted non-symmetric allylic acetates and racemic α-aldimine α-methyl esters; in the presence of a Brønsted base (K_3PO_4, stoichiometric; Fig. 1c) [13]. A palladium species has been used for the first time in such context. This DyKAT process relies on a chiral Pd(0) complex, derived from phosphine/bis(sulfoxide) ligand (*R*,*R*)-**3** [or (*S*,*S*)-**3**], and a chiral Cu(I) complex, derived from ferrocene-based phosphine/oxazoline ligand (*R*,*R*)-**4** [or (*S*,*S*)-**4**]. By switching the absolute configuration of the two chiral catalysts, all four stereoisomeric α-methyl γ,δ-unsaturated α-amino acids (bearing adjacent quaternary/tertiary stereocenters) were obtained in 81–90% yield with 8:1 ~ 14:1 *dr* and 91% ~ >99% *ee*. The key to an efficient DyKAT was considered the *in situ*-generation of two diastereoisomeric π-allyl–Pd(II) species and a chiral five-membered ring-containing copper enolate (azomethine ylide) displaying high steric demand at the α-carbon center. Due to a sufficiently rapid equilibrium between the two palladium intermediates, only one diastereoisomer would be selectively intercepted by the catalytically active soft Cu(I) species; displaying low nucleophilicity.

More recently, You and co-workers have disclosed a distinct method for an overall diastereo- and enantiodivergent AAA between allylic carbonates and α-(2-pyridyl) ketones, by coupling the catalytic C–C bond formation with a stoichiometric C–F bond formation using *N*-fluorobenzenesulfonimide (NFSI; Fig. 1d) [14]. Here, a sequence-dependent strategy has been developed: the use of a single-chiral Ir(I) complex, derived from phosphoramidite ligand (*R*,*R*)-**5** [or (*S*,*S*)-**5**], in the presence of Brønsted bases –LiO^tBu (stoichiometric) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, catalytic)– for the C–C bond formation; coupled with the use of $Li–N(SiMe_3)_2$ for the C–F bond formation. By adjusting both the absolute configuration of the chiral catalyst and the order of reactions (sequence), all four stereoisomeric α-(2-pyridyl) α-fluoro γ,δ-unsaturated ketones (bearing adjacent quaternary/tertiary stereocenters) were obtained in 62–68% yield with 5:1 ~ >19:1 *dr* and 95% ~ 98% *ee*. The configuration of the involved α-(2-pyridyl) lithium enolate intermediates is likely to play a key role in the stereochemical course of both sequences. Considering the similar size of H/F atoms and the steric demand of the (phenyl)allyl group with an existing β-stereocenter, the diastereo-switch (at α) in the overall two-step process would be substrate-controlled

(Fig. 1d): i.e., a neglectable steric impact of the α-substituent in the catalytic AAA (racemic α-fluorinated ketone *vs.* parent ketone) *vs.* a strong steric influence exerted by the α-substituent in the stoichiometric α-fluorination (α-allylated ketone *vs.* parent ketone); the asymmetric induction (at α) in the C–F bond formation of the α-allylated ketone would be controlled by the existing β-stereocenter.

Most recently, You and co-workers have uncovered an enantiodivergent asymmetric allylic amination (dearomatizing Friedel–Crafts-type C–N bond formation) between racemic allylic carbonates and 6-hydroxyisoquinoline to give –time-dependent– each enantiomeric allylic amine product by using a single-enantiomeric Ir(I) catalyst; derived from phosphoramidite/alkene ligand (*S*,*S*)-**1** (Fig. 1e) [15]. The (*S*)-allylic amine product was formed in 80% yield with 94% *ee* (MeOH, 6 min). In the presence of 3,5-dichlorobenzoic acid (DCBA, sub-stoichiometric), the (*R*)-allylic amine product was obtained in 78% yield with 98% *ee* (MeOH, 10 h). Mechanistic experiments revealed that two sequential kinetic resolutions (KRs) would take place (Fig. 1e). The (*S*)-allylic carbonate would be converted with stereoretention to the (*S*)-product (first KR). Under the reaction conditions, the (*S*)-product (less stable) would slowly undergo a stereoretentive methanolysis to form the corresponding (*S*)-allylic ether; with regeneration of 6-hydroxyisoquinoline (second KR). The latter would slowly convert the (*R*)-allylic carbonate with stereoretention to the (*R*)-allylic amine product (more stable); the methanolysis of this product was found to be very slow. This enantiodivergent method has proved applicable to the use of 6-hydroxyisoquinoline derivatives, 8-hydroxyisoquinoline, and aniline derivatives. These studies by You and co-workers [14,15] indicate that both reaction sequence and reaction time may be critically important diastereo- and enantio-determining parameters in the stereodivergent AAA, respectively.

This research highlight introduces the most recent conceptual advances in diastereo- and enantiodivergent AAA, namely two distinct strategies: (i) a synergistic dual catalysis approach exploiting two chiral catalysts (metal/organo or heterobimetallic) for C–C bond formation; (ii) a sequence-dependent approach using a single-chiral metal catalyst for C–C bond formation, coupled with a stoichiometric C–F bond formation. While the former method predominates to date, the latter may open up new synthetic perspectives. The recently reported time-dependent enantiodivergent AAA (dearomatizing C–N bond formation), using a single-enantiomeric metal catalyst, may significantly contribute towards an ultimate synthetic goal in this context: a general fully stereodivergent AAA. In light of the impact and the interdisciplinary importance of chirality [1,2] as well as the advantages of stereodivergent asymmetric synthesis [3,4], further development in stereodivergent AAA will be expected; including: the use of a more sustainable metal catalyst; allylic C–H rather than C–O bond activation (atom-economy); and the use of more challenging pro-nucleophiles (less acidic, hard). Moreover, an expansion to other reaction types beyond simple C–C and C–X bond formations is anticipated, e.g. C–H bond insertion, cycloaddition, and tandem/cascade reactions. More complex stereodivergent transformations could be accomplished *via*: (i) catalyst control (metal, ligand, organic species); (ii) substrate control (steric, electronic); (iii) change of key parameters (e.g. additive, base, solvent, pH value, temperature, light, time); or combinations thereof. Different catalysis types may be exploited as well, including: biocatalysis by engineered enzymes; supramolecular catalysis by artificial molecular machines; H-bonding/anion-binding catalysis; and photoredox catalysis.

Conflict of interest

The authors declare to have no conflict of interest.

Acknowledgments

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