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Enantio- and Diastereodivergent Sequential Catalysis Featuring Two Transition Metal-Catalyzed Asymmetric Reactions

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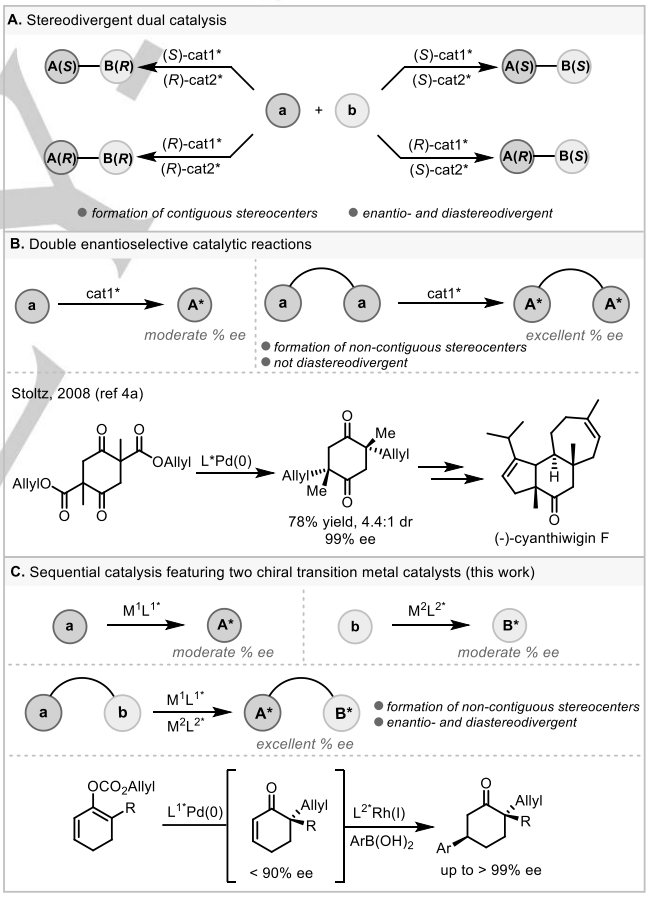
Abstract: This study demonstrates the feasibility and inherent benefits of combining two distinct asymmetric transition metal-catalyzed reactions in one-pot. The reported transformation features a Pd-catalyzed asymmetric allylic alkylation and a Rh-catalyzed enantioselective 1,4-conjugate addition, effectively converting simple allyl enol carbonate precursors into enantioenriched cyclic ketones with two remote stereocenters. Despite the anticipated challenges associated with controlling stereoselectivity in such a complex system, the products are obtained in enantiomeric excesses ranging up to > 99% ee, exceeding those obtained from either of the individual asymmetric reactions. In addition, since the stereoselectivity of both steps is under catalyst-control, this one-pot reaction is enantio- and diastereodivergent, enabling facile access to all stereoisomers starting from the same set of starting materials.

The development of asymmetric transition metal catalysis has played a pivotal role in modern synthetic chemistry. Despite significant achievements, most asymmetric catalytic transformations do not allow straightforward access to all possible stereoisomers when the formation of more than one stereocenter is of interest. In 2013, the Carreira group addressed this limitation by introducing the concept of stereodivergent dual catalysis, where two chiral catalysts work cooperatively to form two adjacent stereocenters (Scheme 1a).[1] In this type of reaction, each chiral catalyst exhibits independent stereocontrol on one of the stereocenters with no appreciable mismatch effects, thereby enabling facile access to all four stereoisomers from a common set of conditions.[2]

Aside from stereodivergence, another advantage of a process forming two or more stereocenters with catalyst-controlled stereoselectivity – as opposed to substrate control – is statistical amplification of the enantiomeric excess.[3] Although this type of statistical amplification has classically been observed in multi-step total syntheses, it can be used strategically in a single pot operation. For instance, recent examples of “double enantioselective catalytic reactions” have emerged, where a single chiral catalyst performs the same reaction twice on distal sites of the same molecule (Scheme 1b).[4] Consequently, high levels of enantiopurity can be obtained even if the individual catalytic transformation is only moderately enantioselective. The Stoltz group reported an elegant application of this concept for the total synthesis of (-)-cyanthiwigin F, in which a double Pd-catalyzed asymmetric allylic alkylation was used to install the key stereocenters.[4a]



Scheme 1. Stereodivergence and enantiomeric enrichment in asymmetric catalysis

In theory, the combination of two *different* asymmetric transition metal-catalyzed processes in one-pot could lead to similar levels of statistical enantiomeric enrichment, while significantly broadening the range of products that could be formed via this approach (Scheme 1c). Yet, to the best of our

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knowledge, the realization of such a process remains unreported.[5] Finding a common set of reaction conditions ensuring complete orthogonality of both steps while simultaneously maintaining high yield and enantioselectivity for each catalytic transformation is a significant challenge. With these concerns in mind, we hypothesized that the benefits of statistical amplification could outweigh the anticipated hurdles.

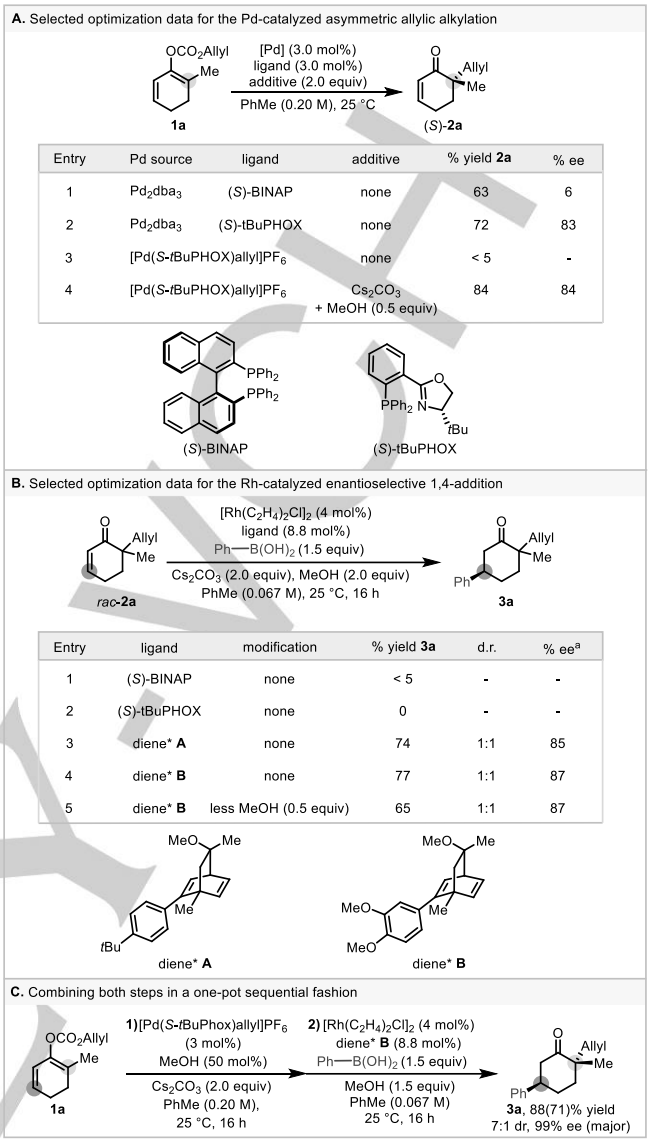
Herein, we report a fully enantio- and diastereodivergent one-pot reaction featuring a Pd-catalyzed asymmetric allylic alkylation[6] and a Rh-catalyzed enantioselective conjugate addition of boronic acids (Scheme 1c).[7] This process meets the expected benefits of orthogonal one-pot catalysis, which aims to maximize efficiency in synthesis by skipping intermediate purification steps, therefore minimizing waste and saving time.[8]

When we initiated this investigation, allyl enol carbonate **1a** was selected as the model substrate in order to control the sequence of events when both catalysts are present at the outset of the reaction. In contrast to allyl β-keto esters, allyl enol carbonates have the added benefit of having the enone functionality masked until it is revealed by the asymmetric allylation step. Although each individual asymmetric transformation is precedented in the literature, development of a one-pot process required optimization to account for compatibility issues between the two reactions. We examined each step, while actively looking for conditions employing a common base, solvent, and temperature.

For the Pd-catalyzed allylation step, the use of (*S*)-BINAP afforded **2a** in good yield, but in very low enantiomeric excess (Scheme 2a, entry 1). On the other hand, (*S*)-tBuPHOX was found to be an efficient ligand for the transformation (entry 2), in accordance with several reports using this metal-ligand combination. We opted for a Pd(II) catalyst with pre-bound ligand as opposed to more standard conditions involving Pd_2dba_3 and a slight excess of (*S*)-tBuPHOX, to reduce the risk for formation of Rh(I)-*t*BuPHOX, which was shown to be an inactive catalyst in the second step (Scheme 2b, entry 2). In the absence of base, the Pd(II) pre-catalyst is inactive (Scheme 2a, entry 3). A combination of cesium carbonate and methanol was found to facilitate the reduction of the Pd pre-catalyst, leading to a satisfactory yield of **2a** (entry 4).[9]

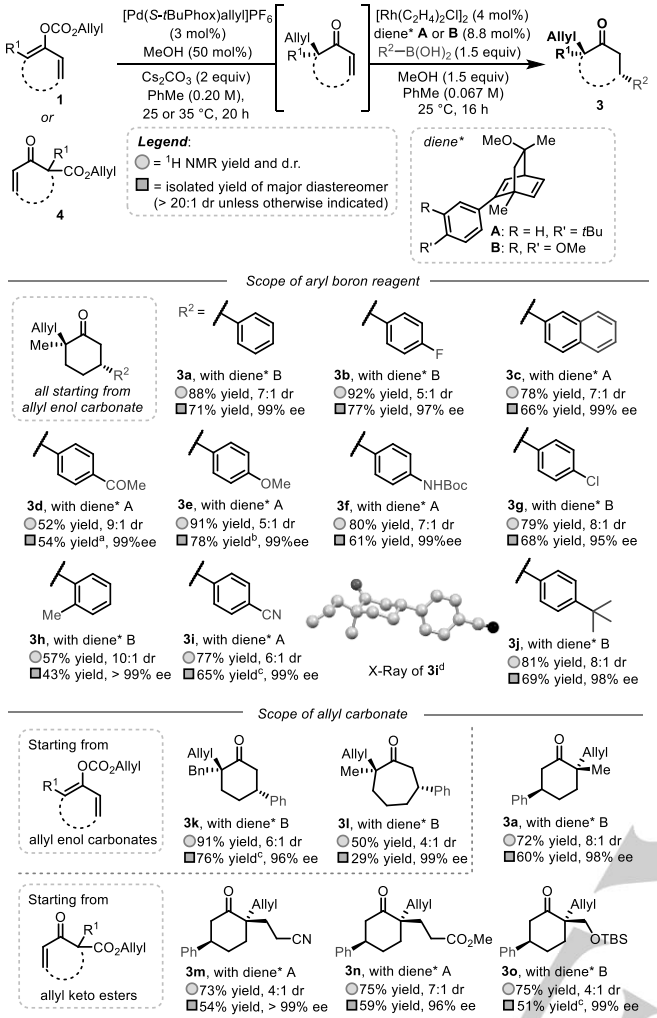
Chiral diene ligand **A**, first developed by the Carreira laboratory[10] and repurposed for Rh-catalyzed 1,4-additions by the Darses group,[7b] was found to be efficient for the Rh-catalyzed transformation (Scheme 2b, entry 3). However, this chiral diene is difficult to separate from **3a** using column chromatography. To alleviate purification issues, a more polar chiral diene ligand **B** was used (entry 4).

In spite of the enantioselectivity of each step being less than ideal (i.e. <90% ee), the combination of both steps in a sequential one-pot protocol leads to outstanding enantiomeric excess of the major diastereomer (Scheme 2c), through statistical amplification. Assuming complete orthogonality and catalyst-controlled stereoselectivity for both steps, the expected diastereomeric ratio and enantiomeric excess are calculated to be 6.4:1 dr and 99% ee for the major diastereomer (see Figure S1 in S.I. for calculations). In fact, allyl enol carbonate **1a** is converted to ketone **3a** in 88% NMR yield (7:1 dr), and the major diastereomer can be isolated in 71% yield and 99% ee.



Scheme 2. Optimization of the sequential protocol. All reactions performed on a 0.20 mmol scale under argon atmosphere, see S.I. for experimental details. ^{1}H NMR yields are reported; isolated yield of major diastereomer in parentheses. [a] % ee of the anti diastereomer is reported and matched the % ee of the syn diastereomer within measurement error.

We next turned our attention to determining the reaction scope (Scheme 3). A variety of aryl boronic acids could be employed. Both electron-poor (**3d**, **3i**) and electron-rich (**3e-f**, **3j**) boronic acids performed well under the reaction conditions. Boronic acids with para-halogens, such as fluoro (**3b**) and chloro (**3g**), were coupled successfully. Notably, boronic acids with functional groups such as acetyl (**3d**), Boc-protected amine (**3f**) and nitrile (**3i**) participated in the reaction. Additionally, an ortho-substituted boronic acid afforded enantiopure product (**3h**), albeit in a modest isolated yield of 43%. Heteroaromatic, vinyl, and aliphatic boronic acids were also screened but were found to be incompatible with this protocol (see S.I., Figure S2).

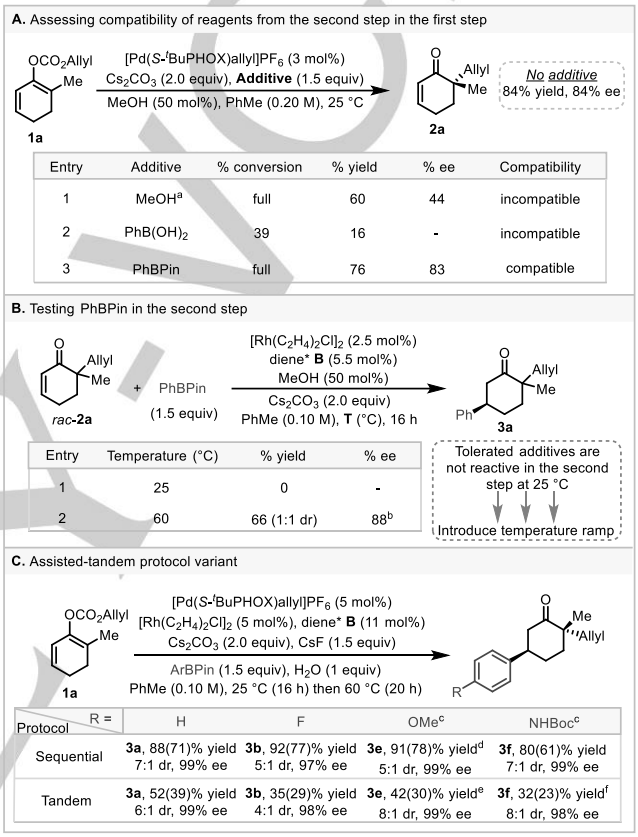


Scheme 3. Scope of the reaction. All reactions performed on a 0.20 mmol scale under argon atmosphere, see S.I. for experimental details. First step carried out at 25 °C for allyl enol carbonates, 35 °C for allyl β-keto esters [a] Isolated in 9:1 dr. [b] Isolated in 8:1 dr. [c] Isolated in 7:1 dr. [d] Hydrogens not shown; carbons shown in light gray, oxygen in dark gray, nitrogen in black.

When investigating the scope of the carbonates, we also studied the more easily prepared allyl β-keto esters to broaden the applicability of the methodology. A methyl (**3a**) or benzyl (**3k**) substituent was tolerated at the alpha position. A more challenging scaffold, derived from heptanone, also gave the desired product in excellent stereoselectivity, albeit in lower yield (**3l**). Starting from allyl β-keto esters, products bearing aliphatic chains with functional groups such as nitrile (**3m**), ester (**3n**), and TBS-protected alcohol (**3o**) could be formed, all in good yields.

Next, we sought to determine whether the sequential protocol could be translated to a one-pot process where all reagents are present from the outset of the reaction. The previously described conditions cannot be directly converted to a tandem process; less than 5% of the desired product is obtained if reagents from the second step are added from the outset (see S.I., Section 2.4). To understand the origins of the problem, we conducted an interference (alternatively called a robustness) screen approach to evaluate which reagents from the second step were incompatible in the first step (Scheme 4a).[11]

It was found that, although traces of methanol can likely assist in the activation of the palladium catalyst, too much methanol leads to a significant decrease in enantioselectivity and a modest decrease in yield (Scheme 4a, entry 1). Phenyl boronic acid was also found to interfere, leading to low conversion and only 16% yield of enone **2a** (Scheme 4a, entry 2). By contrast, phenyl pinacol borate was compatible in the first step (Scheme 4a, entry 3). However, phenyl pinacol borate is unreactive in the second step at 25 °C (Scheme 4b, entry 1), but good conversion can be obtained at 60 °C (entry 2).



Scheme 4. Development of an assisted-tandem variant. All reactions performed on a 0.20 mmol scale under argon atmosphere, see S.I. for experimental details. ^{1}H NMR yields are reported; isolated yields of major diastereomer in parentheses. [a] 2.0 equivalents in total. [b] %ee of the anti diastereomer is reported. [c] Diene* A was used. [d] Isolated in 8:1 dr. [e] Isolated in 10:1 dr. [f] Isolated in 12:1 dr.

Incorporating a temperature change in the assisted-tandem protocol was key to achieve a correct balance between reagent compatibility in the first step and reactivity in the second step. In addition, it was found that switching methanol for a combination of water and cesium fluoride could afford product **3a** in a moderate combined yield of 52% (Scheme 4c). Notably, the stereoselectivity of the reaction remained high: the major diastereomer could be isolated in 39% yield and 99% ee. Other pinacol boronate reagents could be used, and major diastereomers all showed excellent enantiomeric purity. However, purification following this protocol was more challenging and only low to moderate yields are obtained in contrast to the sequential procedure. While we have demonstrated the feasibility of a one-pot procedure where all the reagents are added from the outset

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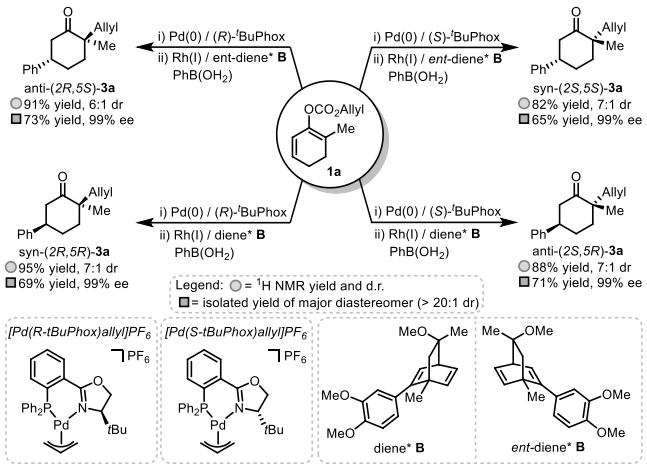
of the reaction, we wish to highlight that the sequential catalysis protocol proved to be far better and more practical.

We were able to validate the stereodivergent nature of the one-pot reaction (Scheme 5). Allyl enol carbonate **1a** was subjected to four different permutations of catalyst/ligand under the standard sequential protocol. All four possible stereoisomers could be isolated in good yield (65-73%) and outstanding ee (99%).



Scheme 5. Demonstrating stereodivergence. All reactions performed on a 0.20 mmol scale under argon atmosphere, see S.I. for experimental details.

In summary, we have developed a one-pot reaction that converts allyl enol carbonates into highly enantioenriched ketones bearing α-quaternary and δ-tertiary stereocenters. Notably, many of the products are obtained in ≥ 99% ee, which exceeds the levels of enantioselectivity expected from either asymmetric transformation alone. This process is fully enantio- and diastereodivergent; all the possible stereoisomers can be synthesized following the same standard protocol. This work fills in a gap in the field of one-pot orthogonal catalysis by demonstrating that combining two asymmetric transition metal-catalyzed processes in a single reaction vessel is, not only a viable synthetic methodology, but constitutes a powerful approach for the obtention of complex products in high enantiopurity.

Acknowledgements

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Keywords: sequential catalysis • asymmetric allylic alkylation • rhodium • palladium • stereodivergent

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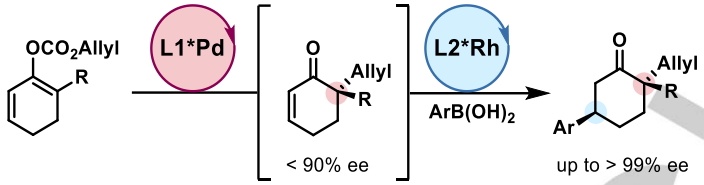

Two catalysts are better than one. Two chiral transition metal catalysts are combined in one-pot to perform orthogonal asymmetric transformations. Simple allyl enol carbonates are converted to ketones bearing two non-contiguous stereogenic centers via a Pd-catalyzed asymmetric allylic alkylation followed by a Rh-catalyzed enantioselective Hayashi-Miyaura conjugate addition. This tandem process is enantio- and diastereodivergent and exhibits statistical amplification of enantiomeric excess.