Stereodivergent, Multicomponent Metal-Catalyzed Couplings Generating Three Stereocenters: Combining Enantioselective Rh-Catalyzed Conjugate Addition and Ir-Catalyzed Allylic Alkylation

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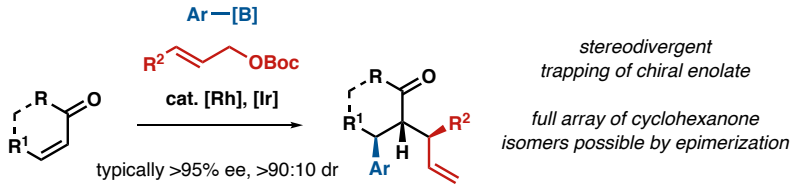
ABSTRACT

Stereodivergent dual catalysis has emerged as a powerful tool to selectively prepare all four stereoisomers in molecules containing two chiral centers from common starting materials. Most processes involve the use of two substrates, and it remains challenging to use dual catalyst approaches to generate molecules having three newly formed stereocenters with high diastereo- and enantioselectivity. Here we report a multicomponent, stereodivergent method for the synthesis of targets containing three contiguous stereocenters by the combination of enantioselective Rh-catalyzed conjugate addition and Ir-catalyzed allylic alkylation methodologies. Both cyclic and acyclic α,β-unsaturated ketones undergo β-arylation using aryl boron reagents to form an enolate nucleophile that can be subsequently allylated at the α-position. The reactions proceed with generally >95% ee and with >90:10 dr. Epimerization at the α-carbonyl center enables the preparation of any of the eight possible stereoisomers from common starting materials, as demonstrated for cyclohexanone products.

TOC GRAPHIC



INTRODUCTION

Stereoselective synthesis plays an important role in the discovery and production of bioactive molecules.[1] Many strategies exist for controlling the configuration of a single stereocenter in a molecule or producing one major diastereomer during a bond forming reaction. The enantio- and diastereoselectivity in reactions that generate more than one stereocenter is often controlled by both the catalyst and substrate/product – chiral catalysts control absolute stereochemistry (enantioselectivity) while the structure of the substrate or product dictate relative stereochemistry (diastereoselectivity).[2]

Attention has recently been placed on developing ways to synthesize all possible stereoisomers of a target with two stereocenters directly through the action of two distinct chiral catalysts.[3] When successful, the four permutations of catalyst combinations can provide access to any of four product stereoisomers from the same set of starting materials. Spurred by Carreira's report on dual catalyst enabled stereodivergent synthesis,[4] there are now an impressive array of processes that achieve this feat in reactions forming two stereocenters (Fig 1a).[5]

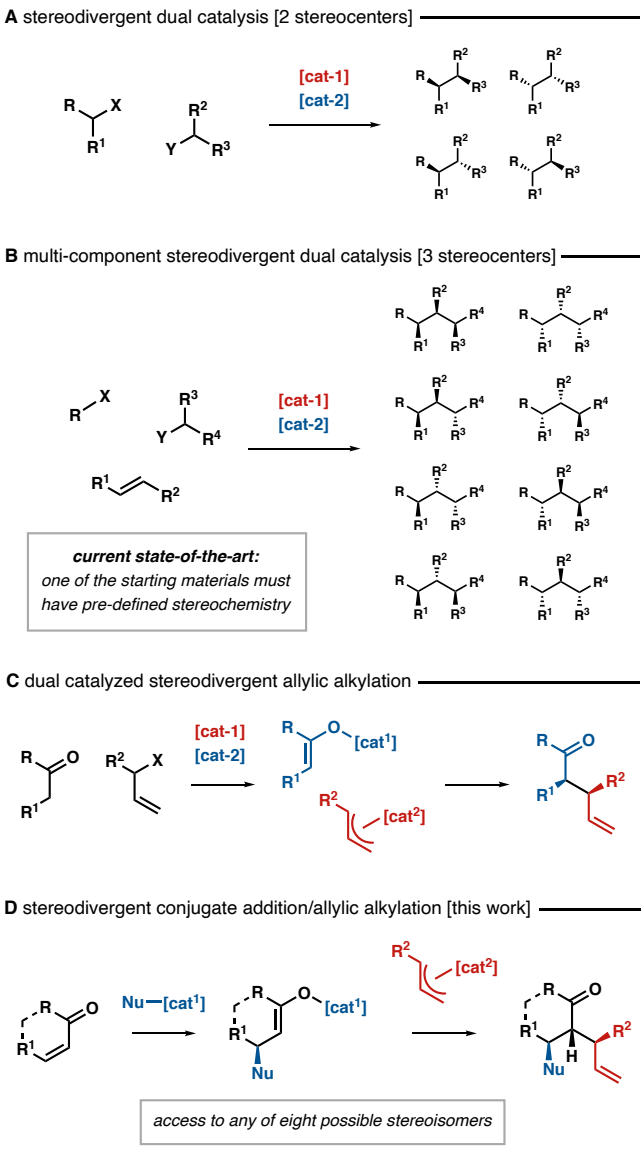


Figure 1. Stereodivergent catalysis – overview of established processes, dual catalyzed allylic alkylation and this work on stereodivergent multi-component coupling to generate products with three stereocenters.

The stereodivergent synthesis of molecules containing three stereocenters is more challenging than those with only two. The few established methods require different isomers of stereodefined starting

materials in order to prepare the full array of eight isomers (Fig 1b).[5b, 5k] In these cases, a coupling partner with an enantioenriched stereocenter[5k] or an alkene substrate with either *E*- or *Z*-configuration[5b] is needed to direct the selectivity at one of the product stereocenters. Reactions that can be used to control the configuration of three newly formed stereocenters from a single set of prochiral starting materials are not established. Given that many targets of interest in drug discovery have more than two stereocenters, multi-component stereodivergent techniques of this type would be desirable to streamline synthetic routes and maximize efficiency.[6]

Of the many reported strategies, transition metal catalyzed allylation has proven to be one of the most successful manifolds for stereodivergent synthesis.[3i] These processes involve the generation of a catalyst-bound nucleophile, for example an enolate, and its subsequent addition to a allyl electrophile generated by a second catalyst (Fig 1c).[7] We questioned whether the reactive nucleophile in an enantioselective allylic alkylation could be generated in-situ by an initial catalytic enantioselective conjugate addition (Fig 1d).[8] This would enable a multicomponent process for the catalytic stereodivergent synthesis of molecules with three adjacent stereocenters.

We focused on combining Rh-catalyzed conjugate addition[9] with Ir-catalyzed allylic alkylation methodologies (Fig 2a).[10-12] This process would require trapping a Rh-enolate intermediate **I**,[13] generated by an enone β-arylation reaction of **III**, with Ir-allyl species **II** generated by allylic carbonate oxidative addition (Fig 2b). Independently, both reactions are among the most reliable methods for enantioselective C–C bond formation. Despite this, the process has conceivable pitfalls. For example, the intermolecular trapping of Rh-enolates generated by conjugate addition by non-proton electrophiles generally results in poor diastereoselecitivies.[14, 15] Additionally, competitive protonolysis of Rh-enolate **I** by water to generate hydroarylation products or the arylation of Ir-allyl **II** by Rh-aryl **III** to form allylic arylation products would need to be suppressed.[16] Rh(I) and Ir(I) would need to react selectively with the correct substrate, despite both metals ability to promote conjugate addition and allylic substitution.[17] Nonetheless, after careful optimization, we report the stereodivergent coupling of aryl boron reagents, enones, and allylic carbonates via dual Rh/Ir-catalysis. The catalysts control absolute stereochemistry at the arylated (β) and allylated (β') positions, while diastereoselective protonation can be used to give access to the *cis*-cyclohexanone set of epimers allowing synthesis of any of the 8 possible stereoisomers for cyclic enone substrates (Fig 2c).

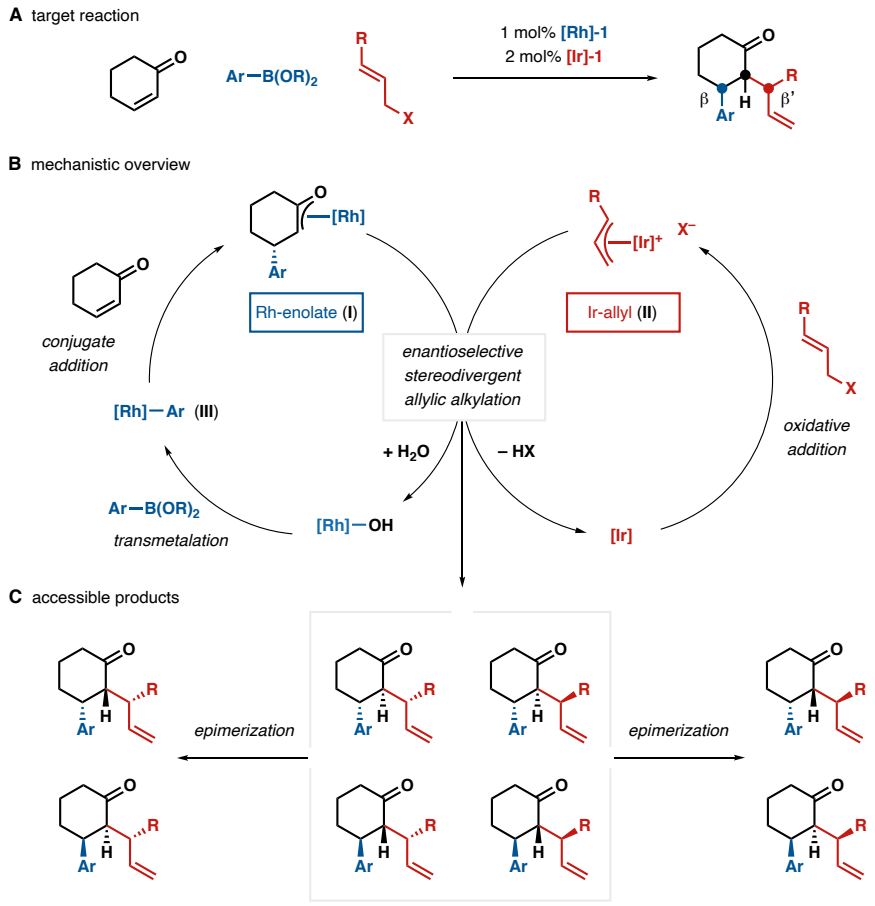


Figure 2. A dual catalysis, multi-component approach for the enantioselective synthesis of the complete set of α,β-difunctionalized cyclohexanone stereoisomers with three adjacent stereocenters by Rh-catalyzed conjugate addition/Ir-catalyzed allylic alkylation.

RESULTS AND DISCUSSION

Three-component coupled product **1** derived from the combination of cyclohexenone, 3-bromophenyl pinacol boronic ester and a cinnamyl carbonate could be obtained in 75% yield, 99% ee, and >98:2 dr using a phellandrene-derived Rh-catalyst (**[Rh]-1**)[18] and a phosphoramidite Ir-catalyst (**[Ir]-1**)[19] (Fig 3a). The minor diastereomer **2**, with inversion at the cyclohexanone α- and β-positions, arises from the minor enantiomer generated in the Rh-catalyzed conjugate arylation step. Use of other Rh-based catalysts (**[Rh]-2**–**5**) resulted in lower yields due to non-productive consumption of substrate, as did other Ir-based catalysts known to promote enantioselective allylic alkylations (**[Ir]-2**–**4**) (Fig 3b-c). Reaction conditions and the aryl boron nucleophile were tuned to maximize the productive reaction between the Rh-enolate and Ir-allyl intermediates while still enabling catalytic turnover via protonolysis (Fig 3d). The use of dioxane solvent with 5 equivalents of H_2O and 3 equivalents aryl–B(pin) nucleophile provided best results. Using less water slowed reaction rates and resulted in poor conversion, while the use of alternative aryl boron species led to increased hydroarylation product **3** (in the case of boronic acid or B(neop)) or simply no reaction (in the case of boroxines or BAr_4). Reactions could be conducted with as

low as 0.5 mol% Rh-dimer and 1% Ir to give **1** in 60% yield and 99% ee. Control experiments showed that the β-aryl cyclohexanone **3** formed by Rh-catalyzed hydroarylation does not re-enter the catalytic cycle. This suggests the process involves the direct reaction between Rh-enolate and Ir-allyl intermediates (Fig 3e). The ee of hydroarylation product **3** decreases slightly over the time scale of the reaction, suggesting the Rh catalyst is prone to degradation over time and explains the formation of **2** as the minor diastereomer, particularly under non-optimal conditions (from >99.5 to 95% ee, see SI for details).

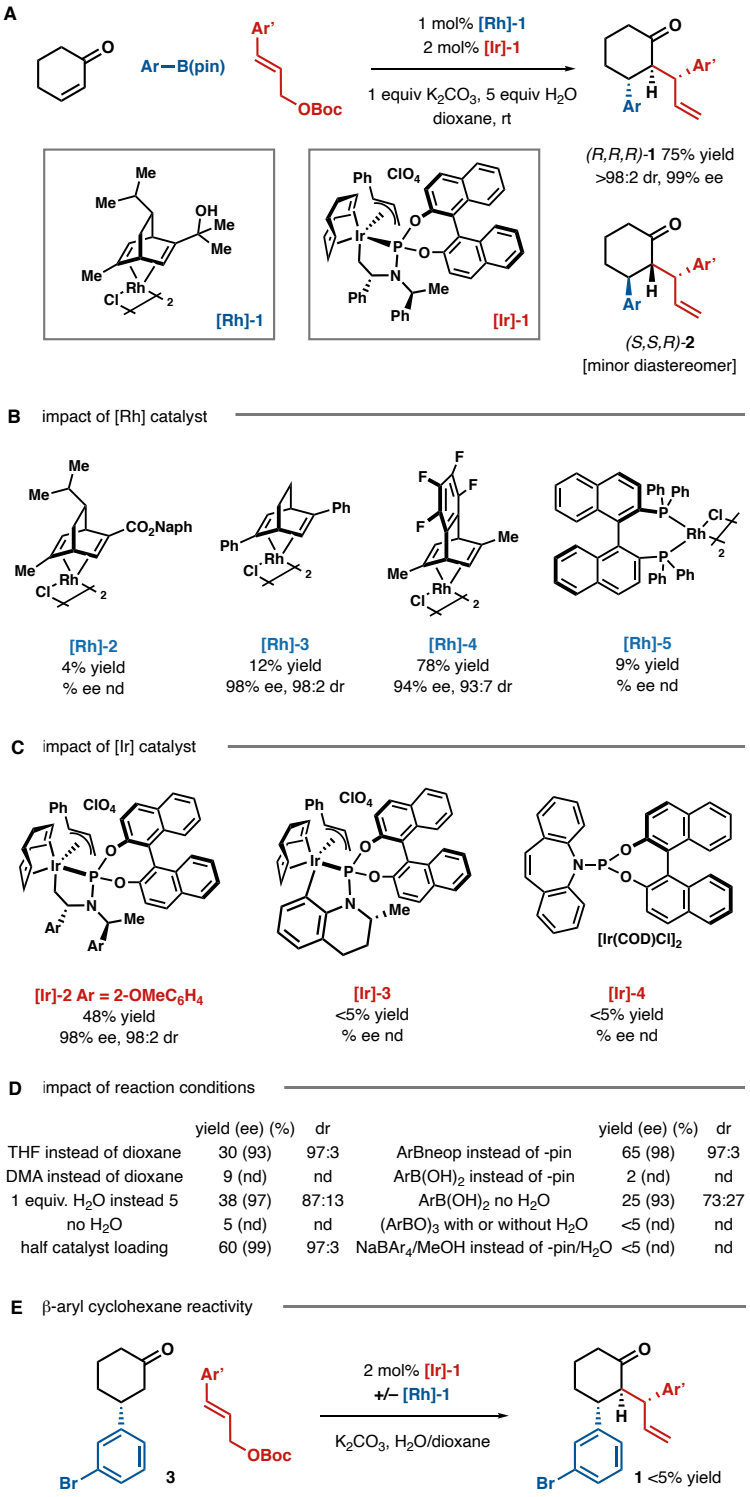


Figure 3. Reaction development. 0.20 mmol scale, enone:ArB(pin):allylOBoc = 3:3:1, 0.25 M, 17–22 h. Yields and dr determined by calibrated ^{1}H NMR, ee determined by chiral HPLC, dr is the ratio of major product to all isomers. Ar = 3-BrC_6H_4, Ar' = 4-OMeC_6H_4.

The combination of a stereodivergent three-component coupling and post-reaction epimerization of the α-ketone stereocenter allows for the synthesis of any of the eight possible stereoisomers of the

coupled products using the reaction between cyclohexenone, 3-bromophenyl boronic ester and cinnamyl carbonate as template. The configuration of Rh- or Ir-catalyst controls the absolute stereochemistry of products at the β and β' positions where α-allylated *trans*-cyclohexanones **4** and **5** can be obtained in 99% ee, 61–42% isolated yield, and >90:10 dr (Fig 4). Control experiments show, as expected, the *trans*-stereoisomers are the thermodynamically more stable products, however the selectivity for this isomer is enhanced by the catalysts (see the SI). Preparation of the *cis*-cyclohexanone series can be accomplished by synthesis of the thermodynamic silylenol ether[20] and subsequent protonation[21] from the less hindered enol face to give diastereomers **6** and **7**.

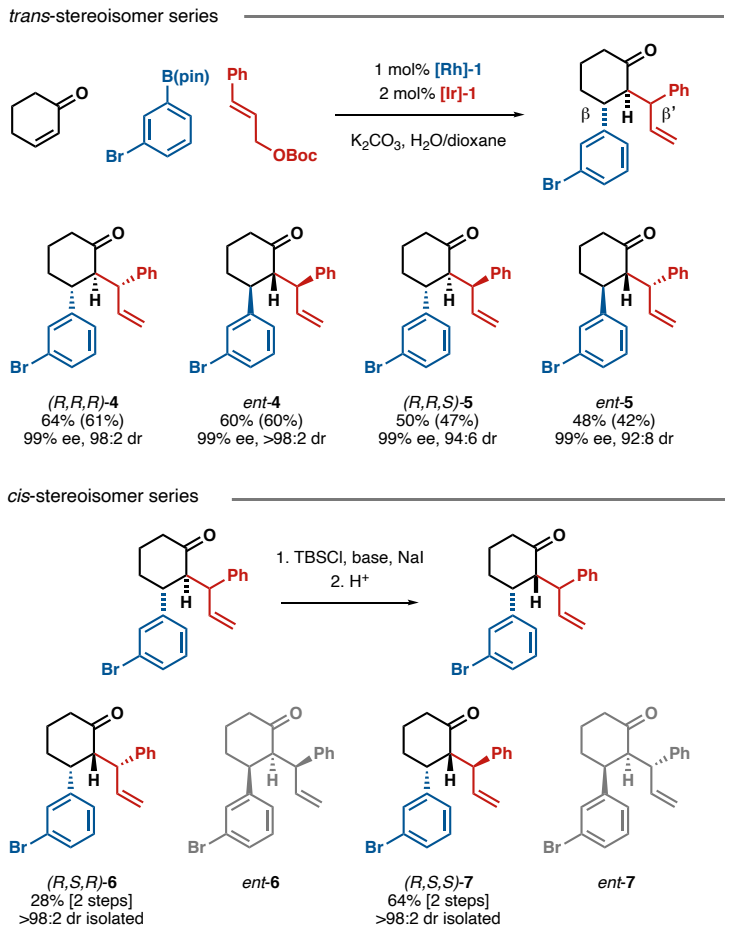


Figure 4. Stereodivergent synthesis of all possible stereoisomers of the three-component enone-aryl boron-cinnamyl carbonate coupling.

The stereodivergent three component coupling reaction was compatible with various aryl boronic ester partners when using cyclohexanone and 4-methoxycinnamyl carbonate (Fig 5, **1**, **8–18**). The reaction proceeds generally with >95% ee and >95:5 dr when using aryl boronic esters with electron-donating (OMe, SMe) or electron-withdrawing groups (CF_3, CO_2Et) as well as halides (Br, Cl), NHBoc groups, and other aromatics (thiophene, naphthyl). In many cases yields are modest (40–60%) as the

isolation of analytically pure material is not trivial. The cinnamyl carbonate unit can also be modified with various substituents, including OMe, Cl, naphthyl, benzodioxole, and thiophene (Fig 5, **1**, **19–22**). Substrate limitations include pyridyl boronic esters and highly electron-poor cinnamyl carbonates (see the SI for details). The reaction was easily scaled to prepare gram quantities of **4** in 99% ee and >98:2 dr.

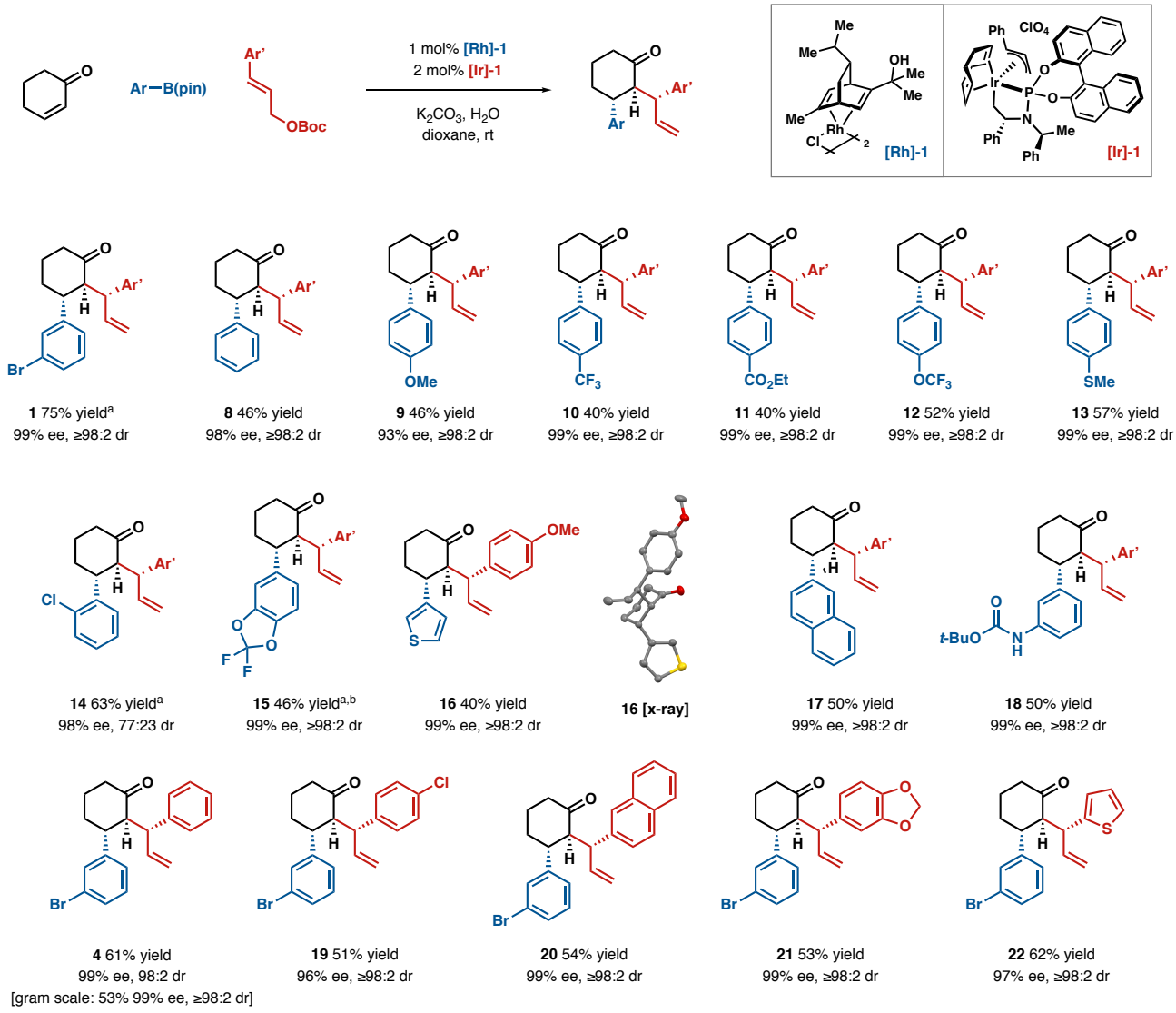
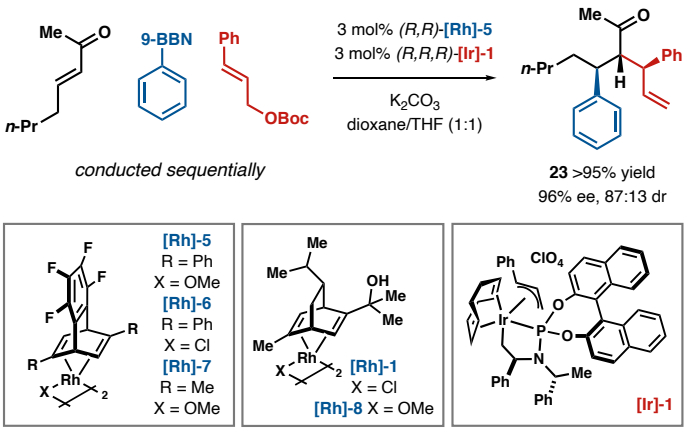


Figure 5 Reaction scope with cyclohexenone. Unless noted, yields are of isolated material. Enone:ArB(pin):allylOBoc = 3:3:1, 0.25 M, 17–22 h. See SI for full details**.** Ar = 3-BrC_6H_4, Ar' = 4-OMeC_6H_4. [a]Yield determined by calibrated ^{1}H NMR. [b]ArB(neop) instead of ArB(pin). Reactions where conducted with (*R,R,R*)-[Rh]-1 and (S,S,S)-[Ir]-1 to give the configuration shown.

Modifications to the standard conditions were required to accommodate other enone substrates. Thankfully, the catalyst platform is modular, and the three-component coupled product **23** derived from an acyclic enone could be obtained in >95% yield and 96% ee with 87:13 dr (Fig 6). The use of

Nishimura's Ph-tfb ligated catalyst **[Rh]-5**[22] and phenyl-9-BBN in place of phenyl boronic ester was essential to improve reaction yields and selectivities. Best results were obtained by the conducting reactions in a sequential order, where the allylic carbonate and **[Ir]-1** were added after the completion of the conjugate addition reaction. Non-sequential addition of reagents and catalysts (all components added at the beginning of the reaction) gave **23** in lower yield and slightly reduced selectivities (62% yield, 93% ee and 81:19 dr). The methoxy-bridged catalyst **[Rh]-5** is particularly effective, as related tfb-ligand based catalysts give lower ee and/or dr. It is likely that these reactions occur via a boron-enolate intermediate.[23]



	yield (ee) (%)	dr
non-sequential addition	62 (93)	81:19
[Rh]-6 instead of **[Rh]-5**	95 (74)	41:59
[Rh]-7 instead of **[Rh]-5**	>95 (93)	73:21
[Rh]-8 instead of **[Rh]-5**	>95 (86)	82:18
[Rh]-1 instead of **[Rh]-5**	60 (70)	67:33
ArB(pin) instead of 9-BBN	<5 (nd)	nd
$ArB(OH)_2$ instead of 9-BBN	70 (72)	60:40
no K_2CO_3	<5 (nd)	<5 (nd)
best conditions from Fig 3	<5 (nd)	<5 (nd)

Figure 6. Reaction optimization with acyclic enones. 0.10 mmol scale, enone:Ph-9-BBN:allylOBoc = 1.2:1.5:1, 0.22 M, room temperature, 17–22 h. Yields and dr determined by calibrated ^{1}H NMR, ee determined by chiral HPLC, dr is the ratio of major product to all isomers.

The alternative optimized conditions enable three component coupling with a variety of enone partners in generally >95% ee (Fig 7). Examples include cyclic (**24**, **25**) and acyclic enones containing *n*-butyl, benzyl, isobutyl, or methyl groups at the enone β-position (**23**, **26**–**28**). The reaction can also accommodate other cinnamyl carbonate (**29**–**30**) and aryl-9-BBN substrates (**31**–**32**). A synergistic effect between catalysts enantiomers is observed in the overall diastereoselectivity of the reaction when using acyclic enones. Product **33**, the diastereomer of **23**, is formed in 96% ee and 77:23 dr from (*R,R*)-Rh/(*S,S,S*)-Ir catalysts compared to 87:13 dr from (*R,R*)-Rh/(*R,R,R*)-Ir catalysts.

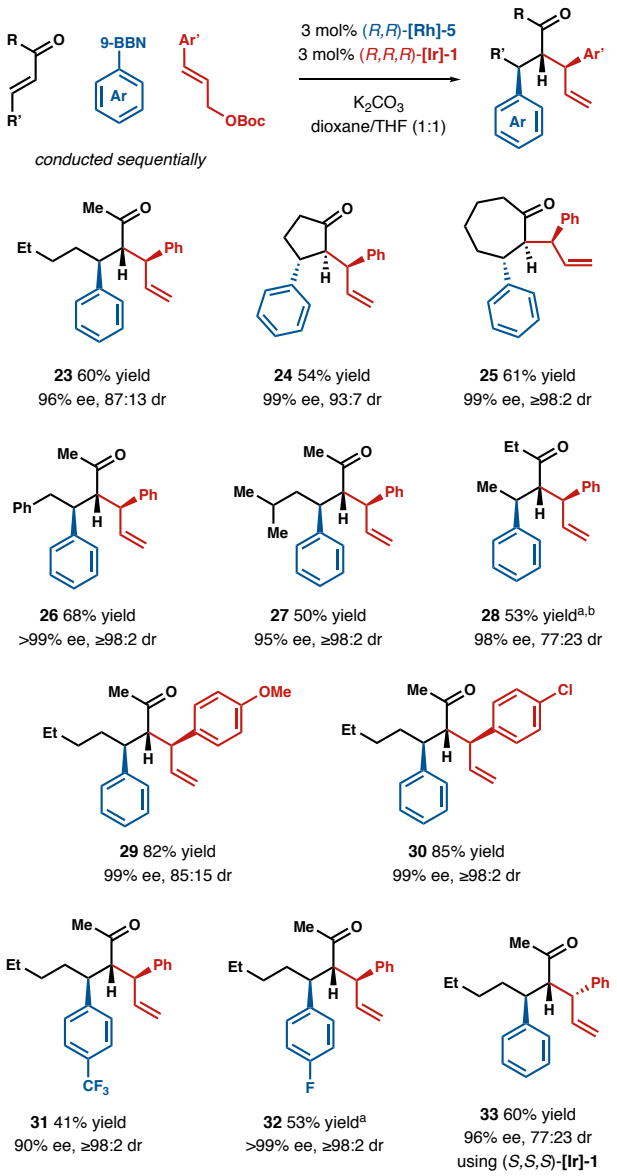


Figure 7. Reaction scope with enones. Enone:Ph-9-BBN:allylOBoc = 1.2:1.5:1, 0.22 M, 17–22 h. Reaction conducted by sequential addition process, adding Ir-catalyst and allylic carbonate after the completion of the Rh-catalyzed conjugate addition. X-ray structure was obtained for **23** to determine relative stereochemistry. Dr reported is the ratio of product:all other diastereomers. Unless noted, yields are of isolated material. See SI for full details**.** [a]Yield determined by calibrated ^{1}H NMR. [b]enone:Ph9-BBN:allylOBoc = 3:3:1.

CONCLUSIONS

In summary, a combination of intermediates generated during the Rh-catalyzed conjugate addition of aryl boron nucleophiles to enones with Ir-allyl electrophiles allows for a multicomponent coupling to generate products with three adjacent stereocenters. Catalyst control enables the stereodivergent access to a set of four different stereoisomers, while in the case of cyclohexanones, the *cis*-diastereomers can be prepared by subsequent enolization and protonation. This work establishes that

the enantioenriched Rh-enolate intermediates can be functionalized by catalytically generated electrophiles in a selective manner. Given the broad scope of Rh-catalyzed conjugate additions,[9b] this approach should be a general platform to rapidly synthesis molecules with multiple adjacent stereocenters in a divergent fashion.

ASSOCIATED CONTENT

Supporting Information: The Supporting Information is available free of charge online. Experimental procedures, HPLC data, NMR data (PDF).

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Author Contributions The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes The authors declare no competing financial interest.

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