Enantio- and *Z*-Selective δ-Hydroarylation of Aryldienes via Rh-Catalyzed Conjugate Addition

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ABSTRACT Metal-catalyzed enantioselective conjugate arylations of electron-poor alkenes are highly selective processes for C(sp^2)–C(sp^3) bond formation. δ-Selective hydroarylations of electron-poor dienes are less well developed and reactions that deliver high enantioselectivity while giving single alkene isomer products are elusive. Here we report the Rh-catalyzed δ-arylation of aryldienes that gives nearly exclusive *Z*-1,4-addition products (generally with >95:5 positional and geometrical selectivity). This remote functionalization provides access to chiral diarylated butenes from readily available precursors poised for further functionalization, including in the synthesis of bioactive molecules. Mechanistic studies suggest that protonolysis of a Rh-allyl intermediate generated by diene insertion into a Rh-aryl is the rate determining step and occurs by an inner-sphere proton transfer pathway.

INTRODUCTION

Catalytic enantioselective conjugate additions are one of the most useful and well-studied reactions for the stereocontrolled formation of C–C bonds.[1] Among these processes, the Rh-catalyzed enantioselective hydroarylation of electron-poor alkenes is a leading method to generate new C(sp^2)–C(sp^3) stereocenters at the β-position relative to an electron-withdrawing group (Fig 1a).[2] Along with providing products in high enantioselectivity, Rh-catalyzed conjugate additions occur under mild, weakly basic conditions using bench-stable and readily available boronic acid derivatives. These reactions can accommodate a wide host of alkene acceptors including α,β-unsaturated esters, -ketones, -amides, and nitro- or sulfonylalkenes. Rh-catalyzed hydroarylations are routinely used in the synthesis of bioactive molecules,[3] in medicinal chemistry programs,[4] and on process-scales.[5] Lam and co-workers comprehensive treatise supports the enormous diversity of substrates and synthetic applications of the reaction (>400 pages, >300 citations).[6] While Rh-catalyzed hydroarylations have enjoyed rapid development since Hayashi and Miyaura's initial report in 1997,[7] some valuable substrate classes, like aryl-activated substrates, remain challenging to use in enantioselective reactions. Because the alkene unit of an arylalkene is inherently less activated by the aryl substituent compared to a

carbonyl and the resulting Rh-intermediates are prone to β-hydride elimination rather than protodemetalation,[8] processes are limited to highly electron-deficient substrates like azaarenes[9] or 4-nitroaromatics[10] (Fig 1a).[11,12]

Electron-poor dienes represent attractive substrates for enantioselective metal-catalyzed conjugate addition because they can allow remote functionalizations relative to an activating group while the products bear an alkene for further functionalization.[13] However, controlling the site of nucleophile addition (β vs δ) and generating single alkene regio- and stereoisomers is a challenge. With respect to metal-catalyzed δ-additions, examples are restricted to Cu-catalyzed alkylations[14] or allylations,[15] and Co-catalyzed alkynylations which each give *E*-alkene products.[16] The hydroarylation of ester or ketone activated dienes with aryl boroxines can be achieved with Ir-based catalysts, however a mixture of positional and geometric isomers are generated and products of the reactions are typically isolated after isomerization to the α,β-unsaturated species or alkene hydrogenation (Fig 1b).[17] Sulfonyldienes have been shown to undergo Rh-catalyzed hydroarylation at the β-position where the selectivity arises from the strongly electron-withdrawing nature of the SO_2F activating group.[18] Aryldiene substrates have been reported to undergo Ni-catalyzed γ-arylation reported with selectivity rationalized by protonation (or hydride addition) to the least sterically hindered site of the diene substrate which varies based on the size of the arylboronic ester unit.[19] Wang and co-workers recently disclosed the Ni-catalyzed *Z*-selective δ-arylation of terminally unsubstituted aryldienes.[20] Given the state-of-the-art of enantioselective diene conjugate additions, particularly with aryldienes, it would be valuable to identify more general, mechanistically understood processes for enantioselective δ-arylations that give single alkene isomer products. This reaction would enable the synthesis of compounds with remote stereocenters difficult to prepare by known methods while possessing an olefin handle for further synthetic elaboration.

We have previously developed catalytic *Z*-selective additions to electron-poor dienes, including transfer hydrogenations,[21] reductive couplings with aldehydes,[22] and enantioselective multicomponent couplings.[23] In these processes, intercepting the Rh-allyl intermediate generated after alkene insertion in a controlled fashion and at a rate faster than isomerization was key to observing high regio- and stereoselectivities. Armed with this understanding we questioned whether weakly activated aryldiene substrates could undergo enantioselective hydroarylation and herein document the development, scope, application, and mechanistic features of such processes.

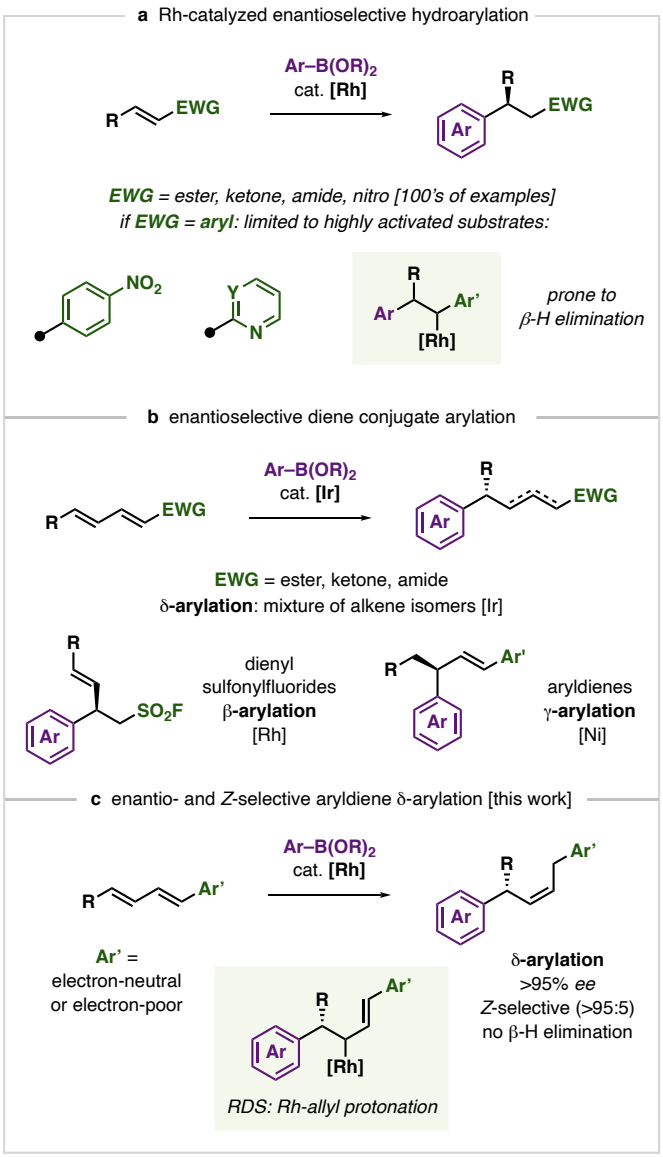

Fig 1. A Overview and limitations of Rh-catalyzed enantioselective conjugate arylations. **B** Established diene hydroarylation reactions using aryl boron nucleophiles. **C** This work reports the *Z*-selective δ-arylation of aryl dienes which proceeds by rate-limiting Rh-allyl protonation.

REACTION DEVELOPMENT

With the aim of developing an enantioselective δ-arylation of diene substate **1**, a range of privileged ligands for conjugate addition and various reaction conditions were surveyed (Fig 2a). It was ultimately found that a Rh-catalyst supported by Nishimura's tetrafluorobenzobarrelene ligand, **Ph-tfb**,[24] provided excellent results, giving **2** in 87% yield, 98% ee, and >95:5 *Z:E*. While the ferrocenyl tfb-ligand analog also gave good results (87% yield, 98% ee), alkylated versions of tfb (Bn or Me) or structurally similar bicyclo[2.2.2]octadienes (**L1**–**L3**) gave product in reduced yields. Use of the less electron-poor, phenyl-substituted ligand **L2** provided similar ee's as **Ph-**

tfb, but with slower rates. The use of MeOH as the reaction solvent was important. Using solvent mixtures common for Rh-catalyzed conjugate additions where the protic additive was diluted with co-solvents like dioxane, toluene, DMF resulted in lower yields (Fig 2b, entries 2–5). Aryl boronic pinacol esters could be used instead of the corresponding boronic acid with nearly identical results (entry 8). This is useful in cases where substrates undergo fast protodeborylation (see below). Ir-based catalysts gave **2** in lower yield but with good enantioselectivity (41%, 92% ee, entry 9). The reaction is not limited to electron-poor aryl dienes. With minor modification to reaction conditions, a phenylbutadiene substrate underwent enantioselective δ-arylation in 70% yield and 99% ee (entry 10). Finally, 3,4-hydroarylation products can be readily generated from the standard 1,4-addition products by treatment with base to isomerize the olefin into conjugation with the Ar' unit without erosion of enantioselectivity (Fig 2c, **3**, 91% yield, 98% ee).

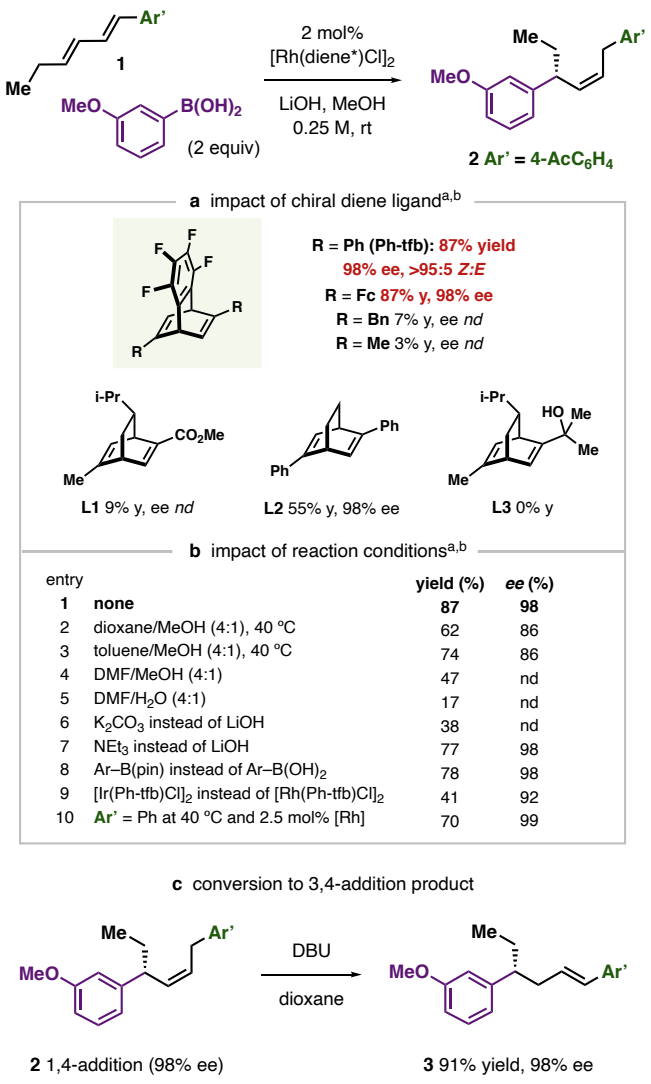

Fig. 2 Reaction Development **A** Impact of ligand structure on reactivity and selectivity. **B** Effect of reaction conditions. **C** Synthesis of enantio-enriched 3,4-hydroarylation product. [a]Yields determined by ^{1}H NMR spectroscopy. [b]ee determined by chiral HPLC after alkene epoxidation, see SI for details.

MECHANISTIC STUDIES

With a selective aryldiene δ-arylation process discovered, mechanistic studies were conducted to probe the origin of desirable reactivity and to contrast with well-established Rh-catalyzed alkene β-arylations. The order of reactants and catalyst was determined by reaction progress kinetic analysis variable time normalization plots[25] of the reaction between diene **1**, 3-methoxyphenyl pinacol boronic ester and $[Rh(Ph\text{-}tfb)Cl]_2$ to generate **2**. The reaction displayed overall zero order kinetics, with some small deviation as full substrate conversion is achieved. The process was found to be zero order in both diene and aryl boronic ester while being first order in catalyst (Fig 3a, see SI for details). The reaction is approximately zero order in base

(LiOH•H_2O), however slightly better overlays are obtained with considering the order to be –0.3 (see SI for plots).

The standard δ-arylation reaction to form **2** exhibited a large primary H/D kinetic isotope effect of ~6 when comparing reaction in conducted MeOH vs d_4-MeOD (Fig 3b). This KIE value is likely an underestimate as some protonated product is observed when using d_4-MeOD due to the presence of LiOH•H_2O. Increasing the Bronsted acidity of the solvent by replacing methanol with 2,2,2-trifluoroethanol decreased reaction rates. More electron-poor aryldienes underwent faster reactions, demonstrated by a series of 4-aryl substituted substrates (Fig 3c; NO_2, Ac, and CF_3). In competition studies between diene substrates, the more electron-poor aryldiene underwent faster reaction but did not inhibit conversion of the more electron-rich aryldiene (see SI for details). Reactions using d_4-MeOD suggest Rh-allyl protonation is diastereoselective as product d_1-**5** was generated with high diastereoselectivity. D-incorporation is observed exclusively at single site at the allylic methylene position (D-incorporation is observed at multiple positions in **2** due to base promoted exchange, see SI for details). The presence of Lewis bases (pyridines, amines) tends to slow the reaction down. Collectively, these results suggest the rate of protonation of the nucleophilic Rh(I)-allyl intermediate is governed by the Rh-center's *Lewis acidity* and the species responsible for protonation (i.e. MeOH) likely coordinates to Rh prior to proton transfer (Fig 3d). This proposal agrees with the need for more electron-withdrawing tfb-type ligands compared to structurally similar bicyclo[2.2.2]octadienes ligands. The high observed regio- and stereochemistry of the *Z*-alkene in the resulting products can be rationalized by a highly ordered transition state akin to that proposed for the *Z*-selective allylrhodation of aldehydes.[22, 26]

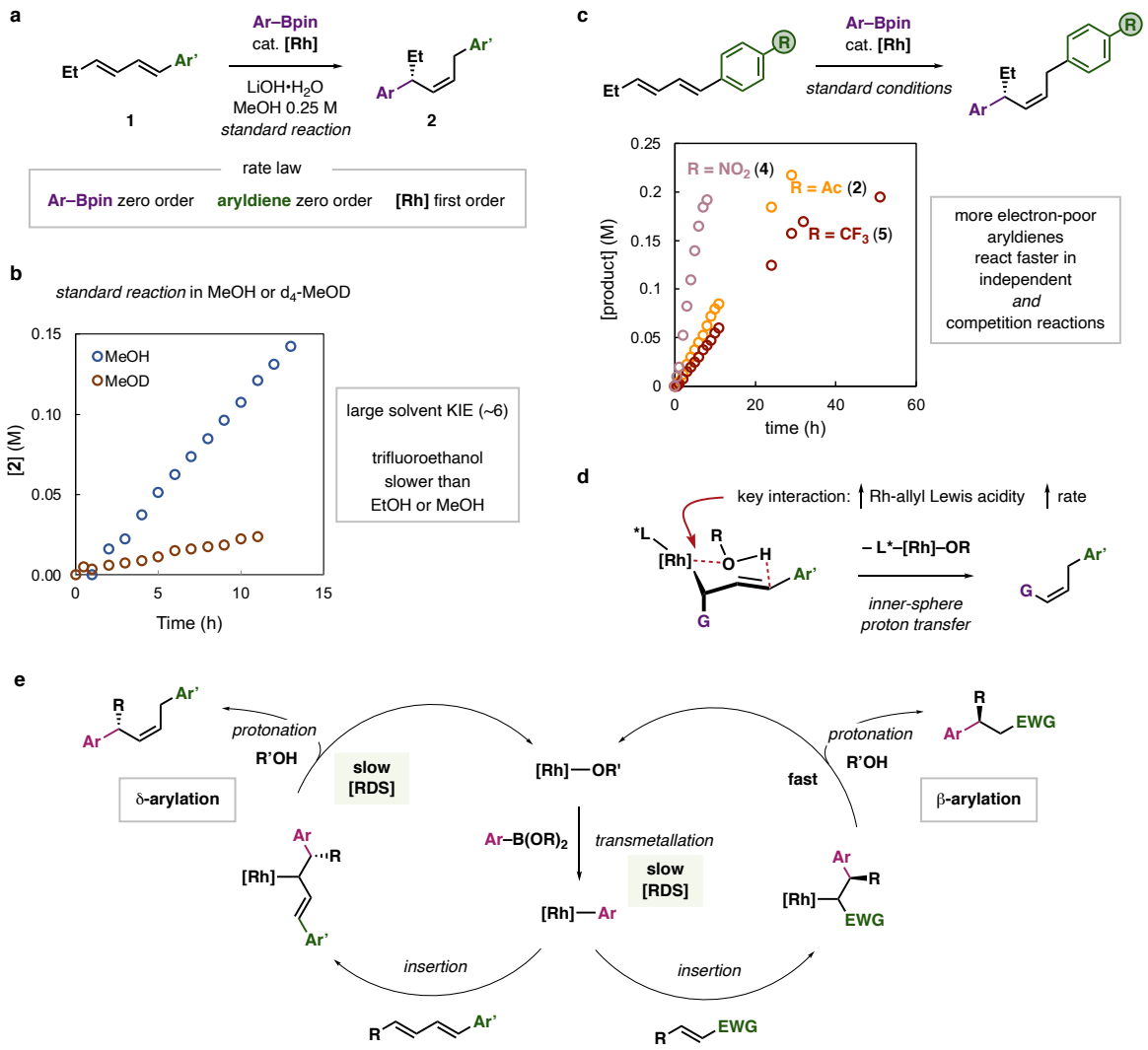

Fig 3. Mechanistic studies **A** Rate law overview determined by variable time normalization plots. **B** Solvent kinetic isotope effect. **C** Reaction rates of differentially substituted aryldienes. **D** Proposed structure required for Rh-allyl protonolysis. **E** Mechanistic proposal and comparison to alkene conjugate arylation. Unless noted Ar = 3-OMeC_6H_4, Ar' = 4-AcC_6H_4

Overall, mechanistic data combined with the established steps of Rh-catalyzed alkene conjugate addition reactions leads to a plausible mechanism where the rate determining step is the protonolysis of a Rh-allyl intermediate by methanol (Fig 3e). This step occurs after transmetallation to generate a Rh-aryl intermediate which can undergo insertion at the 4-position of the aryldiene substrate. The kinetics of aryldiene hydroarylation contrast that of enone hydroarylation, where the reaction is half-order in Rh-catalyst and positive order in arylboronic acid with transmetallation proposed as the rate determining step (Fig 3e).[27] The facial selectivity of diene δ-arylation is the opposite that of alkene β-arylation. The mechanistic differences

between Rh-catalyzed conjugate additions to enones and aryldienes help to explain why mixtures of alkene isomers are commonly generated in previously developed diene hydroarylation reactions. If the Rh-allyl species is long-lived because protonation is slow, isomerization is likely. This step needs to be promoted with a combination of a more electrophilic Rh-center and an appropriate solvent to realize a productive reaction. These findings should have more general application in the design of stereo- and site-selective metal-catalyzed conjugate addition reactions.

REACTION SCOPE

The Rh-catalyzed *Z*- and δ-selective hydroarylation reaction can accommodate a host of aryldiene substrates including those with electron-withdrawing groups (Ac, NO_2, CF_3, CN, SO_2Me; **2**, **4**–**7**), pyridyl-containing diene **10,** and those with a simple phenyl group (**8, 17**) to give products in good to moderate yields and generally ≥94% ee. **2** could be prepared on a 1.2 gram scale in 88% yield and 98% ee. The δ-position of diene substrate where the new stereocenter is formed could bear a host of groups including Me and *i*-Pr units (**16**, **15**), *N*-Boc amines (**11**), alkyl chlorides (**12**), nitriles (**13**), and protected alcohols (**14**) to give δ-arylation products in ≥95% ee. Less successful examples include electron-rich aryldienes like (4-methoxyphenyl)butadiene and 1,4-diarylbutadienes. Aryldiene substrates were generally prepared by a Sonogashira/alkyne isomerization sequence[28] which generally gave products in ~95:5 *E,E*/*E,Z*. Conveniently, the *E,Z*-aryldiene isomers were found to be inert towards hydroarylation and do not impact the reaction so the geometric purity of diene substrate is inconsequential. Of the aryldiene substrates explored, positional selectivity (δ vs β), alkene regioselectivity, and *E/Z*-selectivities each generally remained >95:5. Exceptions are phenyldiene derived products **8** and **17** where ~10% δ-arylated styrene is observed due to post-arylation base-mediated alkene isomerization and the highly activated 4-NO_2 product **4** which is obtained in 89:11 *Z/E*.

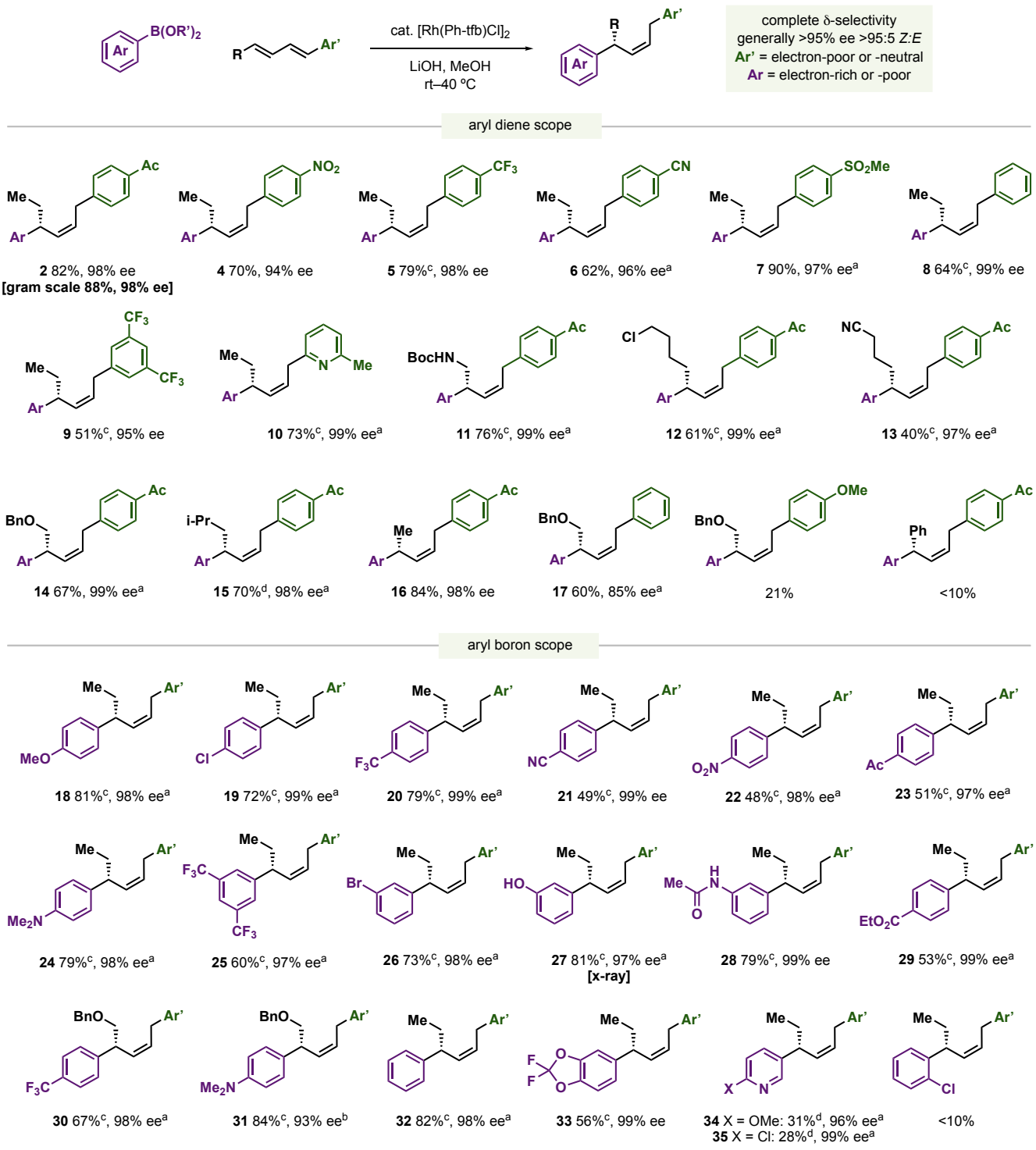

Fig 4. Reaction scope of aryldienes and aryl boron reagents. Ar = 3-OMeC_6H_4, Ar'= 4-AcC_6H_4 Aryldiene:Ar$B(OR)_2$ = 1:2–3, unless noted using 2 mol% [Rh] dimer. Unless noted, yields are of isolated material and ee determined by chiral HPLC after alkene epoxidation. [a]ee determined without derivatization. [b]ee determined after alkene hydrogenation. [c]Using 2.5 mol% [Rh] dimer. [d]Using 5 mol% [Rh] dimer.

Aside from *ortho*-substitution, the scope of aryl boron partners had no significant limitations. Reactions proceed with good yields and ≥93% ee for electron-rich (**18**, **24**, **27**, **28, 31**), -neutral, (**32**) and -poor (**20**, **21**, **22**, **23**, **25**, **29**, **30**) aryl boron substrates. The reaction tolerates aryl bromides (**26**), basic amines (**24**, **31**), unprotected phenols (**27**), and NHAc groups (**28**). Chiral 3-pyridyl containing stereocenters can be generated with high ee (96–99%) although with reduced yields (**34**, **35**). The corresponding aryl boronic pinacol esters were using in examples **21**, **22**, and **24**–**35** due to their improved resistance to protodeboronation. In general, Lewis-basic pyridyl and cyano groups were found to impede the reaction but not completely inhibit it (see SI for details and other unsuccessful substrates).

Enantioselective aryldiene δ-additions can be used to prepare intermediates of compounds that have biological interest in a straight-forward fashion (Fig 5). Compound **36**, a key intermediate in the synthesis of a sphingosine-1 phosphate receptor modulator,[29] was synthesized by cross-metathesis of an allylbenzene and vinylBpin, followed by Suzuki coupling, Rh-catalyzed δ-hydroarylation and hydrogenation in 39% overall yield and 94% ee (Fig 5a). Suzuki coupling of an amino vinyl boronic ester and β-bromostyrene followed by enantioselective diene δ-hydroarylation provides **37** (59% overall yield, 96% ee), an intermediate in the synthesis of inhibitor of human methionine aminopeptidase-1 (Fig 5b).[30] These targets were previously prepared as racemic mixtures. Slight erosion of ee (~2%) was observed upon alkene hydrogenation, presumably due to the sensitive nature of the benzylic stereocenter (see SI for details).

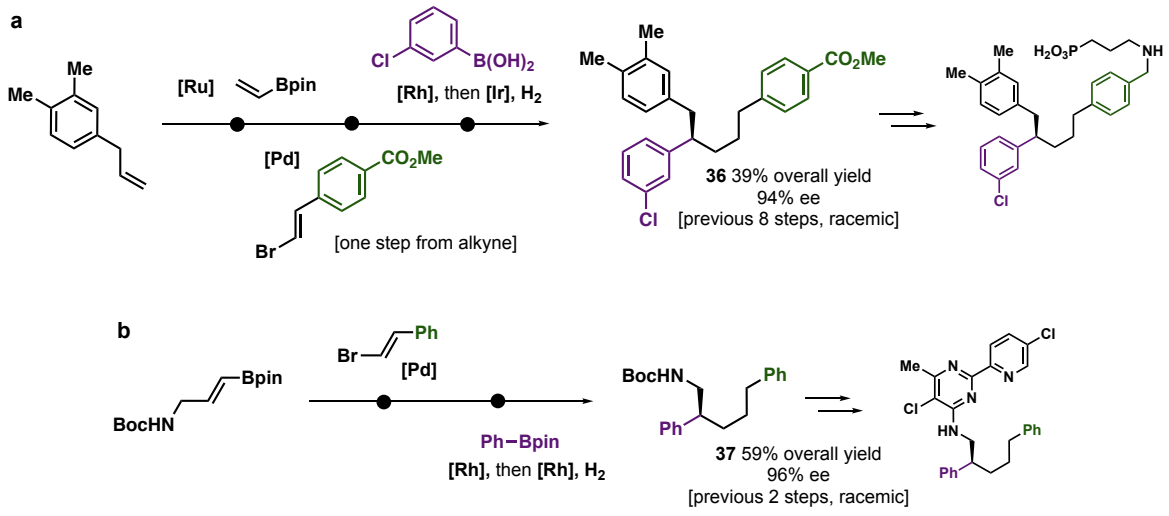

Fig 5. Synthetic applications of Rh-catalyzed enantioselective δ-hydroarylation.

CONCLUSIONS

We have established the Rh-catalyzed δ-selective hydroarylation of aryldienes. The process gives *Z*-alkene containing products generally in >95% ee and does not require strong electron-withdrawing groups on the aryldiene unit while tolerating protic and electrophilic groups on the aryl boronic acid partner. Mechanistic studies suggest inner-sphere proton transfer in a Rh(allyl)(methanol) complex is the rate determining step and enhancing Rh Lewis acidity using an electron-poor chiral diene ligand imparts faster and more selective reactions. These findings should have use in related remote, enantioselective $C(sp^2)$–$C(sp^3)$ bond formations and the design of site-selective metal-catalyzed conjugate-type additions to polyunsaturated substrates.

NOTES

The authors declare no competing financial interest.

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REFERENCES

1. (a) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L., Recent advances in enantioselective copper-catalyzed 1,4-addition. *Chem. Soc. Rev.* **2009,** *38* (4), 1039-1075; (b) Alexakis, A.; Krause, N.; Woodward, S., Copper-Catalyzed Asymmetric Conjugate Addition. In *Copper-Catalyzed Asymmetric Synthesis*, 2014; pp 33-68; (c) Hui, C.; Pu, F.; Xu, J., Metal-Catalyzed Asymmetric Michael Addition in Natural Product Synthesis. *Chem. Eur. J.* **2017,** *23* (17), 4023-4036; (d) Zheng, K.; Liu, X.; Feng, X., Recent Advances in Metal-Catalyzed Asymmetric 1,4-Conjugate Addition (ACA) of Nonorganometallic Nucleophiles. *Chem. Rev.* **2018,** *118* (16), 7586-7656; (e) Vargová, D.; Némethová, I.; Šebesta, R., Asymmetric copper-catalyzed conjugate additions of organometallic reagents in the syntheses of natural compounds and pharmaceuticals. *Org. Biomol. Chem.* **2020,** *18* (20), 3780-3796; (f) Ge, L.; Harutyunyan, S. R., Asymmetric Nucleophilic Addition To Ketones And Ketimines And Conjugate Addition Reactions. In *Catalytic Asymmetric Synthesis*, 2022; pp 617-659.

2. (a) Hayashi, T.; Yamasaki, K., Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev.* **2003,** *103* (8), 2829-2844; (b) Berthon-Gelloz, G.; Hayashi, T., Rhodium- and Palladium-Catalyzed Asymmetric Conjugate Additions of Organoboronic Acids. In *Boronic Acids*, 2011; pp 263-313; (c) Wu, H.-L.; Wu, P.-Y., Rhodium(I)-

Catalyzed Asymmetric Addition of Organometallic Reagents to Unsaturated Compounds. In *Rhodium Catalysis in Organic Synthesis*, Tanaka, K., Ed. 2019; pp 85-116.

3. Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G., Synthetic applications of rhodium catalysed conjugate addition. *Chem. Soc. Rev.* **2010,** *39* (6), 2093-2105.

4. Edelstein, E. K.; Rankic, D. A.; Dudley, C. C.; McMinn, S. E.; Adpressa, D. A., Synthesis of Proline Analogues via Rh-Catalyzed Asymmetric Conjugate Addition. *ACS Catal.* **2021,** *11* (2), 743-749.

5. (a) Simmons, E. M.; Mudryk, B.; Lee, A. G.; Qiu, Y.; Razler, T. M.; Hsiao, Y., Development of a Kilogram-Scale Process for the Enantioselective Synthesis of 3-Isopropenyl-cyclohexan-1-one via Rh/DTBM-SEGPHOS-Catalyzed Asymmetric Hayashi Addition Enabled by 1,3-Diol Additives. *Org. Process Res. Dev.* **2017,** *21* (10), 1659-1667; (b) Howell, G. P., Asymmetric and Diastereoselective Conjugate Addition Reactions: C–C Bond Formation at Large Scale. *Org. Process Res. Dev.* **2012,** *16* (7), 1258-1272.

6. Burns, A. R.; Lam, H. W.; Roy, I. D., Enantioselective, Rhodium-Catalyzed 1,4-Addition of Organoboron Reagents to Electron-Deficient Alkenes. In *Organic Reactions*, 2017; pp 1-415.

7. Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N., Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to Enones. *J. Am. Chem. Soc.* **1998,** *120* (22), 5579-5580.

8. Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B., Rhodium-Catalyzed Coupling Reactions of Arylboronic Acids to Olefins in Aqueous Media. *J. Am. Chem. Soc.* **2001,** *123* (22), 5358-5359.

9. (a) Roy, I. D.; Burns, A. R.; Pattison, G.; Michel, B.; Parker, A. J.; Lam, H. W., A second-generation ligand for the enantioselective rhodium-catalyzed addition of arylboronic acids to alkenylazaarenes. *Chem. Commun.* **2014,** *50* (22), 2865-2868; (b) Pattison, G.; Piraux, G.; Lam, H. W., Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Alkenylheteroarenes. *J. Am. Chem. Soc.* **2010,** *132* (41), 14373-14375.

10. Saxena, A.; Lam, H. W., Enantioselective rhodium-catalyzed arylation of electron-deficient alkenylarenes. *Chem. Sci.* **2011,** *2* (12), 2326-2331.

11. For examples of enantioselective hydroarylations of arylalkenes using aryl electrophiles and hydride donors which general give reversed regioselectivity (α-arylation) see: (a) He, Y.; Liu, C.; Yu, L.; Zhu, S., Enantio- and Regioselective NiH-Catalyzed Reductive Hydroarylation of Vinylarenes with Aryl Iodides. *Angew. Chem. Int. Ed.* **2020,** *59* (48), 21530-21534; (b) Liu, C.-F.; Wang, Z.-C.; Luo, X.; Lu, J.; Ko, C. H. M.; Shi, S.-L.; Koh, M. J., Synthesis of tri- and tetrasubstituted stereocentres by nickel-catalysed enantioselective olefin cross-couplings. *Nat. Catal.* **2022,** *5* (10), 934-942; (c) Chen, Y.-G.; Shuai, B.; Xu, X.-T.; Li, Y.-Q.; Yang, Q.-L.; Qiu, H.; Zhang, K.; Fang, P.; Mei, T.-S., Nickel-catalyzed Enantioselective Hydroarylation and Hydroalkenylation of Styrenes. *J. Am. Chem. Soc.* **2019,** *141* (8), 3395-3399; (d) Friis, S. D.;

Pirnot, M. T.; Buchwald, S. L., Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis. *J. Am. Chem. Soc.* **2016,** *138* (27), 8372-8375.

12. For the addition of alkyl organometallics to aza-arylalkenes see: (a) Jumde, R. P.; Lanza, F.; Pellegrini, T.; Harutyunyan, S. R., Highly enantioselective catalytic synthesis of chiral pyridines. *Nat. Commun.* **2017,** *8* (1), 2058; (b) Jumde, R. P.; Lanza, F.; Veenstra, M. J.; Harutyunyan, S. R., Catalytic asymmetric addition of Grignard reagents to alkenyl-substituted aromatic N-heterocycles. *Science* **2016,** *352* (6284), 433-437.

13. Csákÿ, A. G.; Herrán, G. d. l.; Murcia, M. C., Conjugate addition reactions of carbon nucleophiles to electron-deficient dienes. *Chem. Soc. Rev.* **2010,** *39* (11), 4080-4102.

14. (a) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L., Catalytic Enantioselective 1,6-Conjugate Addition of Grignard Reagents to Linear Dienoates. *Angew. Chem. Int. Ed.* **2008,** *47* (2), 398-401; (b) Tissot, M.; Alexakis, A., Enantio- and Regioselective Conjugate Addition of Organometallic Reagents to Linear Polyconjugated Nitroolefins. *Chem. Eur. J.* **2013,** *19* (34), 11352-11363; (c) Magrez-Chiquet, M.; Morin, M. S. T.; Wencel-Delord, J.; Drissi Amraoui, S.; Baslé, O.; Alexakis, A.; Crévisy, C.; Mauduit, M., Enantioselective 1,6-Conjugate Addition of Dialkylzinc Reagents to Acyclic Dienones Catalyzed by Cu-DiPPAM Complex—Extension to Asymmetric Sequential 1,6/1,4-Conjugate Addition. *Chem. Eur. J.* **2013,** *19* (41), 13663-13667; (d) Guo, Y.; Kootstra, J.; Harutyunyan, S. R., Catalytic Regio- and Enantioselective Alkylation of Conjugated Dienyl Amides. *Angew. Chem. Int. Ed.* **2018,** *57* (41), 13547-13550.

15. (a) Huang, Y.; Torker, S.; Li, X.; del Pozo, J.; Hoveyda, A. H., Racemic Vinylallenes in Catalytic Enantioselective Multicomponent Processes: Rapid Generation of Complexity through 1,6-Conjugate Additions. *Angew. Chem. Int. Ed.* **2019,** *58* (9), 2685-2691; (b) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H., Catalytic enantioselective 1,6-conjugate additions of propargyl and allyl groups. *Nature* **2016,** *537* (7620), 387-393; (c) Shi, C.-Y.; Pan, Z.-Z.; Tian, P.; Yin, L., Copper(I)-catalyzed asymmetric 1,6-conjugate allylation. *Nat. Commun.* **2020,** *11* (1), 5480.

16. Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T., Cobalt-Catalyzed Asymmetric 1,6-Addition of (Triisopropylsilyl)-acetylene to α,β,γ,δ-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2012,** *134* (46), 18936-18939.

17. (a) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T., Iridium/Chiral Diene-Catalyzed Asymmetric 1,6-Addition of Arylboroxines to α,β,γ,δ-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2010,** *132* (23), 7872-7873; (b) Nishimura, T.; Noishiki, A.; Hayashi, T., Electronic tuning of chiral diene ligands in iridium-catalyzed asymmetric 1,6-addition of arylboroxines to δ-aryl-α,β,γ,δ-unsaturated ketones. *Chem. Commun.* **2012,** *48* (7), 973-975.

18. Moku, B.; Fang, W.-Y.; Leng, J.; Kantchev, E. A. B.; Qin, H.-L., Rh(I)–Diene-Catalyzed Addition of (Hetero)aryl Functionality to 1,3-Dienylsulfonyl Fluorides Achieving Exclusive Regioselectivity and High Enantioselectivity: Generality and Mechanism. *ACS Catal.* **2019,** *9* (11), 10477-10488.

19. Marcum, J. S.; Taylor, T. R.; Meek, S. J., Enantioselective Synthesis of Functionalized Arenes by Nickel-Catalyzed Site-Selective Hydroarylation of 1,3-Dienes with Aryl Boronates. *Angew. Chem. Int. Ed.* **2020,** *59* (33), 14070-14075.

20. Chen, K.; Zhu, H.; Liu, S.; Bai, J.; Guo, Y.; Ding, K.; Peng, Q.; Wang, X., Switch in Selectivities by Dinuclear Nickel Catalysis: 1,4-Hydroarylation of 1,3-Dienes to Z-Olefins. *J. Am. Chem. Soc.* **2023,** *145* (45), 24877-24888.

21. Dada, R.; Wei, Z.; Gui, R.; Lundgren, R. J., Chemoselective Synthesis of Z-Olefins through Rh-Catalyzed Formate-Mediated 1,6-Reduction. *Angew. Chem. Int. Ed.* **2018,** *57* (15), 3981-3984.

22. Cooze, C.; Dada, R.; Lundgren, R. J., Direct Formic Acid Mediated Z-Selective Reductive Coupling of Dienes and Aldehydes. *Angew. Chem. Int. Ed.* **2019,** *58* (35), 12246-12251.

23. Cooze, C. J. C.; McNutt, W.; Schoetz, M. D.; Sosunovych, B.; Grigoryan, S.; Lundgren, R. J., Diastereo-, Enantio-, and Z-Selective α,δ-Difunctionalization of Electron-Deficient Dienes Initiated by Rh-Catalyzed Conjugate Addition. *J. Am. Chem. Soc.* **2021,** *143* (28), 10770-10777.

24. (a) Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T., The concise synthesis of chiral tfb ligands and their application to the rhodium-catalyzed asymmetric arylation of aldehydes. *Chem. Commun.* **2009,** (38), 5713-5715; (b) Huang, Y.; Hayashi, T., Chiral Diene Ligands in Asymmetric Catalysis. *Chem. Rev.* **2022,** *122* (18), 14346-14404.

25. (a) Burés, J., Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem. Int. Ed.* **2016,** *55* (52), 16084-16087; (b) Nielsen, C. D. T.; Burés, J., Visual kinetic analysis. *Chem. Sci.* **2019,** *10* (2), 348-353.

26. Groves, A.; Martínez, J. I.; Smith, J. J.; Lam, H. W., Remote Nucleophilic Allylation by Allylrhodium Chain Walking. *Chem. Eur. J.* **2018,** *24* (51), 13432-13436.

27. Kina, A.; Iwamura, H.; Hayashi, T., A Kinetic Study on Rh/Binap-Catalyzed 1,4-Addition of Phenylboronic Acid to Enones: Negative Nonlinear Effect Caused by Predominant Homochiral Dimer Contribution. *J. Am. Chem. Soc.* **2006,** *128* (12), 3904-3905.

28. Yasui, H.; Yorimitsu, H.; Oshima, K., Isomerization of Alkynes to 1,3-Dienes under Rhodium or Palladium Catalysis. *Synlett* **2006,** *2006* (11), 1783-1785.

29. Fang, W. K.; Corpuz, E. G.; Chow, K. Aryl derivatives as sphingosine-1 phosphate receptors modulators, WO2015023837A1. 2015.

30. Zhang, P.; Yang, X.; Zhang, F.; Gabelli, S. B.; Wang, R.; Zhang, Y.; Bhat, S.; Chen, X.; Furlani, M.; Amzel, L. M.; Liu, J. O.; Ma, D., Pyridinylpyrimidines selectively inhibit human methionine aminopeptidase-1. *Bioorg. Med. Chem.* **2013,** *21* (9), 2600-2617.