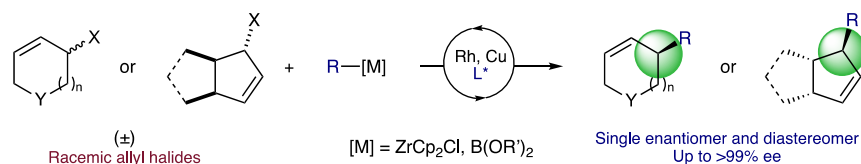


Additions to Racemates: A Strategy for Developing Asymmetric Cross-Coupling Reactions

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Abstract In this account the authors describe their progress in developing catalytic asymmetric $C(sp^3)-C(sp^3)$ and $C(sp^3)-C(sp^2)$ cross-coupling reactions. While most catalytic enantioselective transformations rely on prochiral or *meso* starting materials, strategies that apply racemic starting materials are rare. Key features of these reactions are efficient mechanisms for de-racemization. Here, the authors present copper catalyzed alkylation and rhodium catalyzed Suzuki-Miyaura type arylation reactions, their underlying mechanisms and applications to complex molecule synthesis.

Key words alkylzirconium, asymmetric, boronic acids, copper, cross-coupling, de-racemization, DyKAT, racemate, rhodium, Suzuki-Miyaura.

$C(sp^2)-C(sp^2)$ cross-coupling reactions are well established. Their ubiquity may even bias the structures of drug molecules towards arene-rich, unsaturated scaffolds (Fig. 1a).¹ However, low saturation and the absence of stereogenic centers reduces the chances of success in drug discovery programmes.¹ $C(sp^3)-C(sp^2)$ and $C(sp^3)-C(sp^3)$ couplings (Fig. 1b) are less developed despite providing products with preferable physical properties.^{1,2}

Asymmetric reactions on racemic substrates are useful transformations as there is a theoretically higher number of racemic than prochiral or *meso*-compounds.³ While many kinetic resolution protocols are well established, they suffer from the intrinsic drawback of yields being limited to <50%.⁴ De-racemization processes that convert racemic mixtures quantitatively into enantioenriched products are attractive, waste minimizing alternatives.³

The key challenge associated with developing asymmetric addition reactions to racemic starting materials arises from the addition to two different chiral species (compared to a single species for a prochiral substrate) and the different possible mechanistic pathways for each enantiomer. Additional selectivity problems arise when the starting material bears additional substitution and/or preexisting stereogenic centers so that regioisomeric and/or diastereomeric products can be formed.

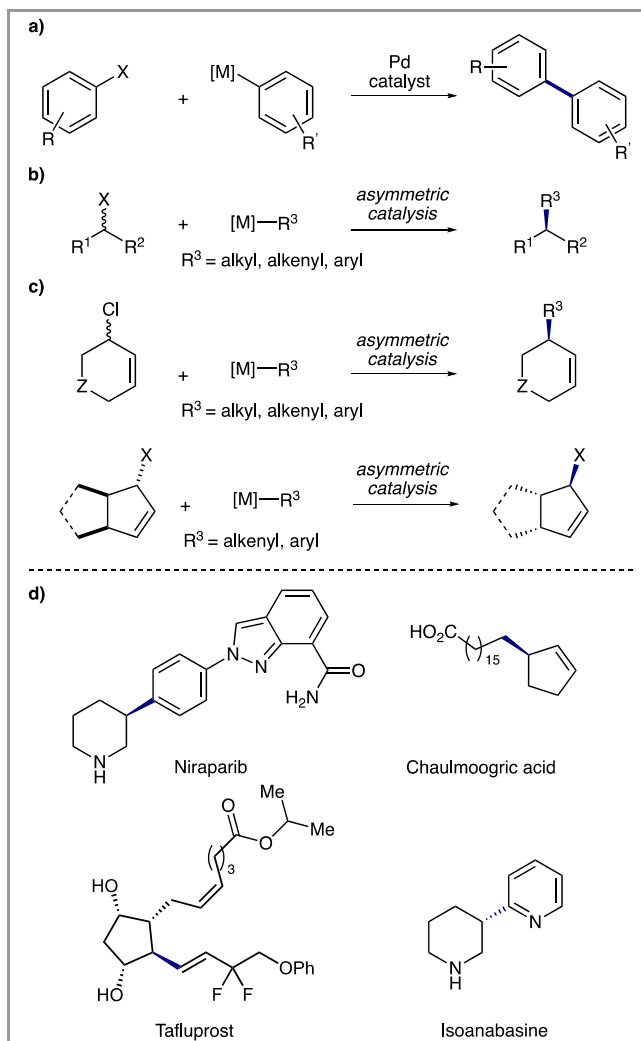


Figure 1 a) Classical $C(sp^2)-C(sp^2)$ cross-coupling reaction. b) There are much fewer reports of cross-coupling protocols using racemic $C(sp^3)$ -hybridized electrophiles. c) *Our work*: Asymmetric cross-coupling between racemic allyl halides and organometallic species. d) Selected examples of bioactive compounds that we prepared *via* asymmetric cross-coupling reactions.

Dynamic kinetic resolutions (DKR) and dynamic kinetic transformations (DyKAT) are two useful strategies that allow for the conversion of a racemate into a highly enantioenriched product – theoretically in up to quantitative yield.^{3,5} In a DKR, both enantiomers of the starting racemize rapidly under the reaction conditions, while just one of the enantiomers is converted into the product. DyKATs operate in the absence of an external racemization of the starting material, and both enantiomers of the starting material are converted into one enantiomer of the product. Here, the de-racemization occurs either *via* the formation of common, *pseudo*-prochiral catalytic intermediate or *via* the fast equilibration of diastereomeric intermediates. Detailed explanations of terminology can be found in reference 3.

Since the first highly enantioselective reports in the 1990's,^{6,7} palladium catalyzed asymmetric allylic substitution reactions on racemates have emerged as one of the few general DyKAT processes.⁸ The de-racemization arises from the formation of a common *pseudo*-prochiral π -allyl complex from both enantiomers and the subsequent enantioselective nucleophilic attack.⁶ Stabilized heteroatom and carbon nucleophiles ($pK_a < 25$) follow an outer-sphere mechanism and many powerful methods have been reported.⁸

Achieving asymmetric induction in palladium catalyzed allylic substitution with non-stabilized nucleophiles ($pK_a > 25$) has been a long-standing challenge and few successful reports are known.^{9,10,11} Non-stabilized nucleophiles show a distinct mechanism which involves transmetalation of the nucleophile, followed by a reductive elimination process.¹²

Inspired by the work by Trost and others on palladium-catalyzed asymmetric allylic alkylation (AAA) with stabilized nucleophiles, many laboratories aimed to extend this strategy to copper-catalyzed alkylation. Contrary to palladium, copper lacks an efficient σ - π - σ allyl isomerization pathway making de-racemization of allylic electrophiles *via* the formation of *pseudo*-prochiral π -allyl complexes challenging.¹³

Pioneering work by Norinder and Bäckvall on copper catalyzed reactions between enantioenriched allylic esters and Grignard reagents showed that copper π -allyl complexes could be formed transiently, suggesting pathways for de-racemization.¹³ Alexakis and co-workers tried to harness copper π -allyl formation for copper-catalyzed AAA and developed an asymmetric alkylation of racemic cyclic allyl bromides.¹⁴ However, detailed mechanistic studies by the same group suggest a different mechanism in which de-racemization is achieved by a regiodivergent oxidative addition step for both enantiomers of the allyl bromide.¹⁵

Our group has long standing interest in developing new metal catalyzed asymmetric carbon-carbon bond forming reactions. Our earlier work showed that alkylzirconium reagents generated *in situ* from alkenes (Fig 2a) can be used in asymmetric conjugate addition (ACA) reactions with a range of cyclic and acyclic Michael acceptors (Figure 2b).¹⁶ Our initial efforts in extending this work to asymmetric allylic alkylation (AAA) reactions involved investigating terminal, prochiral allyl halides (Fig 2c). Those reactions turned out to be challenging to

optimize,¹⁷ and during these studies we examined what happens when we used cyclic, racemic allyl halides.

Upon turning our attention to racemic chloride **6**, we found a unique set of reaction parameters allows for a highly enantioselective AAA protocol. Using chloride as leaving group, and a common monodentate phosphoramidite **L1** ligand in combination with CuI and halogenated solvents gave surprisingly effective reactions (see Scheme 1a,b).¹⁸

A key feature of this reaction is its underlying de-racemization mechanism where the iodide counter ion is crucial. Extensive *in situ* NMR studies demonstrated that an allyl iodide intermediate is slowly and reversibly formed in low quantities (see Scheme 1d,e).^{18,19} NOESY experiments revealed that the allyl iodide racemizes rapidly on the NMR time-scale which facilitates the de-racemization process (Scheme 1c). These experiments also suggest that the catalyst mediated interconversion of allyl halides follows a *syn* S_N2' pathway. An oligomeric copper-ligand complex then selects one of the allyl chloride enantiomers for enantioselective alkylation.^{18,19} *In situ* ¹H NMR spectroscopic kinetic studies allowed the determination of rate constants for the halide interconversion and suggest that the carbon-carbon bond forming reaction step is $>10^2$ times slower. The active catalyst likely evolves over time from (**L1**)₂Cu₂I₂ to a (**L1**)₂Cu₂ClI complex *via* exchange of one halide counter ion, with the latter complex being almost 3 times faster and inducing higher levels of enantioselectivity. The matching of these racemization and addition steps ultimately allows for the highly enantioselective AAA.

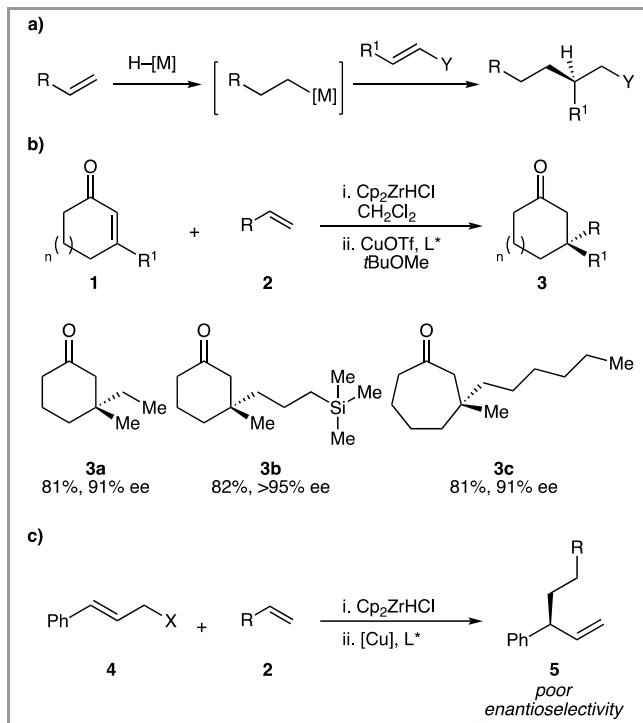
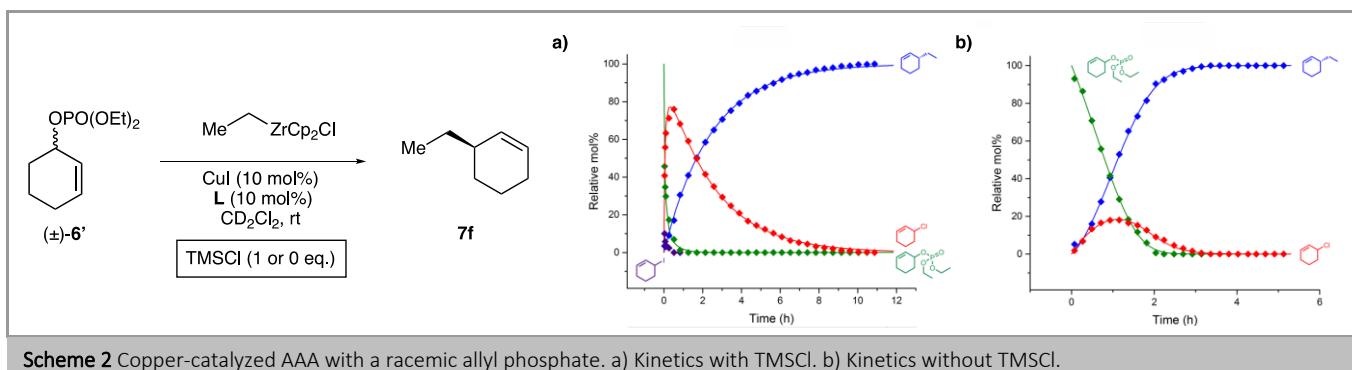
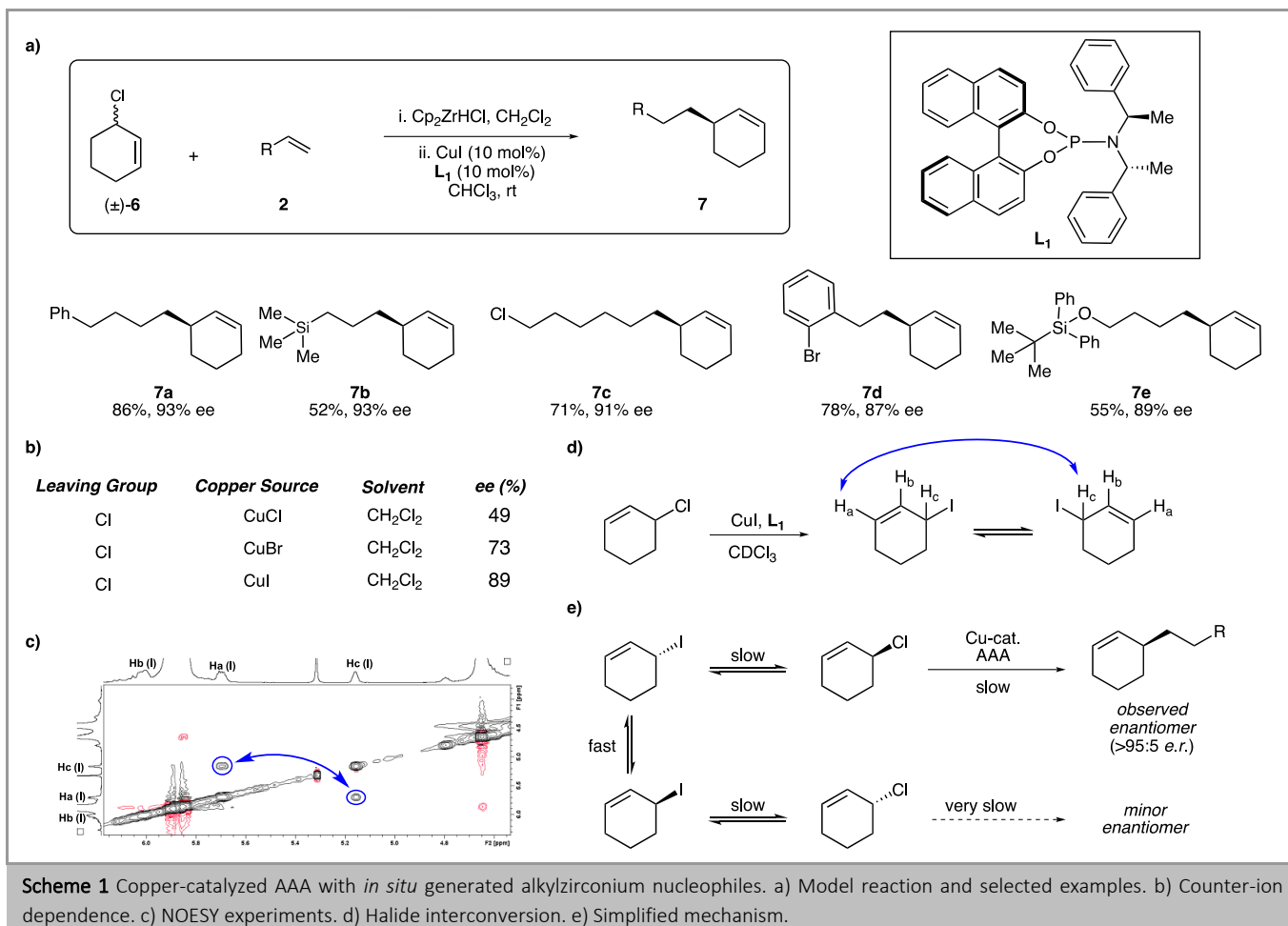


Figure 2 a) *In situ* generation of nucleophiles *via* hydrometalation of alkenes. b) Copper-catalyzed asymmetric 1,4-addition with alkylzirconium nucleophiles. c) Attempted AAA with prochiral starting materials.

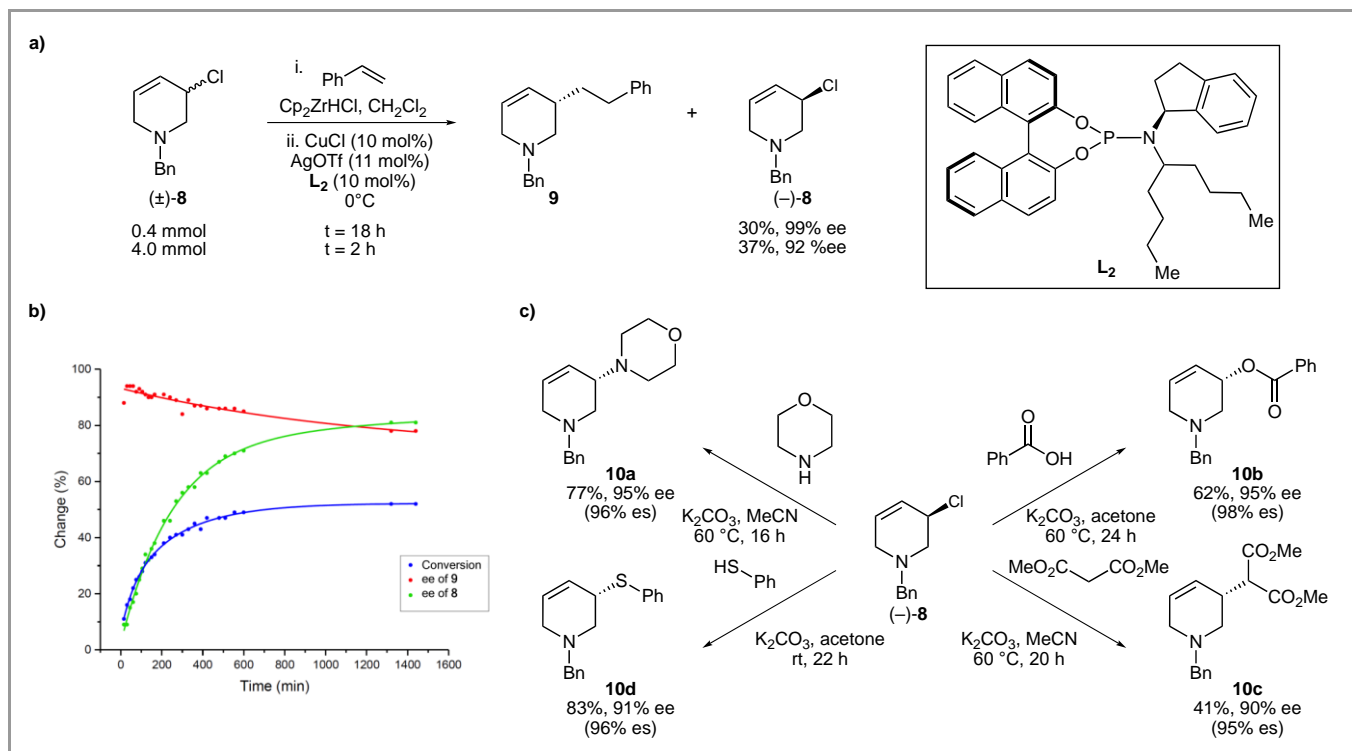


The reaction conditions are very robust with regard to the alkylzirconium species and many functional groups including alkyl- and arylhalides and silyl protected alcohols are tolerated (Scheme 1a).¹⁸ It is noteworthy that the reaction proceeds under mild conditions and can be easily performed on gram-scale enabling efficient asymmetric syntheses of the cyclopentene containing natural products Chaulmoogric acid (Fig. 1d), Hydnocarpic acid and Anthelminthincin C.¹⁸

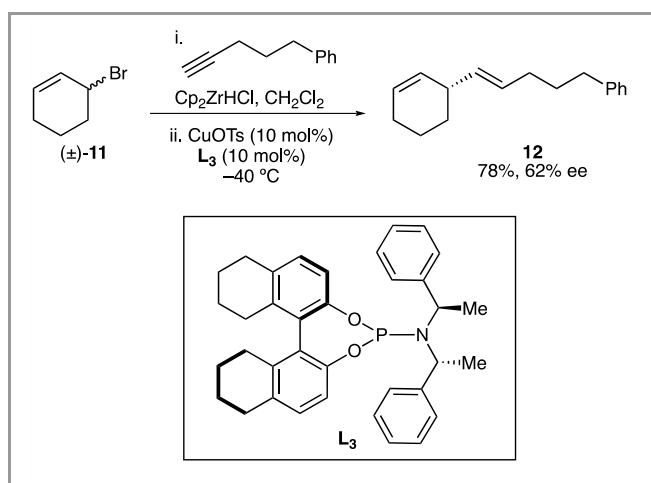
Unfortunately, the scope of the transformation is somewhat limited for the allyl chloride coupling partner. While good yields and enantioselectivities were obtained with 5-membered and 7-membered allyl chlorides and those with symmetric substitution about the allyl moiety,^{18,19} other substitution

pattern on the allyl chloride and 3-chloro-3,6-dihydro-2H-pyran have thus far proven difficult to optimize.^{19,20}

Allyl chlorides are reactive electrophiles that are sometimes difficult to handle and prone to decomposition. Therefore, we became interested in developing an alternative AAA protocol for more chemically stable electrophiles. After investigating different leaving groups and optimization of the system, we found that allyl phosphates in combination with trimethylsilyl chloride (TMSCl) gave moderate to good results.¹⁹ Much to our surprise, following the kinetics of this process revealed that the reaction actually proceeds *via* an allyl halide intermediate (see Scheme 2).



Scheme 3 Copper-catalyzed kinetic resolution of tetrahydropyridines. a) Model reaction. b) Conversion and enantioenrichment of starting material and product over time. c) Enantiospecific addition reactions.



Scheme 4 Copper-catalyzed de-racemization process with *in situ* generated alkenylzirconium nucleophiles.

While *in situ* formation of the allyl chloride *via* the action of trimethylsilyl chloride is straightforward, we observed that the reaction proceeded *via* the allyl chloride even in its absence. Either the solvent, Cp_2ZrHCl or a derived zirconium species must have been the initial Cl-source, and it seems likely that some other reactions with allylic electrophiles may also proceed *via* hidden allyl halide intermediates.

On investigating racemic 3-chloro-1,2,3,6-tetrahydropyridine (\pm)-**8** as a substrate for copper-catalyzed AAA, we were surprised to observe a kinetic resolution giving highly enantioenriched and configurationally stable ($-$)-**8** in addition to the coupling product **9** (Scheme 3a,b).²¹ Optimal results were obtained with *in situ* generated $\text{CuOTf}\cdot\text{L}_2$ and styrene as *pre-*

nucleophile. Allyl chloride ($-$)-**8** can undergo enantiospecific catalyst-free substitution reactions with N, O, C and S-based nucleophiles (>94% es) (Scheme 3c) and serve as a building block for the synthesis of 3-substituted enantioenriched piperidines – a common motif in several approved medical drugs.

Based on our mechanistic work above, we believed that we found a general de-racemization strategy – rapid catalyst mediated racemization of the starting material and subsequent enantioselective addition to one enantiomer. And so, we aimed to extend this approach toward $\text{C}(\text{sp}^2)$ nucleophiles generated *in situ* from alkynes. This, however, turned out to be more challenging than expected and despite extensive optimization studies we were only able to obtain practically useless (~60% ee) enantioselectivities on simple model systems (Scheme 4) – most likely due to the reaction proceeding by a different mechanism.²²

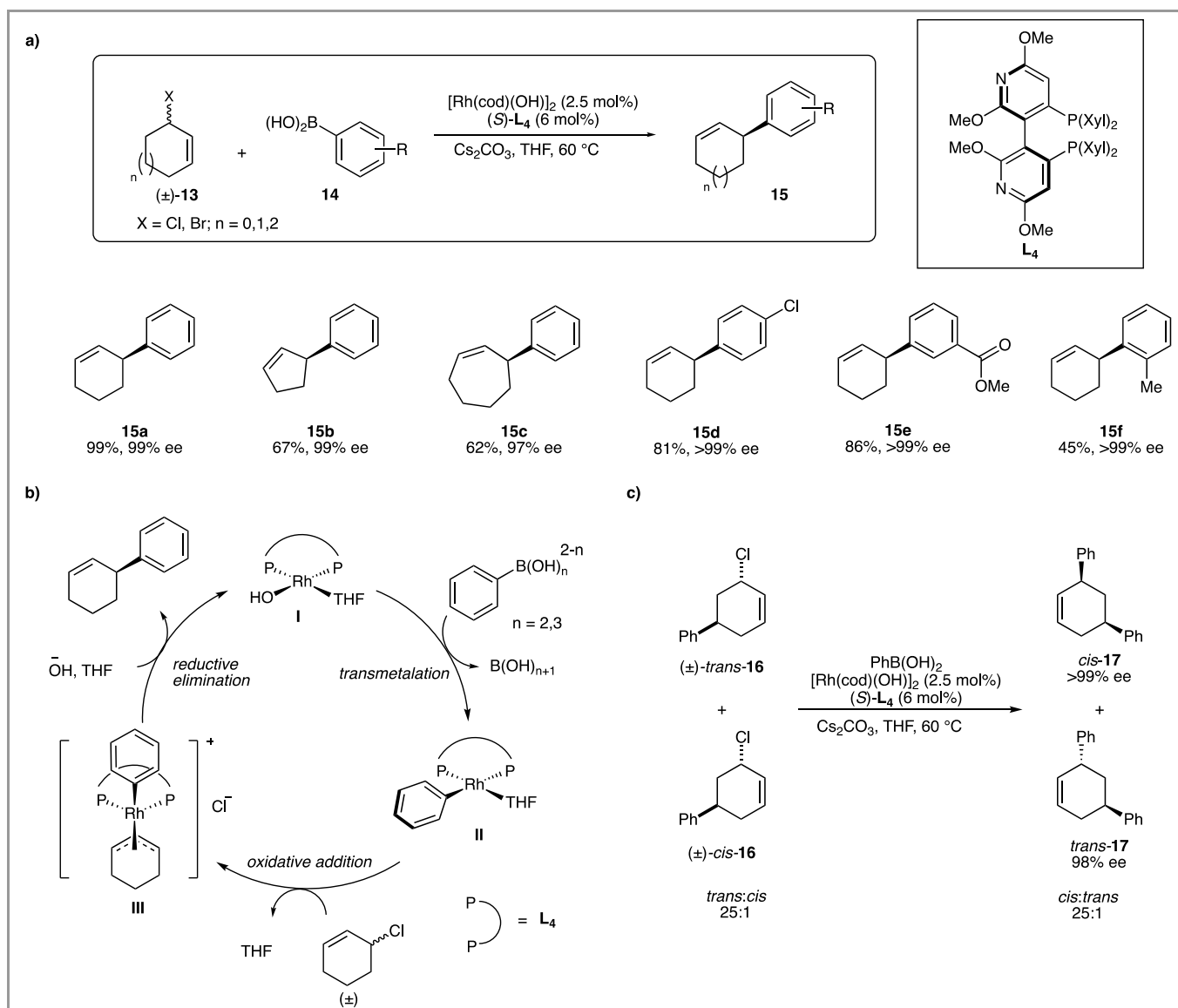
Grounded by these results, we reflected on our initial goals to develop broadly applicable $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ coupling reactions. We reasoned that a $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2)$ variant of the Suzuki-Miyaura coupling between racemic cyclic allyl halides and arylboronic acids might be a useful transformation. This would enable the synthesis of 3-dimensional and $\text{C}(\text{sp}^3)$ -rich scaffolds and use of organoboron coupling partners is attractive due to their commercial availability, functional group compatibility and experimental convenience.^{23,24,25}

Initially we aimed to harness the de-racemization mechanism we observed for copper above. Inspired by pioneering work by Hayashi and Miyaura on rhodium catalyzed asymmetric 1,4-additions with arylboronic acids,²⁶ we began exploring arylation conditions that were successful in 1,4-addition reactions. These conditions did not give us much success for quite a long time, but when we used similar conditions to those reported by Lautens and co-workers for the desymmetrization of achiral *meso*-cyclic allylic dicarbonates,²⁷ we achieved very good results.

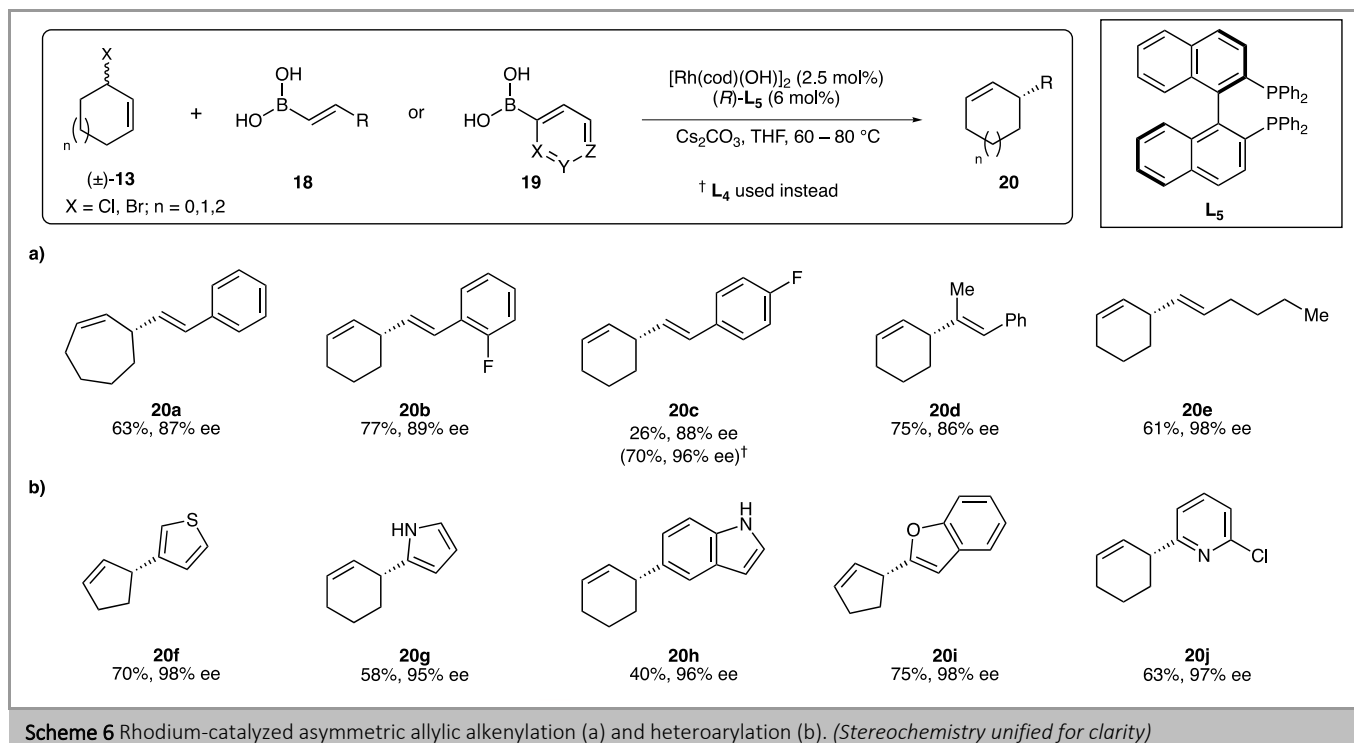
A suitable reaction system involves an *in situ* generated catalyst from [Rh(cod)(OH)]₂ and bidentate phosphine (*S*)-P-Xyl-Phos (**L**₄) and Cs₂CO₃ as base (Scheme 5a).²⁸ This protocol gives consistently excellent levels of enantioselectivity (generally 94–>99% ee), is applicable to different ring sizes, and tolerates a broad range of functionality in the boronic acid coupling partner. In most cases good results are obtained with racemic allyl chloride coupling partners. However, in some cases like for

ortho-substituted **15f**, better yields can be achieved using the allyl bromide.

We aimed to get in-depth understanding of rhodium-catalyzed arylation.²⁹ Ultimately, contrary to our initial expectations, it turned out to work nothing like the copper chemistry above. Using optimized conditions, the reactions are quite fast and many of the starting allyl halides are labile which made our initial attempts at mechanistic studies difficult. The first set of experiments that were really useful in understanding how these reactions work involved natural abundance ¹³C kinetic isotope effects (KIE). These were technically challenging but provided good quantitative data which could also be used to guide theoretical DFT studies and further experiments. Describing these KIE experiments is beyond the scope of this article but they are available here (reference 29). In combination with isotope labeling experiments using derivatives of configurationally stable **8**, competition experiments, and detailed kinetic investigations allowed us to propose a reasonable mechanism.



Scheme 5 Rhodium-catalyzed asymmetric allylic arylation. a) Model reaction and selected examples. b) Proposed de-racemization mechanism via a common pseudo-prochiral η^3 π -allyl complex. c) Diastereoselective cross-coupling via *anti* oxidative addition.



We suggest that fast and irreversible transmetalation of the arylboronic acid to a rhodium (I) complex (**I** to **II**) is followed by irreversible oxidative addition to both enantiomers of the allyl halide to give a common *pseudo*-prochiral η^3 π -allyl complex (**II** to **III**).^{28,29} Enantiodetermining reductive elimination and active catalyst regeneration aided by base completes the proposed catalytic cycle. Experiments with 5-phenyl substituted allyl chloride (**(±)-16**) resulted in overall enantioselective inversion of the relative stereochemistry suggesting an *anti* oxidative addition (Scheme 5c), but we know from our other studies that both *syn* and *anti*-oxidative addition are viable pathways (cf. Scheme 8).^{28,29}

We subsequently expanded this work both in direction of the allyl halide and the boronic acid coupling partner. The extension from arylboronic acids to alkenylboronic acids in asymmetric addition reactions is often not straightforward due to their different shape and electronics. Several alkenyl- and styreneboronic acids gave good results (Scheme 6a).^{28,30} In most cases BINAP was the ligand of choice. However, in some cases better yields and/or enantioselectivity were obtained with P-Xyl-Phos (**L₄**) (Scheme 6a, see **20b**, **20c**) but so far, we do not fully understand the underlying trends for this behavior.

One of the most popular features of the classical Suzuki-Miyaura coupling is its ability to couple heterocycles. Therefore, we targeted using heterocycles as both allyl halide and boronic acid coupling partners for rhodium-catalyzed allylic arylations. Polar functional groups and free basic sites present in substrates and reagents often impose a significant challenge for the development of practical asymmetric synthesis protocols.² In addition, many heteroarylboronic acids suffer from fast protodeborylation.³¹

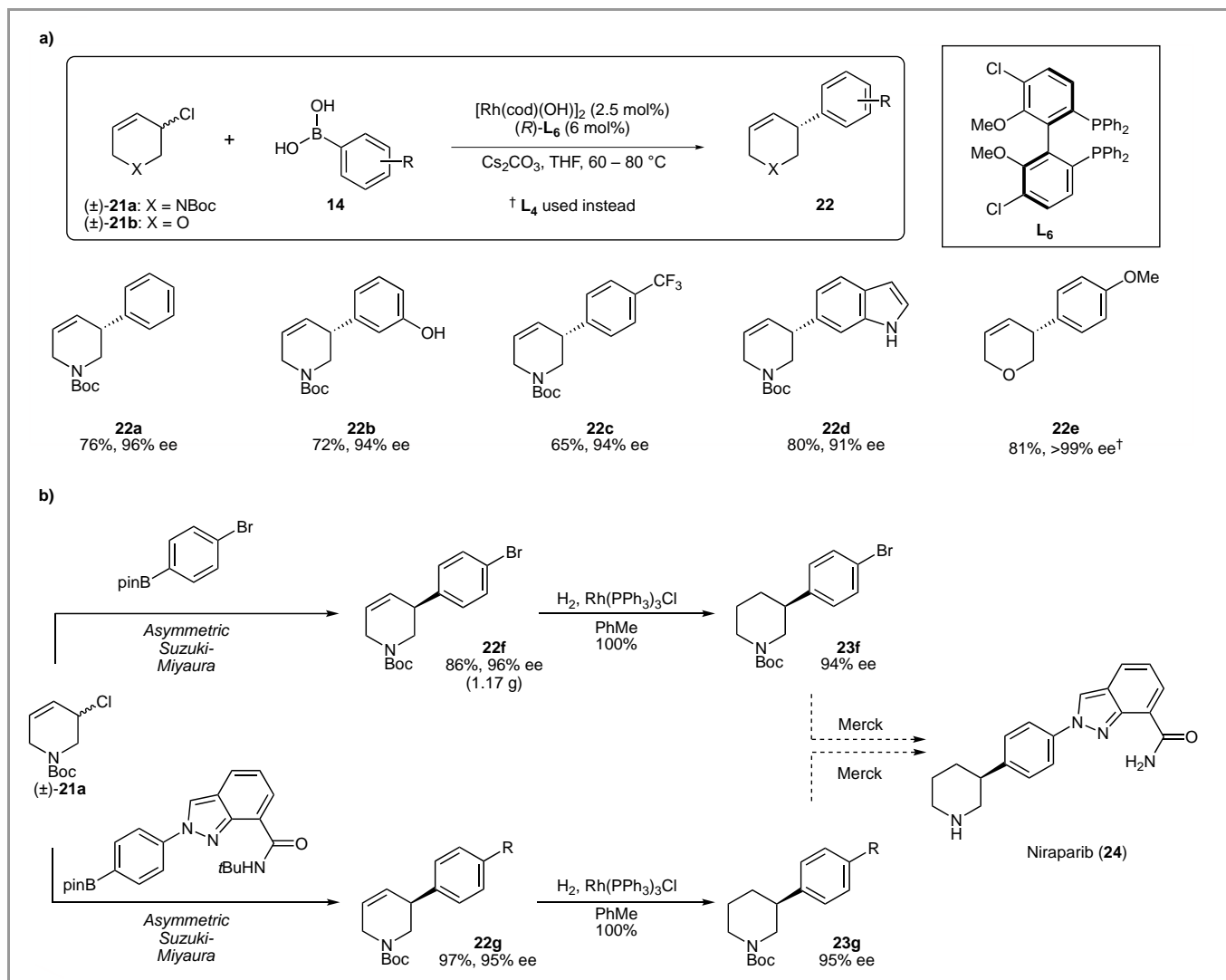
Several heteroarylboronic acids can be used with enantioselectivities of generally >90% although the yields can vary (Scheme 6b).³⁰ The protocol tolerates basic or acidic sites,

different heteroaromatic ring sizes (five-membered, six-membered, bicyclic) and different substitution pattern. Fine-tuning of the reaction parameters (temperature, ligand, addition of water, stoichiometry of catalyst and reagents) for a specific combination of coupling partners often gave improved results.

The use of pyridine organometallics – especially 2-pyridines in catalytic C(sp²)-C(sp²) cross-coupling reactions has often been problematic, and a variety of solutions to this problem have been reported.³² While free pyridine boronic acid inhibits the catalytic cycle, we found that 2-halopyridines can be used as a pyridine surrogate (Scheme 6b, **20j**) and the halide can be removed subsequently or used for additional functionalization.³⁰

Minor alterations of the reaction conditions were sufficient to achieve good results for heterocyclic dehydropiperidine based allyl chloride (**(±)-21a**) (Scheme 7a, **22a-22c**). We were pleased to find that even two heterocyclic coupling partners can be coupled (for example Scheme 6a, **22d**). Good results were also obtained for dehydropyran based allyl chloride (**(±)-21b**) (Scheme 7a, **22e**). Deuterium labeling studies suggest that allyl chloride (**(±)-21a**) undergoes *syn* oxidative addition likely due to steric reasons (cf. Scheme 5b,c).²⁸

Niraparib (**24**; Zejula®, MK-4827) – discovered by Merck Sharp and Dohme and developed by Tesaro – is a poly (ADP-ribose) polymerase inhibitor and anti-cancer drug bearing a 3-aryl-piperidine core.³³ Merck's reported process routes follow either chiral resolution or enzymatic cyclization strategies. We developed three syntheses using our asymmetric Suzuki-Miyaura technology as key enantiodetermining steps to showcase the practicality of our approach (Scheme 7b; only two depicted).^{30,34} Upon re-optimization of the cross-coupling steps, we found that pinacol esters could be used instead of boronic acids. In the case of the coupling with 4-bromophenylboronic acid, better and highly reproducible results were achieved with the pinacol ester on a gram scale.³⁴



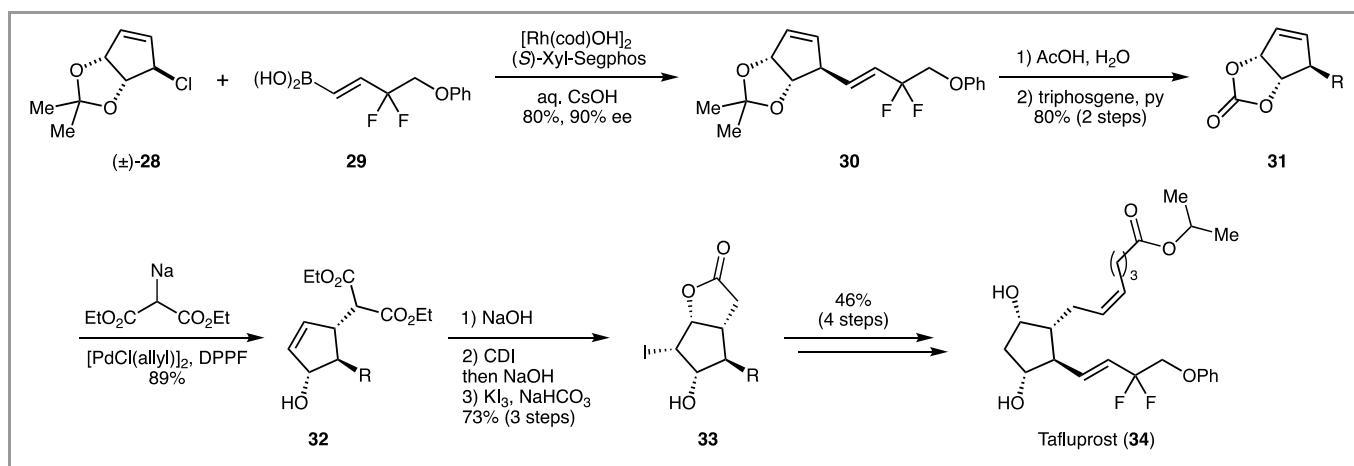
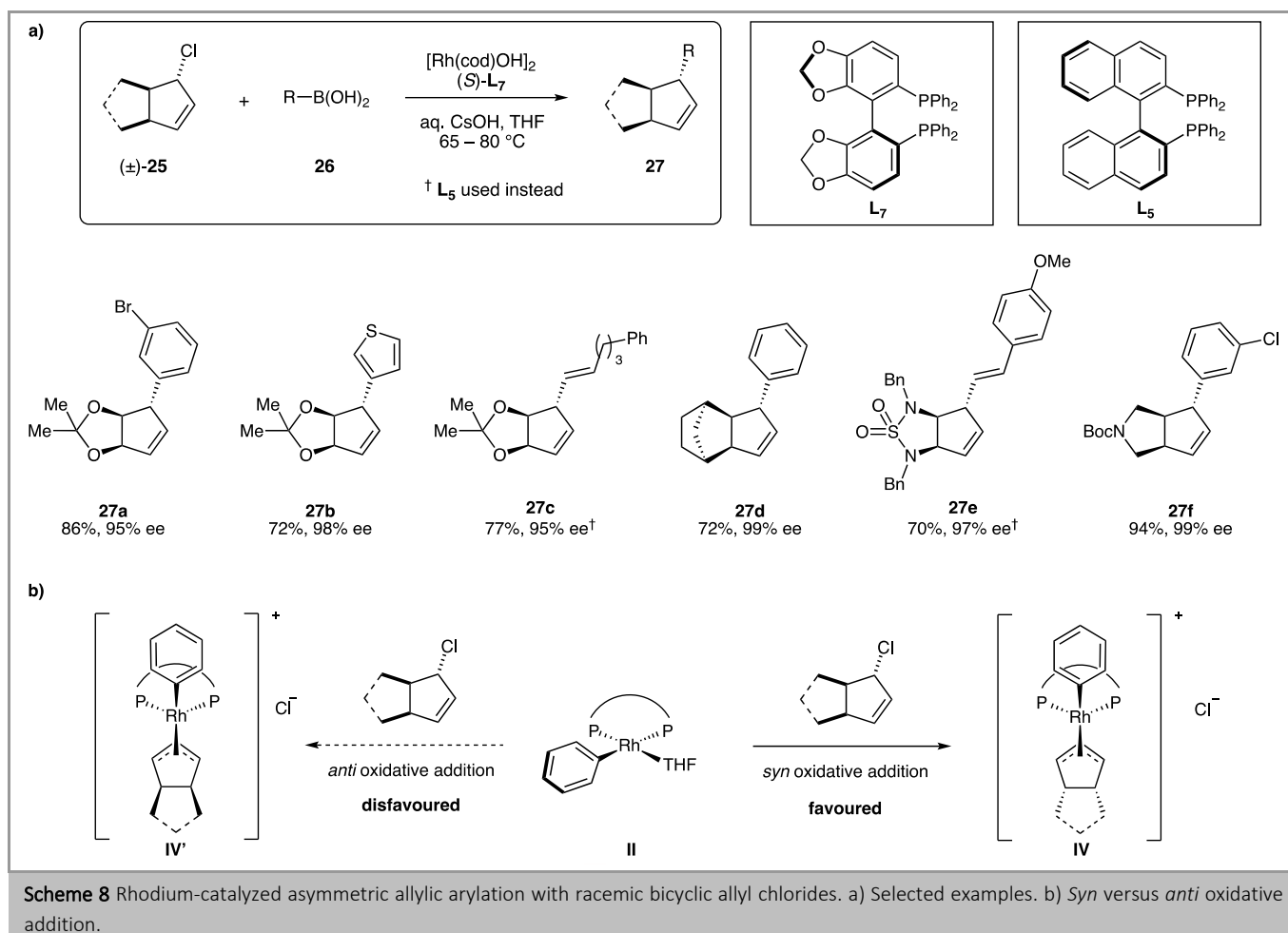
Scheme 7 Rhodium-catalyzed asymmetric allylic arylation with heterocyclic allyl chlorides. a) Selected scope. b) Asymmetric syntheses of Niraparib. (Stereochemistry unified for clarity).

Having achieved de-racemization in cross-coupling reactions with several allyl halides *via pseudo-prochiral* η^3 π -allyl complexes (cf. Scheme 5b), we became interested in the question whether we could control multiple stereogenic centers in a coupling with a racemic precursor. We chose fused bicyclic racemic allyl chlorides as model substrates and hypothesized that diastereoselective formation of a *pseudo-meso* η^3 π -allyl complex followed by enantioselective reductive elimination would set three continuous stereogenic centers in a single step (Scheme 8a,b).

Our reaction optimization revealed that good levels of enantiocontrol could be achieved using the ligand Segphos (**L**₇).³⁵ The reaction is highly diastereoselective (>20:1 dr) and proceeds with overall retention of the relative stereochemistry. We measured the enantiomeric excess of the allyl halide starting material and observed enantioenrichment of the allyl chloride over the course of the reaction. Both enantiomers undergo *syn* oxidative addition at different rates to give a common π -allyl complex. It is noteworthy that the steric congestion of the allyl halide changes the mechanism of oxidative addition from *anti* as observed for monocyclic allyl halide (±)-**13** (Scheme 5c) to *syn*

(Scheme 8b). Substrates without *pseudo*-symmetry gave a regioisomeric mixture with each regioisomer being highly enantioenriched. As before, several aryl-, heteroaryl- and alkenylboronic acids give good results (Scheme 8a, **27a–27c**), and also all-carbon and nitrogen containing bicyclic allyl chlorides are suitable precursors (Scheme 8a, **27d–27f**).

To showcase the potential of cross-coupling reactions with racemic bicycles, we developed a concise synthesis of Tafluprost (**34**) (Scheme 9) – a prostaglandin analogue used for the treatment of intraocular pressure in open-angle glaucoma and ocular hypertension.³⁶ We used an enantio- and diastereoselective Suzuki-Miyaura coupling to install the alkenyl side-chain and set the stereochemistry of the hydroxyl groups of the cyclopentane core.³⁷ Then, we converted the cyclic acetal protecting group into a carbonate as a traceless activating strategy for a palladium-catalyzed diastereo- and regioselective allylic alkylation with a malonate nucleophile. Subsequent decarboxylation and iodolactonization gave **33** which was converted to the target compound in four well precedented synthetic steps.



While we are working on broadening the scope of these cross-coupling reactions, there are some major challenges that remain. The current methods are limited to substrates that are *pseudo*-symmetric about the allyl halides functional group. If non-symmetrical substrates could be used in enantio- and regioselective reactions it would significantly broaden the synthetic opportunities of our approach. How to control the large number of potential mechanistic pathways in unsymmetrical substrates however poses a significant

challenge. Other useful advances would be methods that can use acyclic racemic allyl halides and construct more sterically congested systems. Asymmetric cross-coupling protocols are still at their infancy and extending those beyond simple benchmark substrates offers many exciting opportunities in the future.

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Biosketches

	<p>F. Wieland Goetzke obtained his B.Sc. in Chemistry from the University of Cologne (Germany) in 2015 where he worked with Prof. Dr. Albrecht Berkessel, and his M.Sc. in Chemistry from ETH Zurich (Switzerland) in 2017 conducting research with Prof. Dr. Erick M. Carreira and Prof. Dr. François Diederich. In 2017, he moved to the University of Oxford. There, his research with Steve Fletcher focuses on the development of enantio- and diastereoselective cross-coupling reactions.</p> <p>Stephen Fletcher received a BSc from Mount Allison University (Canada) where he worked with Professors Richard Langer and Stephen Westcott, and a PhD working with Derrick Clive at the University of Alberta. After postdoctoral work with Ben Feringa (Groningen) and Jonathan Clayden (Manchester) he moved to the University of Oxford where he is currently Professor of Chemistry and a Fellow at Keble College. His research interests include asymmetric catalysis, the origin of life, and dynamic stereochemistry.</p>
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