Asymmetric synthesis of nortropanes *via* Rh-catalysed allylic arylation

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Dedicated to the memory of Stephen A Westcott.

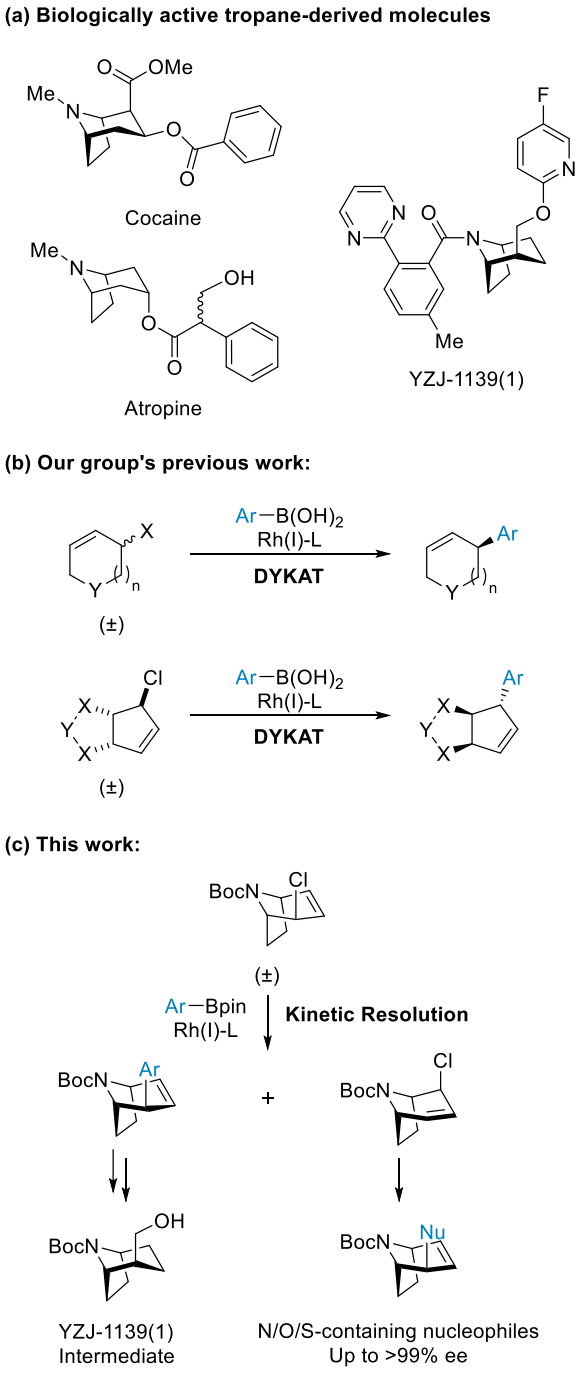
Abstract: *Tropane derivatives are extensively used in medicine, but catalytic asymmetric methods for their synthesis are underexplored. Here we report Rh-catalysed asymmetric Suzuki-Miyaura type cross-coupling reactions between a racemic N-Boc-nortropane-derived allylic chloride and (hetero-)aryl-boronic esters. The reaction proceeds via an unexpected kinetic resolution, and the resolved enantiopure allyl chloride can undergo highly enantiospecific reactions with N, O, and S-containing nucleophiles. The method was applied in a highly stereoselective formal synthesis of YZJ-1139(1), a potential insomnia treatment that recently completed Phase II clinical trials. Our report represents the first synthesis of YZJ-1139(1) and related compounds using asymmetric catalysis.*

Molecules with *N*-methyl-8-aza-bicyclo[3.2.1]octane scaffolds, generally known as the tropane alkaloids, display a wide array of biological and pharmaceutical activities.[1-3] Tropane derivatives, for example cocaine (Scheme 1a) and scopolamine, are well-known for displaying psychoactive effects, and other tropane-derivatives, including atropine (Scheme 1a), are used as anticholinergics and stimulants for treatment of neurological and psychiatric disorders such as Parkinson's disease and depression.[4-6] A 8-aza-bicyclo[3.2.1]octane (nortropane) derived molecule YZJ-1139(1) (Scheme 1a) was also reported recently as an orexin receptor antagonist which has completed Phase II clinical trials and may become a treatment for insomnia.[7]

Historically the tropane alkaloids had been extracted from plants, but their unique biological activities have inspired the development of synthetic routes to tropane derivatives. Willstätter's first synthesis of cocaine[8] and Robinson's highly efficient double-Mannich approach towards tropinone[9] are early milestones in this highly active field. Many strategies toward enantioenriched tropanes rely on the derivatisation of natural tropane alkaloids, chiral resolution, and the synthesis from the chiral pool.[10]

Given the fame of these molecules, and their importance to medicine - it is remarkable that stereoselective methods using achiral starting materials are limited.[3] Current methods largely use one of two approaches: 1) desymmetrisation of *meso* tropinone and its derivatives with stochiometric chiral lithium amide bases,[11-14] and 2) enantioselective synthesis of the tropane-scaffold where the stereo-chemical information is introduced concomitant with the formation of the bicycle.[15] Chiral auxiliary[16-20] and asymmetric catalytic approaches are known for the latter.[21-27]

Previously our group reported Suzuki-Miyaura type cross-coupling type reaction with racemic mono- and bicyclic allyl chlorides



Scheme 1 (a) Selected examples of bioactive tropane alkaloids. (b) Rh-catalysed Suzuki-Miyaura cross-coupling reactions of racemic mono- and bi-cyclic allyl chlorides. (c) This work: asymmetric synthesis of nortropanes *via* Rh-catalysed allylic arylation.

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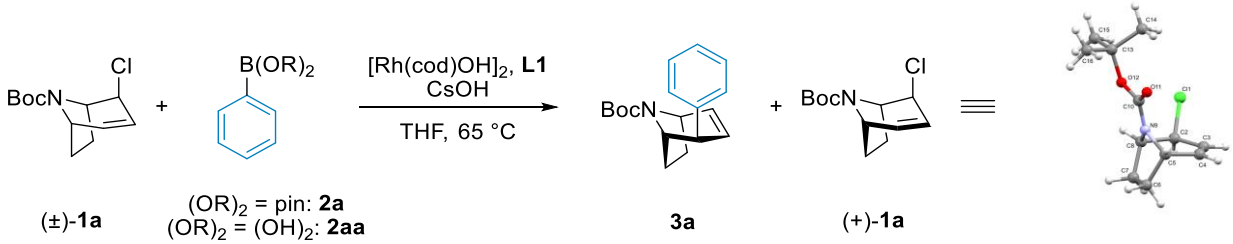
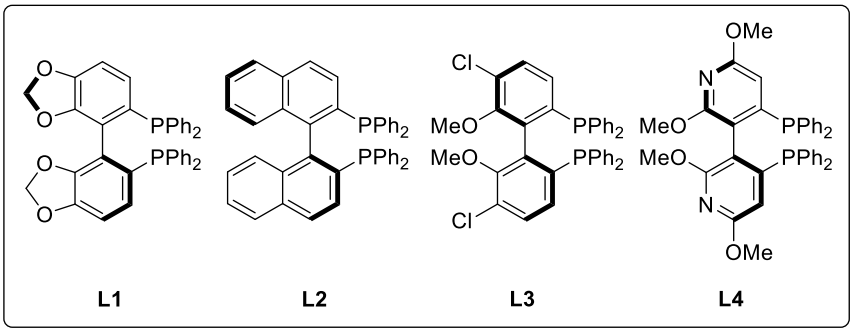
Table 1 Selected Optimisation Experiments

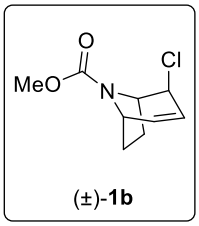


(±)-**1a** (OR)$_2$ = pin: **2a** (OR)$_2$ = (OH)$_2$: **2aa** **3a** (+)-**1a**

Entry	Ligand	Reaction conditions	Time	Yield of **3a**/%[b]	ee/%[c]	d.r.[d]
1	**L1**	**2aa** (2 equiv.) + aq. CsOH (1 equiv.), 0.1 M	o/n	28	94	>20:1
2	**L2**	**2aa** (2 equiv.) + aq. CsOH (1 equiv.), 0.1 M	o/n	23	81	>20:1
3	**L3**	**2aa** (2 equiv.) + aq. CsOH (1 equiv.), 0.1 M	o/n	35	85	>20:1
4	**L4**	**2aa** (2 equiv.) + aq. CsOH (1 equiv.), 0.1 M	o/n	11	92	>20:1
5	**L1**	**2aa** (4 equiv.) + aq. CsOH (3 equiv.), 0.2 M	o/n	52	94	>20:1
6	**L1**	**2a** (4 equiv.) + aq. CsOH (3 equiv.), 0.2 M	o/n	53 (21)[e]	93 (>99)[e]	>20:1
7	**L1**	**2a** (4 equiv.) + aq. CsOH (3 equiv.), 0.2 M	0.5 h	47 (44)[e]	96 (97)[e]	>20:1
8	**L1**	**2a** (3 equiv.) + aq. CsOH (2 equiv.), 0.2 M	0.5 h	44 (39)[e]	95 (97)[e]	>20:1
9	**L1**	**2aa** (3 equiv.) + aq. CsOH (2 equiv.), 0.2 M	0.5 h	28 (26)[e]	94 (98)[e]	>20:1
10	**L1**	**2a** (3 equiv.) + aq. CsOH (2 equiv.), 0.2 M	1 h	50 (37)[e]	95 (>99)[e]	>20:1
11	**L1**	(±)-**1b** used, **2a** (4 equiv.) + aq. CsOH (3 equiv.), 0.2 M	o/n	67	95	5.9:1

a. Rh[(cod)OH]$_2$ (2.5 mol%), ligand (6 mol%), (±)-**1a** (0.2 mmol), **2aa** or **2a**, CsOH (50 wt% aq.), THF, 65 °C. **b**. Isolated yield. **c**. Enantiomeric excess determined by Supercritical Fluid Chromatography (SFC) analysis on a chiral non-racemic stationary phase. **d**. Diastereomeric ratio determined by integration of ^{1}H NMR spectra. **e**. Numbers brackets refer to the yield and ee of recovered allyl chloride.





(Scheme 1b).[28-32] In these highly enantioselective transformations, both enantiomers of the starting material are converted into a single enantiomer of the product. The deracemization is believed to occur *via* the formation of a common *pseudo*-prochiral or meso Rh-π-allyl complex (DYKAT type II).[33-34] We wondered if we could apply a related strategy to the catalytic asymmetric synthesis of sterically congested bicyclic *N*-heterocycles, and by that develop an asymmetric cross-coupling approach to the nortropane scaffold.

A suitable nortropane-derived allyl chloride (±)-**1a**, was synthesised from *N*-Boc-nortropinone in 5 synthetic steps (See Supporting Information). Using previously reported conditions for Rh-catalysed Suzuki-Miyaura cross-couplings established by our group,[31] the reaction of allyl chloride (±)-**1a** with phenyl boronic acid **2aa** afforded **3a** in 94% enantiomeric excess as a single diastereomer (>20:1), albeit only in 28% yield (Table 1, Entry 1).

We extensively examined the influence of temperature, solvent, base, boronic acid derivatives, catalyst loading, equivalents of reagents, and the use of additives (selected examples are presented in Table 1). The protecting group on nitrogen, and the leaving group of the nortropinone-derived substrate were investigated. We found that **L1** was superior to related bidentate phosphine ligands regarding both reactivity and enantioselectivity (Table 1, Entry 1-4). An increase in yield was observed by increasing both the equivalents of the base and coupling partner (Entry 5). Similar results were obtained using phenyl boronic pinacol ester **2a** as the nucleophile (Entry 6), and along with the **3a**, we also isolated enantiopure (>99% ee) allyl chloride (+)-**1** in 21% yield.

Upon shortening the reaction time from overnight to 0.5 h, the yields of **3a** were similar, but the yield of (+)-**1a** increased to 37% (Entry 7) with a slight decrease in ee (97% ee). We attribute

the decreased yield of (+)-**1a** at longer times to the slower but competitive hydrolysis of **1a** under the reaction conditions. Using less equivalents of boronic pinacol ester and base (Entries 7 and 8) gave similar results but purification by column chromatography was easier. Here, using the pinacol ester gave superior results compared to the free boronic acid (Entries 8 and 9); at 1 h reaction time, **3a** was isolated in 50% yield (95% ee), and enantiopure (+)-**1a** was isolated in 37% yield (Entry 10).

Changing the protecting group on nitrogen from *N*-Boc to methyl carbamate resulted in a higher yield at 63% and ee of 93% (Entry 11). However, the diastereoselectivity decreased drastically from >20:1 to 5.9:1, likely due to steric reasons.

A highly selective kinetic resolution would intrinsically limit the obtained yields of these reactions to 50%, but we also speculated that catalyst deactivation or decomposition of the boronic ester could limit conversion. In order to help distinguish between these scenarios, we subjected (+)-**1** (>99% ee) instead of racemic allyl chloride to our standard reaction conditions and allowed the reaction to occur overnight (Scheme 2a). Small amounts of the desired coupling product were obtained (7%), albeit to our surprise only with 60% ee. Additionally, some enantiopure allyl chloride (+)-**1a** (50%) was recovered, while the rest of the substrate was hydrolysed to the corresponding allyl alcohol.

This result indicates that, unlike the previous DYKAT process developed by our group, where both the enantiomers form a common symmetric Rh-π-allyl-complex intermediate, when using **L1**, oxidative addition of (+)-**1a** either does not occur, or does not give the same intermediate as the enantiomer (–)-**1a** (Scheme 2c), and product formation *via* (+)-**1a** is slow.

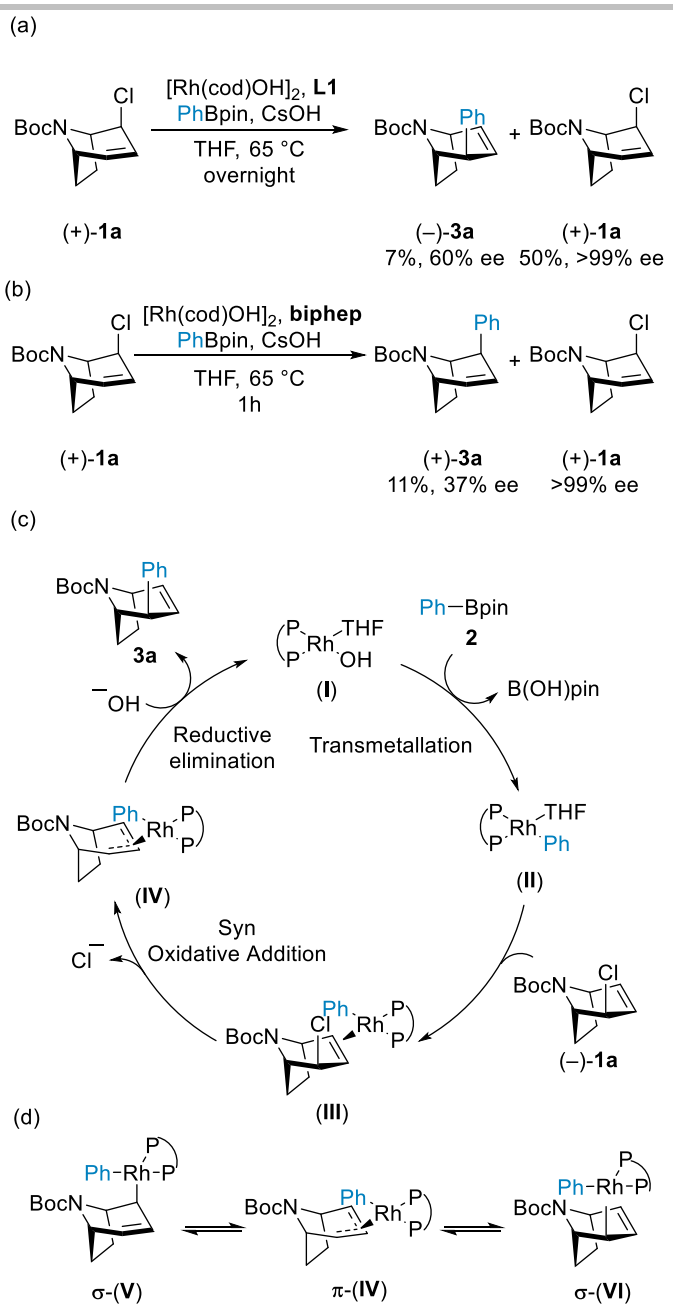
In order to test if oxidative addition (–)-**1a** would result in the formation of *meso* π-complex, which would result in complete loss in stereochemical information upon oxidative addition, we performed a cross-coupling reaction with enantiopure allyl chloride (+)-**1a** and the achiral ligand biphep (Scheme 2b). Under those conditions, we obtained (+)-**3a** in 11% yield and 37% ee. The significant loss in ee suggests that reductive elimination is at least partially enantiodetermining and is controlled by the ligand when Segphos is used. We attribute the partial, but not complete loss in stereochemical information in the experiment with biphep, to either σ-π-σ isomerisation mechanism (Scheme 2d), which occurs at a rate similar to reductive elimination, or to a lack of selectivity amongst different oxidative addition type pathways when biphep is used.

A range of arylboronic pinacol ester with electron-withdrawing and donating substituents at the *para*- and *meta*-position yielded the desired coupling products typically in 40-50% yield (Scheme 3, **3a**-**h**, **3l**-**o**) and >94% ee as single diastereomers (>20:1 d.r.). These examples included various aryl halides, alkoxy groups, ester and an aryl silane, which are useful intermediates for further reactions.

More challenging coupling partners featuring an iodide, cyano or acetyl group (**3i**-**k**) resulted in diminished yields but consistently high enantioselectivity.

We observed only trace product formation with 2-methylphenylboronic pinacol ester (**2u**), likely due to steric and/or competitive protodeborylation.[35]

Heteroarylboronic pinacol esters can be used. 2-furanyl- and 2-chloropyridyl-boronic pinacol esters performed well with yields over 40% and high enantioselectivities (**3p**, **3q**). 3-furanylboronic pinacol esters gave only 15% yield, likely due to rapid



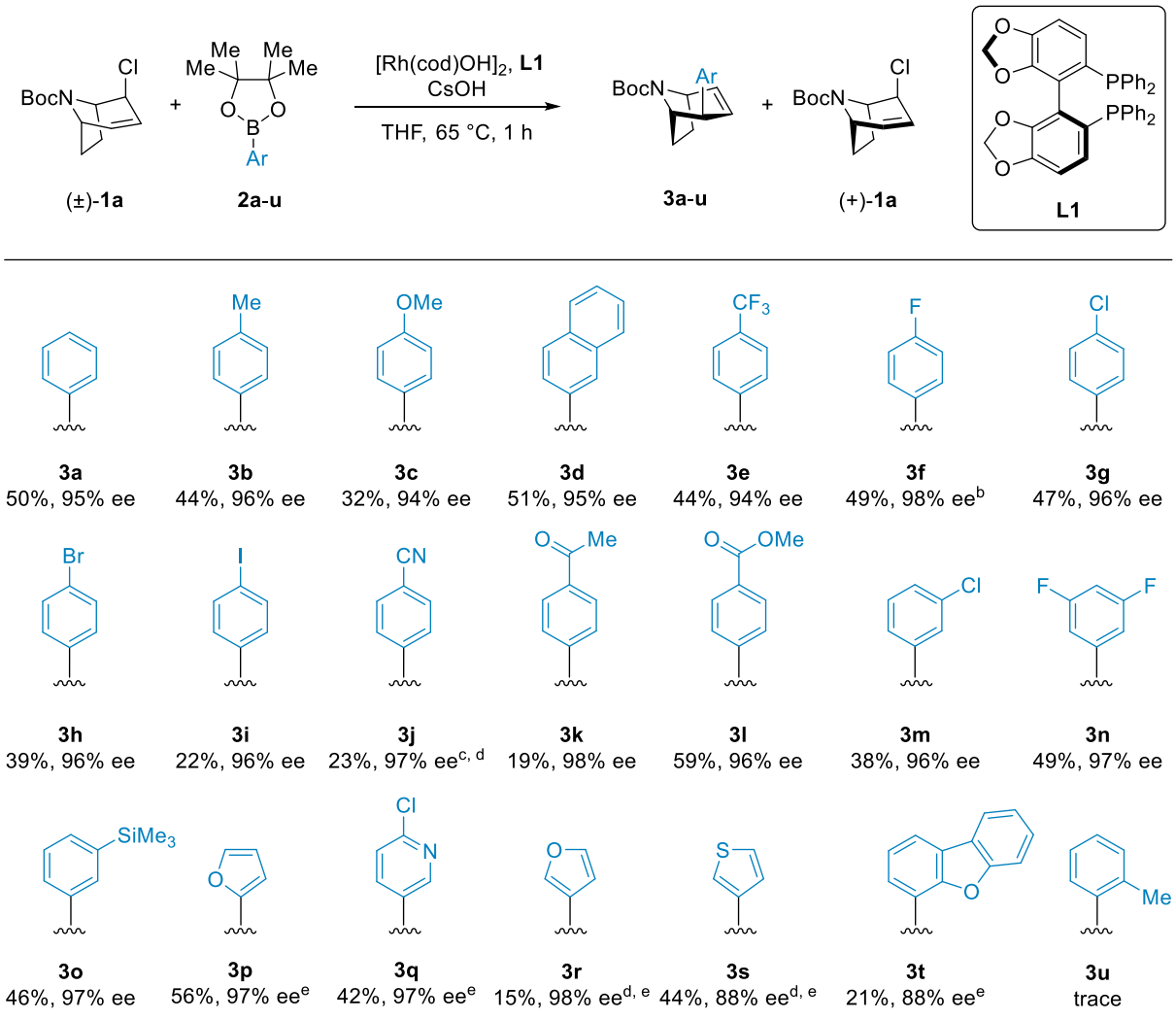
Scheme 2 (a) Rh-catalysed Suzuki-Miyaura coupling reaction with (+)-**1a** and **2a**. (b). Rh-catalysed Suzuki-Miyaura coupling reaction with (+)-**1a** and biphep as ligand. (c) Proposed mechanism. (d) Equilibration between two Rh-σ-complexes.

protodeborylation – a common problem with heterocyclic boronic acids and esters.[36]

Interestingly a few examples gave >50% yield (**3l** and **3p** gave 59 and 56% yield respectively), which we have briefly investigated but still do not fully understand, and the yield of **3p** was found to further improve upon scale up (see below).

The absolute and relative stereochemistry of product and resolved allyl chloride (Scheme 3a and 4a) were determined by single X-ray diffraction of single crystal X-ray diffraction of **3p** and (+)-**1a**.[37-38]

In order to demonstrate the synthetic utility of our method, we applied the Rh-catalysed Suzuki–Miyaura coupling with allyl chloride (±)-**1a** to a formal synthesis of the orexin receptor



Scheme 3. Scope of reaction. **a**. $Rh[(cod)OH]_2$ (2.5 mol%), **L1** (**6** mol%), (±)-**1a** (0.2 mmol, 1.0 equiv.), **2** (3.0 equiv.), CsOH (50 wt% aq.; 2.0 equiv.), THF (0.2 M), 65 °C, 1 h. All yields presented are isolated yield. Enantiomeric excess determined by Supercritical Fluid Chromatography (SFC) analysis on a chiral non-racemic stationary phase. Single diastereomer (>20:1) obtained unless stated. **b**. 4 h. **c.** Dioxane instead of THF, 80 °C overnight. **d**. **3j** :18:1 d.r., **3r**: 17:1 d.r., **3s**: 19:1 d.r.. **e**. 2 h.

antagonist YZJ-1129(1) (Scheme 4a and b),[39] which recently passed Phase II clinical trials for the treatment of sleep disorders. To the best of our knowledge, the only other previously reported syntheses of YZJ-1129(1) were recently reported by a process chemistry group and relied on preparative HPLC separation of the enantiomers or a chiral auxiliary approach.[7]

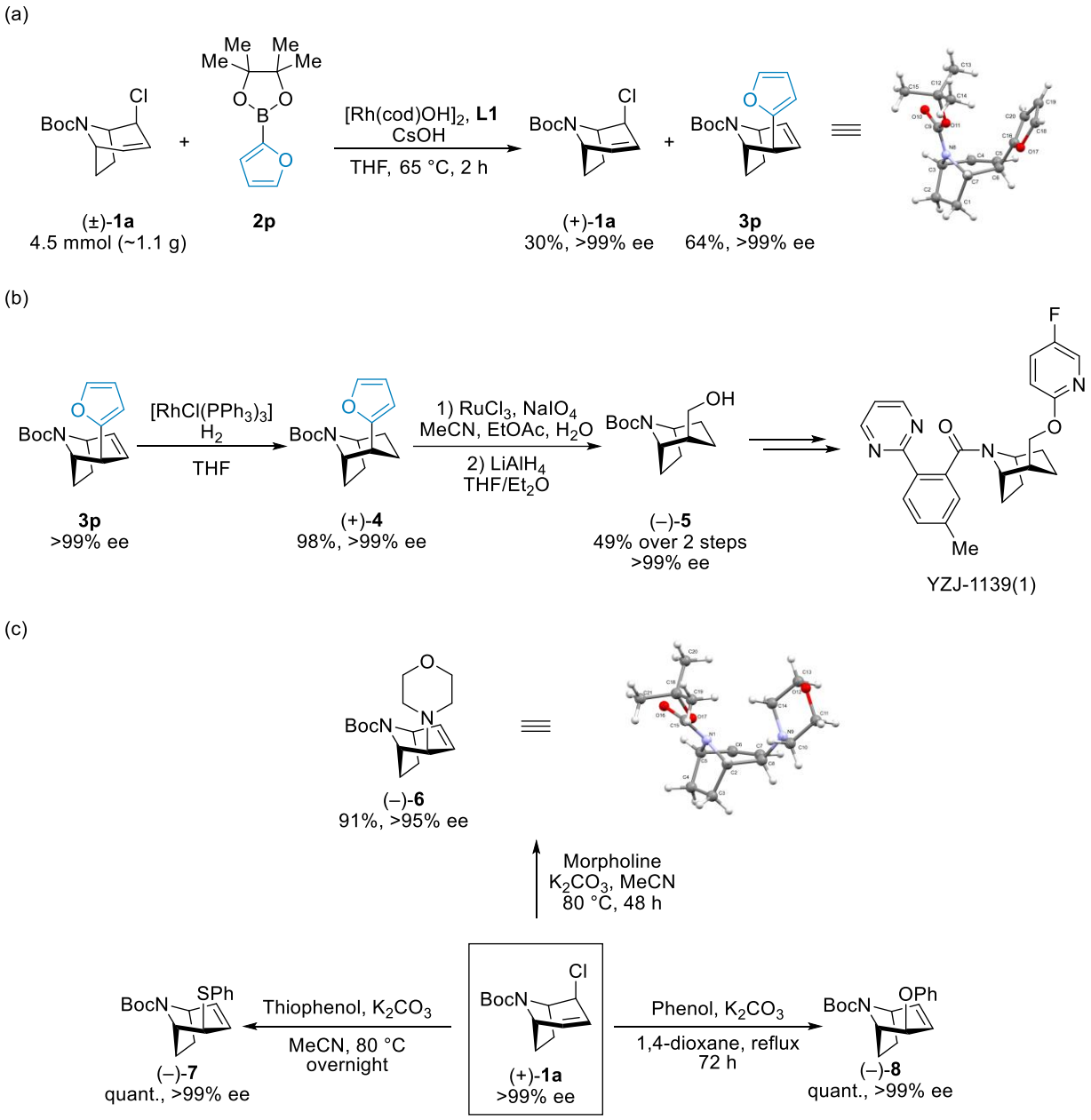
A gram scale cross-coupling reaction between (±)-**1a** and 2-furanylboronic pinacol ester afforded **3p** in 64% isolated yield and >99% ee (Scheme 4a). The enantioenriched allyl chloride (+)-**1a** was isolated in 30% yield and >99% ee.

Reduction of **3p** with Wilkinson's catalyst gave (+)-**4** in 98% yield and >99% ee. The furyl group was then converted into a hydroxymethyl group *via* a two-step oxidative cleavage / reduction protocol to give (–)-**5** in 49% yield, a previously reported intermediate in the synthesis of YZJ-1129(1).

Previously, our group reported a Cu-catalysed kinetic re solution reaction of a piperidine-derived allyl chloride, and the enantioenriched allyl chloride was used in enantiospecific substitution reactions with heteroatom-based nucleophiles,[40] and we wondered if related substitutions with (+)-**1a** were possible.

The substitution with morpholine, thiophenol and phenol gave (–)-**6**, (–)-**7** and (–)-**8** in excellent yield and enantiospecificity (Scheme 4c). Other enantiospecific substitution reactions with this substrate are likely possible. The absolute stereochemistry of (–)-**6** was determined by single crystal X-ray diffraction, [37-38] and this combined with knowledge of the absolute configuration of the starting material, indicates that the substitution reaction proceed *via* an *syn*-S_N2' pathway (Scheme 4c) The relative stereochemistry of (–)-**7** and (–)-**8** are assigned in analogy to (–)-**6**.

In summary, we developed an efficient kinetic resolution of a nortropane-derived allyl chloride *via* Rh(I)-catalysed Suzuki-Miyaura cross-couplings. The reaction tolerates a range of different aryl- and heteroaryl boronic pinacol esters with synthetically useful functional groups in high enantioselectivity and diastereoselectivity. The coupling product with 2-furanyl pinacol ester was used in a formal asymmetric synthesis of YZJ-1129(1). Further, the resolved enantiopure allyl chloride can undergo enantiospecific *syn*-Sn2' reactions with O, S, and N-



Scheme 4 (a) Reaction at 1 gram scale with 2-furanyl boronic pinacol ester **2p**. (b) Formal synthesis of YZJ-1139(1). (c) Enantiospecific transformation of enantiopure allyl chloride (+)-**1a**.

nucleophiles. Overall this work provides access to a wide range of enantiomerically enriched tropane derivatives.

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Data availability

Crystallographic data for (+)-**1a**, **3a** and (–)-**6** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2156812, 2156553, 2156805, and can be obtained *via* www.ccdc.cam.ac.uk/data_request/cif

Conflicts of interest

Oxford University Innovation has filed a patent application (PCT/GB2016/051612) with S.P.F. named as an inventor. Y.Z. F.W.G. and K.E.C. declare no competing financial interests.

Keywords: alkaloids • asymmetric catalysis • bicycles • rhodium • Suzuki-Miyaura coupling

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