

Stereodivergent Synthesis of Arylcyclopropylamines by Sequential C–H Borylation and Suzuki–Miyaura Coupling**

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Abstract: A step-economical and stereodivergent synthesis of privileged 2-arylcyclopropylamines (ACPAs) through a C–(sp^3)–H borylation and Suzuki–Miyaura coupling sequence has been developed. The iridium-catalyzed C–H borylation of *N*-cyclopropylpivalamide proceeds with *cis* selectivity. The subsequent *B*-cyclopropyl Suzuki–Miyaura coupling catalyzed by $[PdCl_2(dppf)]/Ag_2O$ proceeds with retention of configuration at the carbon center bearing the Bpin group, while epimerization at the nitrogen-bound carbon atoms of both the starting materials and products is observed under the reaction conditions. This epimerization is, however, suppressed in the presence of O_2 . The present new ACPA synthesis results in not only a significant reduction in the steps required for making ACPA derivatives, but also the ability to access either isomer (*cis* or *trans*) by simply changing the atmosphere (N_2 or O_2) in the coupling stage.

2-Arylcyclopropylamines (ACPAs) have received much attention from the organic and medicinal community because of their unique biological activity (Figure 1a).^[1,2] However, there is significant room for improvement in the synthesis of ACPAs, particularly when rapid structural diversification is desired for biological testing. Conventionally, ACPAs are synthesized in multistep sequences consisting of Wittig

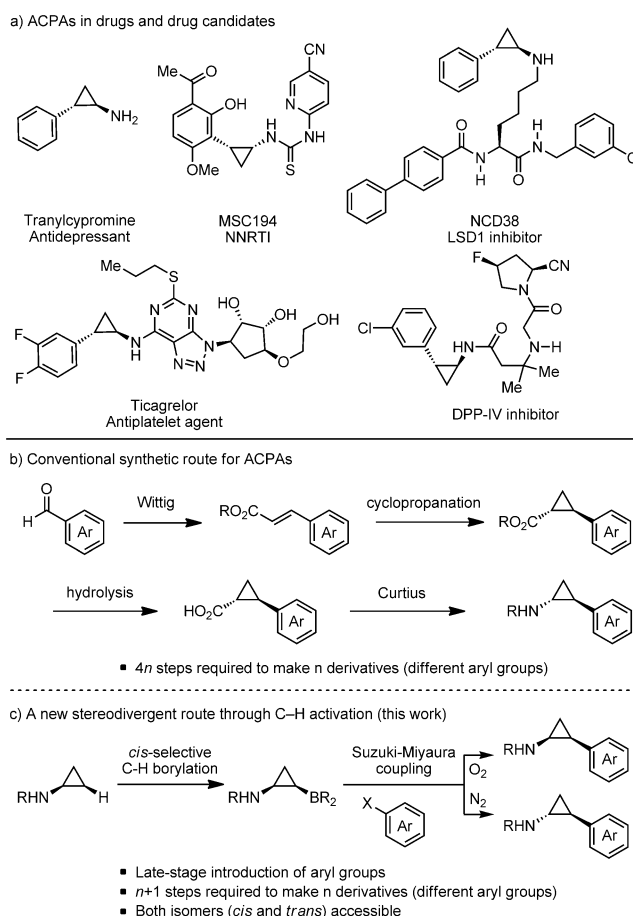


Figure 1. a) Arylcyclopropylamine (ACPA)-containing drugs and drug candidates. b) Conventional synthetic route for ACPAs. c) A new stereodivergent route for ACPAs through C–H activation.

reactions on aldehydes, cyclopropanation of the resulting alkenes, hydrolysis of esters, and subsequent Curtius rearrangement (Figure 1b).^[3,4] Following this conventional route, to make n ACPA derivatives with different aryl groups, as many as $4n$ steps are required. During our studies directed towards developing inhibitors of lysine-specific demethylase 1 (LSD1),^[2c,d] the difficulty posed by the lack of a concise synthesis became immediately evident. We envisaged that applying emerging C–H functionalization logic^[5] would provide a new step-economical, stereodivergent route for ACPAs. In planning ACPA synthesis through diversity-oriented C–H functionalization, we decided to explore the stereoselective C(sp^3)–H borylation^[6,7] of readily available cyclopropylamine (\$3.87 per gram from Sigma–Aldrich) or its

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[**] We thank Dr. Yasutomo Segawa for assistance with X-ray crystal structure analysis. This work was supported by the Funding Program for Next Generation World-Leading Researchers from JSPS (K.I.), and a Grant-in-Aid for Scientific Research on Innovative Areas “Molecular Activation Directed toward Straightforward Synthesis” (25105720 to J.Y.), KAKENHI (25708005 to J.Y.) from MEXT. ITbM is supported by the World Premier International Research Center (WPI) Initiative (Japan).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201409186>.

derivatives (Figure 1 c). Furthermore, with recent advances in stereoretentive or stereoinvertive *B*-alkyl Suzuki–Miyaura cross-coupling^[8] and the precedent of stereospecific coupling of cyclopropylboronic acids (or esters),^[9] we expected chiral aminocyclopropylboronic esters to be valuable substrates for conversion into various ACPAs through coupling chemistry. Thus herein we report a new ACPA synthesis which permits not only a significant reduction in the number of steps required for making ACPA derivatives ($n+1$ steps for n derivatives), but also the production of either isomer (*cis* or *trans*) by slightly changing the atmosphere in the coupling stage (Figure 1 c).

Our first goal was to find appropriate conditions for the stereoselective C(sp³)–H borylation of cyclopropylamines. Although cyclopropanes have been rarely investigated in C–H borylation chemistry,^[10] Hartwig recently reported a *trans*-selective C–H borylation of cyclopropanes catalyzed by $[\{\text{Ir}(\text{OMe})(\text{cod})\}_2]$ and 2,9-dimethylphenanthroline (2,9-Me₂phen).^[11] However, in early experiments, we found that simple application of this catalyst system to the reaction of unprotected cyclopropylamine and bis(pinacolato)diboron (B₂pin₂) did not lead to the C–H borylation product at all.

After extensive screening of N substituents on the cyclopropylamine unit, we determined that *N*-cyclopropylpivalamide (**1a**) was a viable substrate. For example, the treatment of **1a** (1.0 equiv) and B₂pin₂ (0.5 equiv) in the presence of $[\{\text{Ir}(\text{OMe})(\text{cod})\}_2]$ (2.5 mol %) and 2,9-Me₂phen (10 mol %) in cyclohexane at 70 °C furnished the C–H borylation product **2a** in 6 % yield with most of starting material remaining intact (Table 1, entry 1). Very interestingly, we found that the C–H borylation proceeded in a *cis*-selective manner, which is opposite to the finding of Liskey and Hartwig for cyclo-

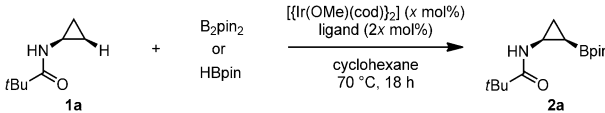
propane C–H borylation (steric-controlled, *trans*-selective).^[11] This outcome clearly indicates that the pivaloylamide group on **1** functions as a directing group during the C–H activation step.^[12] It should be noted that the group of Sawamura recently reported a heteroatom-directed *cis*-selective C–H borylation of cyclopropanes by silica-supported monophosphine iridium catalysts.^[13]

Possible modes of action for the pivaloylamide directing effect might be worth mentioning. Given that most *ortho*-directed C–H borylations require an iridium (or rhodium) center to have two accessible coordination sites and that phenanthroline ligands are unsuitable for providing them, we assume that the pivaloylamide group was interacting with a boryl ligand on iridium either by coordination of Lewis basic atom (O or N) to boron^[14] or by hydrogen bonding of the acidic proton (N–H) to the pinacolboryl oxygen atom.^[15]

Based on this auspicious result, we optimized the reaction conditions using **1a** as a substrate (Table 1). When 4,4'-di-*tert*-butylpyridine (4,4'-dibpy) was used as the ligand instead of 2,9-Me₂phen, the yield of **2a** increased slightly (entry 2). Changing the ligand to 3,4,7,8-tetramethylphenanthroline (3,4,7,8-Me₄phen)^[11,16] provided the best result, thus giving **2a** in 31 % yield (entry 3). Interestingly, when the amount of both iridium and ligand were decreased from 2.5 mol % to 0.5 mol %, the yield of **2a** increased to 43 % (entry 4). The use of HBpin instead of B₂pin₂ resulted in a similar yield of **2a** (entry 5). We also found that the amount of iridium and ligand are critically important for the reaction efficiency. Thus, with 0.5 mol % of $[\{\text{Ir}(\text{OMe})(\text{cod})\}_2]/3,4,7,8\text{-Me}_4\text{phen}$ catalyst, **1a** (7.1 mmol) reacted with HBpin (1.5 equiv) to give **2a** in 85 % yield as determined by NMR spectroscopy (62 % yield upon isolation).^[17,18] Interestingly, under these reaction conditions employing excess amounts of HBpin, a double C–H borylation product was observed only in a trace amounts.

We also conducted C–H borylation of the cyclopropylamines **1b–j** with various substituents (see the Supporting Information for details). The pivaloyl group is by far the best N substituent in this particular reaction. Although there exist other protecting groups providing C–H borylation products to some extent [e.g., *N*-cyclopropylisobutyramide (**1b**) and *N*-cyclopropyl-2,2,2-trifluoroacetamide (**1e**)], careful optimization will be needed to achieve a synthetically useful level of efficiency. We also found that the C–H borylation of the *n*-propyl-substituted cyclopropylamide **1j** proceeded in a regio- and stereoselective manner, albeit with low reaction efficiency [23 % yield upon isolation; Eq. (1)]. Judging from

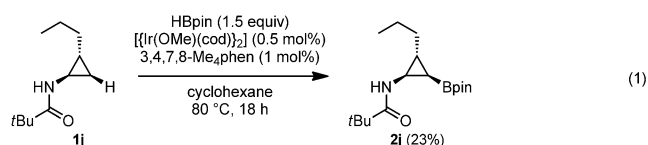
Table 1: Iridium-catalyzed *cis*-selective C–H borylation of the cyclopropylamine **1a**.^[a]

				
Entry	Boron reagent (equiv)	x (mol %)	Ligand	Yield [%] ^[b]
1	B ₂ pin ₂ (0.5)	2.5	2,9-Me ₂ phen	6
2	B ₂ pin ₂ (0.5)	2.5	4,4'-dibpy	15
3	B ₂ pin ₂ (0.5)	2.5	3,4,7,8-Me ₄ phen	31
4	B ₂ pin ₂ (0.5)	0.5	3,4,7,8-Me ₄ phen	43
5	HBpin (1.0)	0.5	3,4,7,8-Me ₄ phen	49
6	HBpin (1.5)	0.5	3,4,7,8-Me ₄ phen	61
7 ^[c]	HBpin (1.5)	0.5	3,4,7,8-Me ₄ phen	67
8 ^[d]	HBpin (1.5)	0.5	3,4,7,8-Me ₄ phen	19
9 ^[c,e]	HBpin (1.5)	0.5	3,4,7,8-Me ₄ phen	85 (62) ^[f]

[a] Reaction conditions: **1a** (1.6 mmol, 1.0 equiv), boron reagent, $[\{\text{Ir}(\text{OMe})(\text{cod})\}_2]$ (x mol %), ligand ($2x$ mol %), cyclohexane, 70 °C, 18 h.

[b] Yield of **2a** based on **1a**, as determined by NMR analysis. [c] The reaction was conducted at 80 °C. [d] THF was used as solvent. [e] **1a** (7.1 mmol) was used. [f] Yield of isolated product.

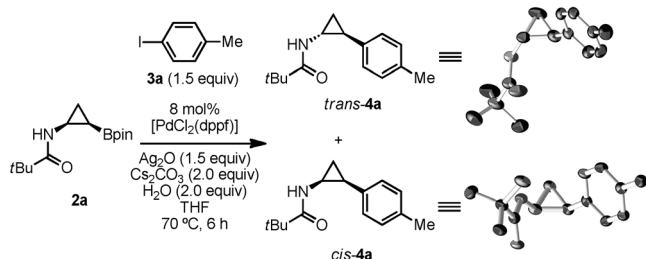
B₂pin₂ = bis(pinacolato)diboron, cod = 1,5-cyclooctadiene, HBpin = pinacolborane, 2,9-Me₂phen = 2,9-dimethylphenanthroline, 4,4'-dibpy = 4,4'-di-*tert*-butylpyridine, 3,4,7,8-Me₄phen = 3,4,7,8-tetramethylphenanthroline.



NOE experiments, the boryl group was introduced *cis* to the amide group and *trans* to the *n*-propyl group. As the present study is directed towards the development of LSD1 inhibitors having cyclopropylamine moiety with one aryl substituent on the cyclopropyl ring,^[2c,d] substituted cyclopropanes are beyond the scope of this paper.

With stereoselective C–H borylation conditions established, we next examined the *B*-alkyl Suzuki–Miyaura cross-coupling of **2a** with haloarenes to provide ACPAs.^[9] We were initially expecting that stereoretentive and/or stereoinvertive *B*-alkyl coupling conditions established by the groups of Crudden^[8a] and Sugimoto^[8b] would transform **2a** into the corresponding *cis* and *trans* isomers of ACPAs. However, the outcome was very surprising, even though the stereodivergent production of both isomers was possible (Table 2). The first

Table 2: Palladium-catalyzed Suzuki–Miyaura coupling of **2a** and **3a**.^[a]

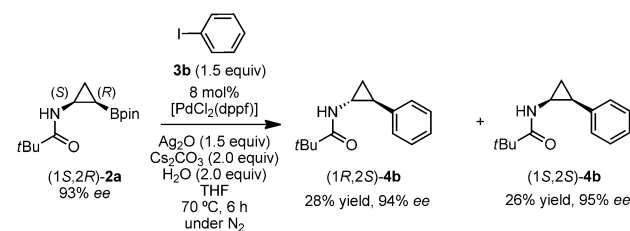


Entry	Atmosphere	Yield [%] ^[b]	<i>trans</i> - 4a / <i>cis</i> - 4a
1	N ₂	87	77:23
2	O ₂	67	16:84

[a] Reaction conditions: **2a** (1.0 equiv), **3a** (1.5 equiv), [PdCl₂(dppf)]·CH₂Cl₂ (8 mol %), Ag₂O (1.5 equiv), Cs₂CO₃ (2.0 equiv), H₂O (2.0 equiv), 70 °C, 6 h, under N₂ or O₂. [b] Combined yield of isolated *trans*-**4a** and *cis*-**4a**. In the ORTEP drawings of *trans*-**4a** and *cis*-**4a**, hydrogen atoms are omitted for clarity and the thermal ellipsoids are drawn at 50% probability.^[21] dppf = bis(diphenylphosphino)ferrocene, THF = tetrahydrofuran.

optimal reaction conditions^[19] were established by modifying the Crudden protocol.^[8a,20] Thus cross-coupling of **2a** (1.0 equiv) and 4-iodotoluene (**3a**; 1.5 equiv) was carried out in the presence of [PdCl₂(dppf)] (8 mol %), Ag₂O (1.5 equiv), Cs₂CO₃ (2.0 equiv), and H₂O (2.0 equiv) in THF at 70 °C for 6 hours under an N₂ atmosphere to afford the coupling products, *trans*-**4a** and *cis*-**4a**, in 87% combined yield (*trans*/*cis* = 77:23, entry 1). These *cis* and *trans* isomers were readily separated by silica-gel column chromatography and their structures were unambiguously confirmed by X-ray crystal structure analysis. The key features found during reaction optimization were: 1) Ag₂O is crucial for reactivity; 2) dppf is the most effective ligand; and 3) rate acceleration is observed by the addition of Cs₂CO₃ and H₂O. Surprisingly, the *trans* product (*trans*-**4a**) was preferentially formed from the *cis*-configured starting material (*cis*-**2a**) under what is expected to be stereoretentive conditions. While trying to identify the controlling factors in this coupling, we found that the preferential production of *cis*-**4a** could be achieved by simply performing the reaction under O₂ atmosphere (entry 2; 67% combined yield, *trans*/*cis* = 16:84).

To understand how these *cis* and *trans* products are formed, we investigated the Suzuki–Miyaura cross-coupling reaction using the enantioenriched **2a** (Scheme 1). Thus (1*S*,2*R*)-**2a** (93% *ee*), which was prepared according to the literature,^[9e] was coupled with iodobenzene (**3b**) under our standard reaction conditions (N₂ atmosphere), thus giving



Scheme 1. Suzuki–Miyaura coupling of enantioenriched (1*S*,2*R*)-**2a** with **3b**.

(1*R*,2*S*)-**4b** (28% yield) and (1*S*,2*S*)-**4b** (26% yield). This result clearly shows that the coupling proceeds with complete retention of configuration at the carbon center bearing the Bpin group and that epimerization occurs at the nitrogen-bound carbon atom.

This somewhat unexpected epimerization at the nitrogen-bound carbon under palladium catalysis could possibly occur before and/or after the cross-coupling reaction. Thus, to shed light on this epimerization reaction, we monitored the isomerization of the coupling products **4a** as well as the starting **2a** under coupling conditions. Firstly, the purified products, *trans*-**4a** and *cis*-**4a**, were individually treated with the standard reaction conditions (but without iodoarene) under N₂ or O₂ atmosphere as outlined in Figure 2a. Both *trans*-**4a** and *cis*-**4a** isomerized under N₂. The compound *cis*-**4a** underwent significant isomerization under N₂ after 48 hours to give a mixture of isomers favoring the *trans* isomer (*trans*/*cis* = 63:37), and *trans*-**4a** also isomerized, but to a lesser extent as both isomers appeared to trend towards an equilibrium point slightly enriched in *trans* (Figure 2a). In contrast, exposing either the *cis* or the *trans* to the reaction conditions in the presence of O₂ resulted in virtually no

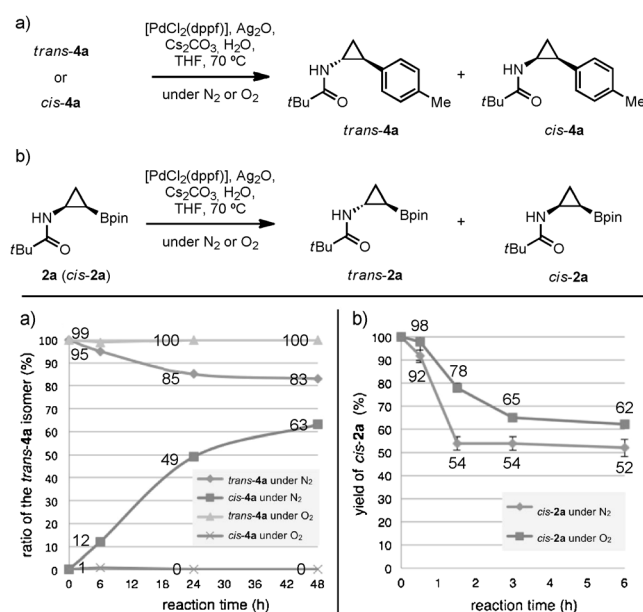


Figure 2. a) Isomerization experiments of *trans*-**4a** and *cis*-**4a**. b) Isomerization experiments of *cis*-**2a**.

isomerization. These results strongly suggest that O₂ helps prevent the isomerization of both isomers.

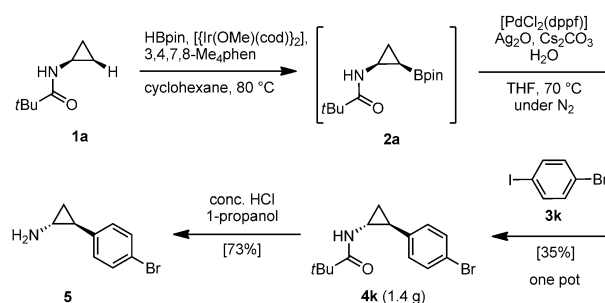
Next, *cis*-**2a** was subjected to the standard reaction conditions without iodoarene to examine the isomerization reaction (Figure 2b). The isomerization of *cis*-**2a** also occurred to give a mixture of *cis*-**2a** and *trans*-**2a**, and it was found that the isomerization was faster under N₂ (*cis/trans* = 54:46 after 1.5 h) than that under O₂ (*cis/trans* = 78:22 after 1.5 h). These results clearly show that isomerization at the C–N bond occurred from **2a** as well.

We found that when the coupling reaction of *cis*-**2a** and **3a** was performed with 10 mol % of BHT (dibutylhydroxytoluene) under N₂, the isomerization was suppressed (*cis*-**4a** 55 %, *trans*-**4a** 6 %). We initially assumed that this BHT effect is a testimony to the occurrence of radical-based isomerization under the standard reaction conditions. However, other radical scavengers such as DHA (dihydroanthracene) and TEMPO (10 mol % employed) had almost no effect in suppressing the *cis*–*trans* isomerization. Although the precise mechanism of epimerization at the nitrogen-bound carbon atom and the inhibiting action of O₂ and BHT remain unclear, the atmosphere-controlled stereodivergent production of ACPAs is of great importance from synthetic point of view.

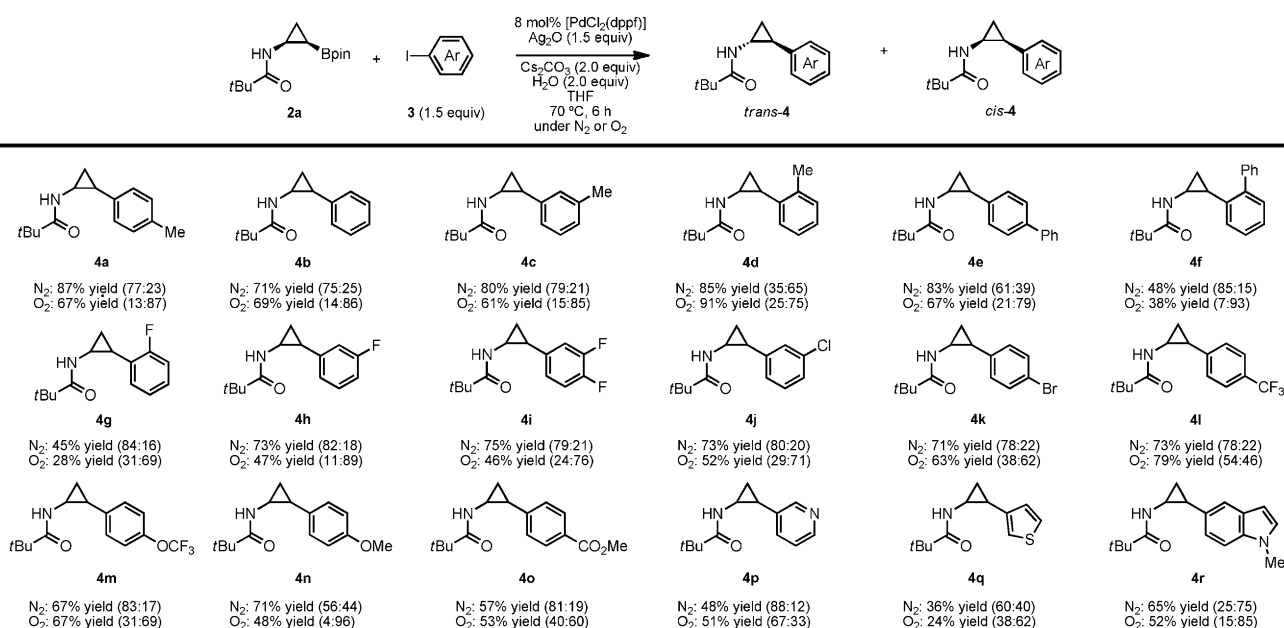
With reaction conditions in hand to preferentially produce either stereoisomer, we examined the substrate scope of the Suzuki–Miyaura cross-coupling reaction of *cis*-**2a** with various aryl iodides under N₂ and O₂ (Scheme 2). A broad range of aryl iodides containing groups such as phenyl (**3b**), *meta*-tolyl (**3c**), *ortho*-tolyl (**3d**), *para*-phenyl (**3e**), *ortho*-phenyl (**3f**), *ortho*-fluoro (**3g**), *meta*-fluoro (**3h**), and difluoro (**3i**), can be coupled with **2a** under N₂ and O₂ to afford the corresponding coupling products **4a–h** in good to moderate yields. When *meta*-chloro- (**3j**) and *para*-bromo-substituted (**3k**) aryl iodides were used, the reaction proceeded selectively at the iodine atom to afford the corresponding coupling

products **4j** and **4k** in moderate yields. Aryl iodides with a functional group on the benzene ring at the C4 position such as trifluoromethyl (**3l**), trifluoromethoxy (**3m**), methoxy (**3n**), and methoxycarbonyl (**3o**) were coupled with **2** to furnish the expected products **4l–o** in moderate yields. Heteroaryl iodides bearing pyridine (**3p**), thiophene (**3q**), and indole (**3r**) also gave the corresponding coupling products **4p–r**, albeit in lower yields. With some exception (**4d**, **4l**, **4p**, and **4r**), the *trans* ACPAs were preferentially obtained under N₂, and the *cis* isomers were obtained as major products under O₂.

Finally, we demonstrated a one-pot borylation/arylation resulting in a gram-scale synthesis of ACPA (Scheme 3). The compound **1a** (14 mmol) was borylated with HBpin under the optimized reaction conditions, followed by a Suzuki–Miyaura cross-coupling reaction with **3k** to afford 1.4 grams of the



Scheme 3. One-pot borylation/arylation and gram-scale synthesis of ACPA **5**. Reaction conditions: a) **1a** (14.2 mmol, 1.0 equiv), HBpin (1.5 equiv), [Ir(OMe)(cod)]₂ (0.5 mol %), 3,4,7,8-Me₄phen (1.0 mol %), cyclohexane, 80 °C, 18 h; removal of the solvent; **2a**, **3a** (1.5 equiv), [PdCl₂(dppf)]·CH₂Cl₂ (8 mol %), Ag₂O (1.5 equiv), Cs₂CO₃ (2.0 equiv), H₂O (2.0 equiv), 70 °C, 6 h, under N₂, 35 % yield (one pot). b) **4k** (5.3 mmol, 1.0 equiv), conc. HCl (1.0 mL), 1-propanol (2.0 mL), 100 °C, 60 h, 73 % yield.



Scheme 2. Substrate scope. Yield is that of the two isolated product isomers. Ratios represent the *trans*/*cis* products.

coupling product **4k** in one pot (35% yield). Thereafter, treatment of **4k** with HCl in 1-propanol gave 2-arylcyclopropylamine **5** in 73% yield.

In summary, we have developed a step-economical and stereodivergent synthesis of privileged 2-arylcyclopropylamines through a sequence of C(sp³)–H borylation and Suzuki–Miyaura coupling. The iridium-catalyzed C–H borylation of *N*-cyclopropylpivalamide proceeds with *cis* selectivity. The subsequent *B*-cyclopropyl Suzuki–Miyaura coupling catalyzed by [PdCl₂(dppf)]/Ag₂O proceeds with retention of configuration at the carbon atom bearing the Bpin group, while epimerization at the nitrogen-bound carbon centers of both starting materials and products is observed under the reaction conditions, epimerization which is suppressed in the presence of O₂. This unprecedented atmosphere-controlled epimerization process allowed access to both the *cis* and *trans* isomers of ACPAs in a rapid and operationally simple manner. Further mechanistic investigations of pivaloyl-directed C–H borylation and epimerization of cyclopropylamines as well as the development of ACPA-based LSD1 inhibitors are now ongoing.

Received: September 17, 2014

Published online: October 27, 2014

Keywords: C–H activation · cross-coupling · boron · iridium · small ring systems

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- [19] For details of optimization, see the Supporting Information.
- [20] The reaction conditions reported by Suginome et al. (Ref [8b]) did not work in our case.
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