Small Ring Systems

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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 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 4*n* 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

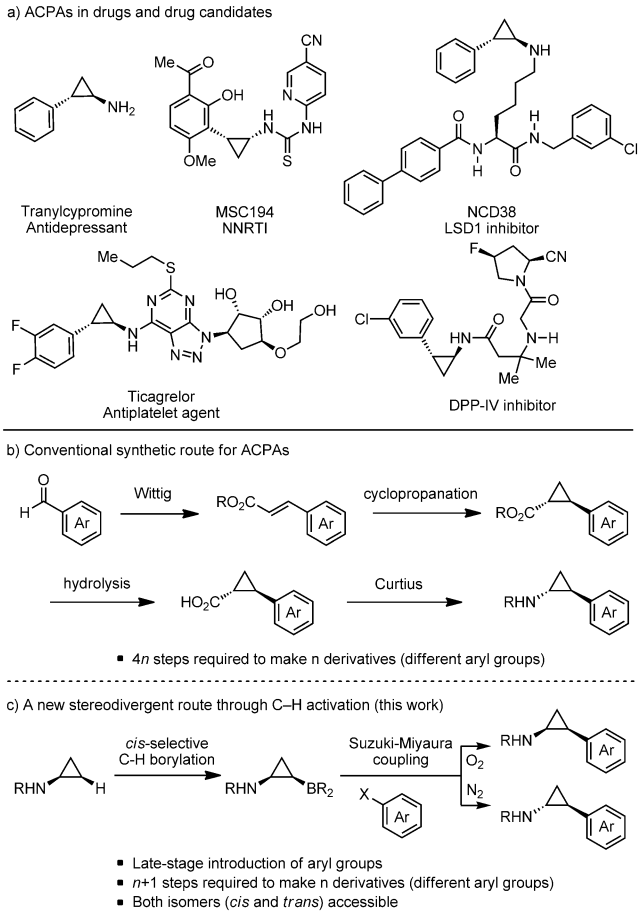

Figure 1. a) Arylcyclopropylamine (ACPA)-containing drugs and drug candidates. b) Conventional synthetic route for ACPAs. c) A new stereodivergent route for ACPAs through C–H activation.

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derivatives (Figure 1c). 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 1c).

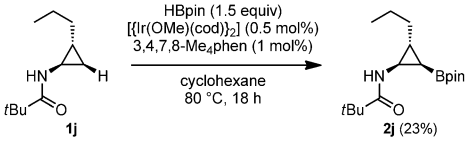
Our first goal was to find appropriate conditions for the stereoselective C(sp^3)–H borylation of cyclopropylamines. Although cyclopropanes have been rarely investigated in C–H borylation chemistry,[10] Hartwig recently reported a *trans*-selective C–H borylation of cyclopropanes catalyzed by [{Ir(OMe)(cod)}$_2$] and 2,9-dimethylphenanthroline (2,9-Me$_2$phen).[11] However, in early experiments, we found that simple application of this catalyst system to the reaction of unprotected cyclopropylamine and bis(pinacolato)diboron (B_2pin_2) 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 B_2pin_2 (0.5 equiv) in the presence of [{Ir(OMe)(cod)}$_2$] (2.5 mol%) and 2,9-Me$_2$phen (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 cyclopropane 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-Me$_2$phen, the yield of **2a** increased slightly (entry 2). Changing the ligand to 3,4,7,8-tetramethylphenanthroline (3,4,7,8-Me$_4$phen)[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 B_2pin_2 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 [{Ir(OMe)(cod)}$_2$]/3,4,7,8-Me$_4$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.

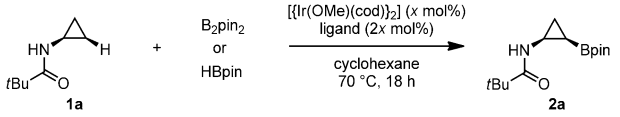
We also conducted C–H borylation of the cyclopropylamines **1b–j** with various substituents (see the Supporting Information for details). The pivaloyl group is by far the best N substituent in this particular reaction. Although there exist other protecting groups providing C–H borylation products to 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



(1)

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.

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_2pin_2 (0.5)	2.5	2,9-Me$_2$phen	6
2	B_2pin_2 (0.5)	2.5	4,4′-dibpy	15
3	B_2pin_2 (0.5)	2.5	3,4,7,8-Me$_4$phen	31
4	B_2pin_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, [{Ir(OMe)(cod)}$_2$] (*x* mol%), ligand (2*x* 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.
B_2pin_2 = bis(pinacolato)diboron, cod = 1,5-cyclooctadiene, HBpin = pinacolborane, 2,9-Me$_2$phen = 2,9-dimethylphenanthroline, 4,4′-dibpy = 4,4′-di-*tert*-butylpyridine, 3,4,7,8-Me$_4$phen = 3,4,7,8-tetramethylphenanthroline.

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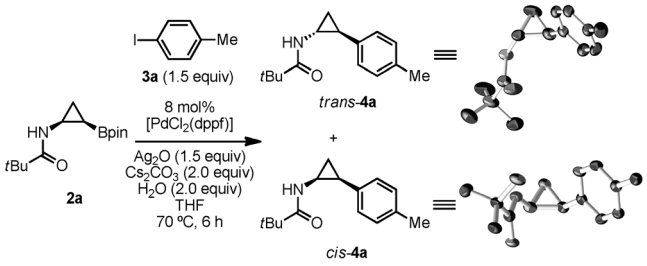
With stereoselective C–H borylation conditions established, we next examined the *B*-alkyl Suzuki–Miyaura cross-coupling of **2a** with haloarenes to provide ACPAs.[9] We were initially expecting that stereoretentive and/or stereoinvertive *B*-alkyl coupling conditions established by the groups of Crudden[8a] and Suginome[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]

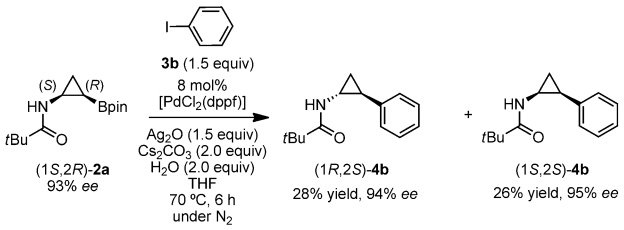


Entry	Atmosphere	Yield [%][b]	*trans*-**4a**/*cis*-**4a**
1	N_2	87	77:23
2	O_2	67	16:84

[a] Reaction conditions: **2a** (1.0 equiv), **3a** (1.5 equiv), [$PdCl_2$-(dppf)]·CH_2Cl_2 (8 mol%), Ag_2O (1.5 equiv), Cs_2CO_3 (2.0 equiv), H_2O (2.0 equiv), 70°C, 6 h, under N_2 or O_2. [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 [$PdCl_2$(dppf)] (8 mol%), Ag_2O (1.5 equiv), Cs_2CO_3 (2.0 equiv), and H_2O (2.0 equiv) in THF at 70°C for 6 hours under an N_2 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) Ag_2O is crucial for reactivity; 2) dppf is the most effective ligand; and 3) rate acceleration is observed by the addition of Cs_2CO_3 and H_2O. 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 O_2 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 (N_2 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 N_2 or O_2 atmosphere as outlined in Figure 2a. Both *trans*-**4a** and *cis*-**4a** isomerized under N_2. The compound *cis*-**4a** underwent significant isomerization under N_2 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 O_2 resulted in virtually no

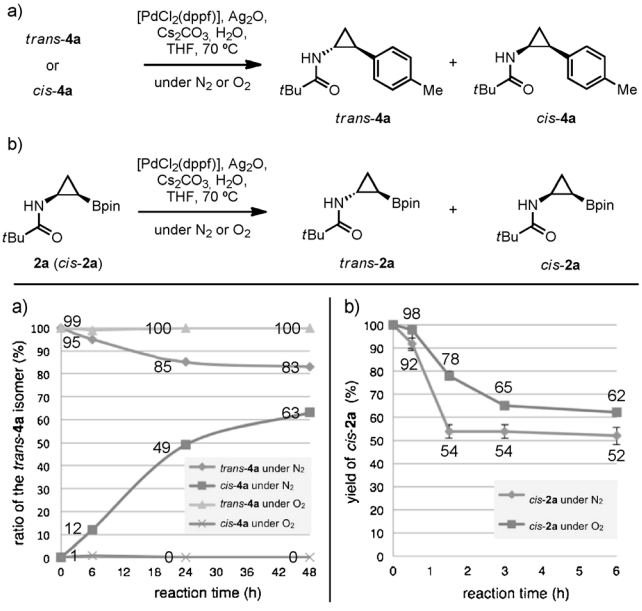


Figure 2. a) Isomerization experiments of *trans*-**4a** and *cis*-**4a**. b) Isomerization experiments of *cis*-**2a**.

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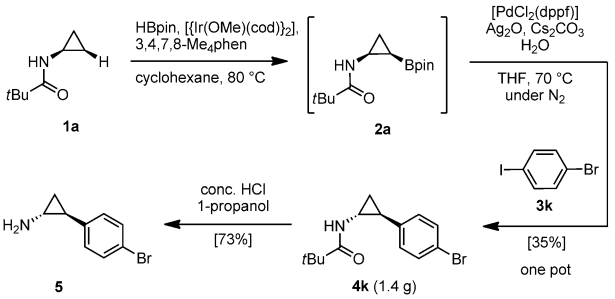
isomerization. These results strongly suggest that O_2 helps prevent the isomerization of both isomers.

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 N_2 (*cis*/*trans* = 54:46 after 1.5 h) than that under O_2 (*cis*/*trans* = 78:22 after 1.5 h). These results clearly show that isomerization at the C–N bond occurred from **2a** as well.

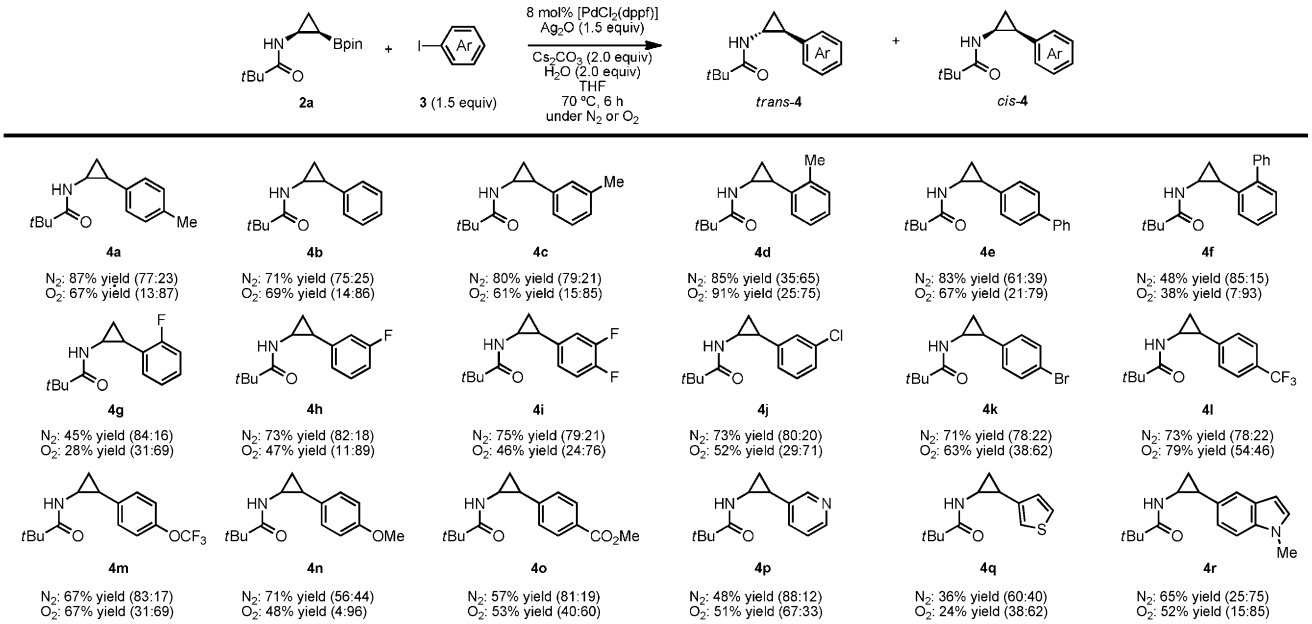
We found that when the coupling reaction of *cis*-**2a** and **3a** was performed with 10 mol% of BHT (dibutylhydroxytoluene) under N_2, the isomerization was suppressed (*cis*-**4a** 55%, *trans*-**4a** 6%). We initially assumed that this BHT effect is a testimony to the occurrence of radical-based 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 O_2 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 N_2 and O_2 (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 N_2 and O_2 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* APCAs were preferentially obtained under N_2, and the *cis* isomers were obtained as major products under O_2.

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-Me$_4$phen (1.0 mol%), cyclohexane, 80°C, 18 h; removal of the solvent; **2a**, **3a** (1.5 equiv), [PdCl$_2$(dppf)]·CH$_2$Cl$_2$ (8 mol%), Ag$_2$O (1.5 equiv), Cs$_2$CO$_3$ (2.0 equiv), H$_2$O (2.0 equiv), 70°C, 6 h, under N_2, 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.

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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(sp^3)–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 [$PdCl_2$(dppf)]/Ag_2O 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 O_2. 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.

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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.
[21] CCDC 1030537 (*trans*-**4a**), CCDC 1030536 (*cis*-**4a**), and CCDC 1030538 (*cis*-**8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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