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Metal-free thermal organocatalytic pinacol coupling of arylaldehydes using an isonicotinate catalyst with bis(pinacolato)diboron†

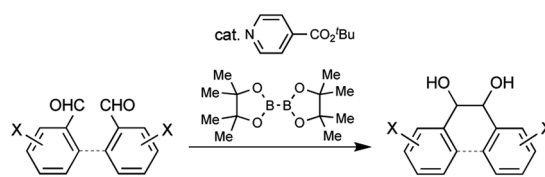
 Masamichi Yasui, Kengo Hanaya, Takeshi Sugai  and Shuhei Higashibayashi *

The metal-free thermal organocatalytic pinacol coupling of arylaldehydes has been developed. The intermolecular coupling of arylaldehydes catalyzed by *t*-butyl isonicotinate with bis(pinacolato)diboron as the co-reducing agent afforded 1,2-diphenylethane-1,2-diols. This reaction was also applicable to the intramolecular coupling of 1,1'-biphenyl-2,2'-dicarbaldehydes to afford 9,10-dihydrophenanthrene-9,10-diols. Various functional groups were tolerated under this coupling condition.

Pinacol coupling, a reductive coupling reaction between carbonyl groups, is one of the most useful carbon–carbon bond-forming reactions. Many kinds of coupling methods using stoichiometric amounts of metals or metal catalysts with co-reducing metals have been developed to date and applied to the syntheses of various biologically active compounds.¹ A recent advance in pinacol coupling is the development of photoredox catalysts in combination with organic co-reducing agents. Coupling reactions by photoredox Ir or Ru catalysts with tertiary amines as co-reducing agents under visible light were reported by Rueping *et al.* and Yang *et al.*, respectively.² While these examples required precious metal catalysts, metal-free pinacol coupling using organic photoredox catalysts has also been achieved.³ Yanagida *et al.* and Sudo *et al.* developed the coupling reaction using poly(*p*-phenylene) or perylene as an organic photoredox catalyst with amines as co-reducing agents under visible light. Yao *et al.* reported the reaction using Eosin Y Na₂ as a catalyst with a 1,4-dihydropyridine derivative as a co-reducing agent under visible light. In these examples, photoexcitation of the catalysts is an indispensable process to generate the strong one-electron reducing agents, since the organic co-reducing agents are weak electron donors. Given this background, the development of a metal-free organocatalytic pinacol coupling with an organic co-reducing agent without photoexcitation is recognized to be a challenging task. In order to realize such metal- and light-free organocatalytic pinacol coupling, we focused on the generation of a pyridine-boryl radical from 4-cyanopyridine and bis(pinacolato)diboron, reported by Li *et al.*, and its application as a reducing agent for azo compounds, sulfoxides, and quinones.^{4a} Li *et al.* also reported the addition reaction of ketyl radicals generated from aldehydes

by a 4-(4-cyanophenyl)pyridine catalyst and bis(pinacolato)diboron to afford 1,1-diarylethylenes.^{4b} Inspired by their reports, we initiated the development of pinacol coupling using a pyridine catalyst and a diboron as a co-reducing agent and achieved the pinacol coupling of arylaldehydes. Recently, Choi and Chung *et al.* also reported organocatalytic pinacol coupling of diaryl ketones with a pyridine catalyst and a diboron as a co-reducing agent.⁵ Here, we report inter- and intra-molecular organocatalytic pinacol coupling of arylaldehydes by an isonicotinate catalyst with bis(pinacolato)diboron (Scheme 1).

We initiated the screening of various pyridine catalysts 2 (10 mol%) with bis(pinacolato)diboron (B₂pin₂) (0.6 equiv.) in cyclopentyl methyl ether (CPME) for the pinacol coupling of arylaldehydes (Table 1). 3-Bromobenzaldehyde (**1a**) was chosen as the substrate, since we expected that the mild organic reducing agent would allow the desired coupling without dehalogenation in contrast to strong metal reducing agents. Using 4-cyanopyridine (**2a**)^{4a} as a catalyst at reflux for 6 h, we succeeded in obtaining diol **3a** in 49% yield with 33% recovery of the starting material **1a** without dehalogenation (entry 1). Quenching with aq. KHF₂ was effective for recovering the diol from the aqueous layer of the reaction mixture.⁵ The diastereometric ratio (dr) of the diol was about 1 : 1, which was determined by ¹H NMR spectrum. 4-(4-Cyanophenyl)pyridine

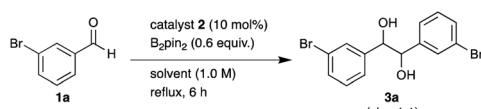



Scheme 1 Inter- and intramolecular metal-free thermal organocatalytic pinacol coupling of arylaldehydes by a nicotinate catalyst and bis(pinacolato)diboron as the co-reducing agent.

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
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra04443e




Table 1 Screening of pyridine catalysts and solvents^a





2a




2b




2c




2d



2e



2f



2g

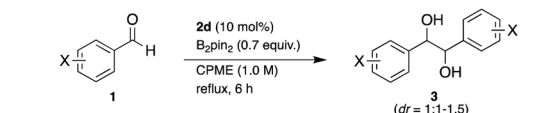
Entry	catalyst	solvent	(%) ^b yield	
			1a	3a
1	2a	CPME	33	49
2	2b	CPME	53	38
3	2c	CPME	20	52
4	2d	CPME	5	78
5	2e	CPME	92	7
6	2f	CPME	96	Trace
7	2g	CPME	93	Trace
8	2d	MTBE	32	54
9	2d	THF	52	37
10	2d	1,4-dioxane	62	24
11	2d	PhCF ₃	41	39
12	2d	Cyclohexane	6	70
13	2d	Toluene	16	69
14	2d	CH ₃ CN	81	6
15 ^c	2d	CPME	Trace	81


^a Reaction conditions: **1a** (1.0 mmol), catalyst **2** (0.10 mmol), B₂pin₂ (0.60 mmol), solvent (1.0 mL). ^b Yields determined by ¹H NMR analysis with CH₃NO₂ as an internal standard. ^c B₂pin₂ (0.7 equiv.).

(**2b**)^{4b} was less efficient, giving **3a** in 38% yield (entry 2). Using methyl isonicotinate (**2c**) reported by Choi and Chung *et al.*,⁵ the yield of **3a** was increased up to 52% yield (entry 3). When *t*-butyl isonicotinate (**2d**)^{6a} was used as a catalyst, the yield of **3a** was further improved up to 78% yield (entry 4). In contrast, 4-phenylpyridine (**2e**),^{6b,c,d,e} 4-(naphthalen-1-yl)pyridine (**2f**),^{6f} and 4-(4-methoxyphenyl)pyridine (**2g**) showed lower reactivity, giving **3a** in low yields (entries 5, 6 and 7). The catalyst screening results indicate that the electron-withdrawing group at the C4 position is crucial for the catalytic activity for this coupling. The higher catalytic activity of **2d** than **2c** (entries 4 vs. 3) could be due to the higher stability of catalyst **2d** under the reaction conditions.^{6a} Next, solvents were screened with catalyst **2d** under reflux conditions (entries 4, 8–14). Among the eight screened solvents, CPME gave the best yield at 78% (entry 4). Cyclohexane and toluene also gave good yields (70% and 69% yields, respectively) (entries 12 and 13). Although 1,4-dioxane and PhCF₃ were reported to be good solvents for the pinacol coupling of diaryl ketones by Choi and Chung *et al.*,⁵ they were not effective for this pinacol coupling of arylaldehydes, giving only 24 and 39% yields, respectively (entries 10 and 11). The yield of **3a** was further improved up to 81% yield with 0.7 equiv. of B₂pin₂ (entry 15).


With the optimized reaction conditions in hand, we investigated the reaction scope on a series of substituted benzaldehydes (Table 2). The coupling of 2-bromobenzaldehyde (**1b**), 4-

bromobenzaldehyde (**1c**), and 3,5-dibromobenzaldehyde (**1d**) gave the corresponding diols **3b**, **3c**, and **3d** in 80%, 60%, and 94% yields, respectively. While the reaction of **1b** required a slightly longer time (8 h) than that of **1a**, the bromine atom at the *ortho* position did not inhibit the coupling, affording the high yield. Aldehyde **1c** showed lower reactivity than **1a** and **1b**. The reaction was applicable to arylaldehydes with fluorine, chlorine, and iodine atoms at the 3-position, furnishing the coupling products **3e**, **3f**, and **3g** in 87%, 89%, and 72% yields, respectively. The coupling product of simple benzaldehyde **1h** was formed in 75% yield in 12 h. The reaction was applied to arylaldehydes with other electron-withdrawing groups. The reaction of **1i** with a 3-trifluoromethyl group, **1j** with a 3-methoxycarbonyl group, **1k** with a 3-cyano group, and **1l** with an acetyl group afforded diols **3i**, **3j**, **3k**, and **3l** in 74%, 70%, 73%, and 63% yields, respectively. The ester, nitrile, and ketone functional groups remained intact under this condition, showing the high chemoselectivity of this coupling reaction. Applicability to electron-rich aldehydes was also investigated. The coupling of 2-methylbenzaldehyde (**1m**) gave the product **3m** in 74% yield. Encouraged by the tolerance of the reaction to steric hindrance, the reaction was applied to 2-ethylbenzaldehyde (**1n**). Although the reaction was slower (24 h), the


Table 2 Substrate scope of arylaldehydes^a




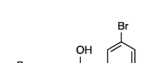
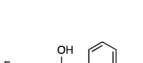
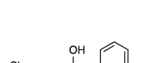
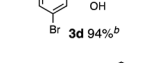
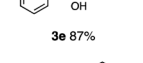
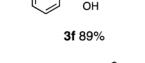
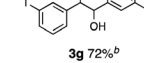
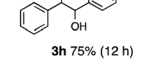
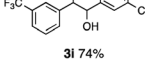
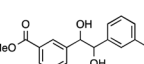
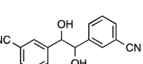
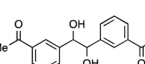
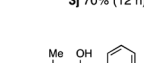
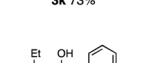
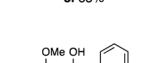
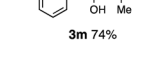
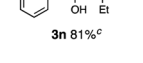
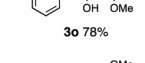
2d



B₂pin₂



CPME

 3a 81%	 3b 80% (8 h)	 3c 60% (12 h)
 3d 94% ^b	 3e 87%	 3f 89%
 3g 72% ^b	 3h 75% (12 h)	 3i 74%
 3j 70% (12 h)	 3k 73%	 3l 63%
 3m 74%	 3n 81% ^c	 3o 78%
 3p 69% ^c	 3q 57% ^d	 3r 62%

^a Reaction conditions: **1** (1.0 mmol), **2d** (0.10 mmol), B₂pin₂ (0.70 mmol), CPME (1.0 mL). Isolated yield. ^b **1** (0.50 mmol). ^c 24 h. ^d **2d** (20 mol%), B₂pin₂ (1.0 equiv.), 16 h.

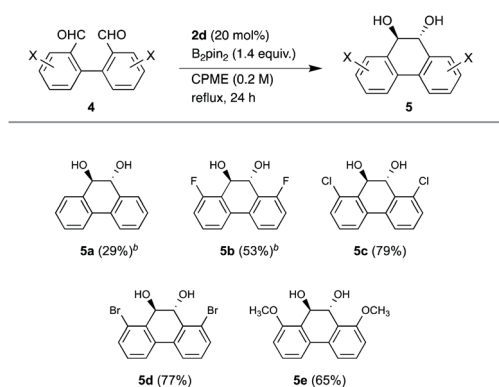


desired product **3n** was obtained in 81% yield. Arylaldehydes **1o**, **1p**, **1q**, and **1r** with strong electron-donating methoxy groups at the 2-, 3-, 4- and 3,5-positions also gave the coupling products **3o**, **3p**, **3q**, and **3r** in 78%, 69%, 57%, and 62% yields, respectively. The diastereomeric ratios were 1 : 1 to 1.5, which were determined by ^1H NMR spectra. These results revealed that this coupling method has wide applicability regarding the functional groups on the aryl group. Particularly, it is noteworthy that the coupling of the *ortho*-substituted benzaldehydes also gave the desired products in high yields.

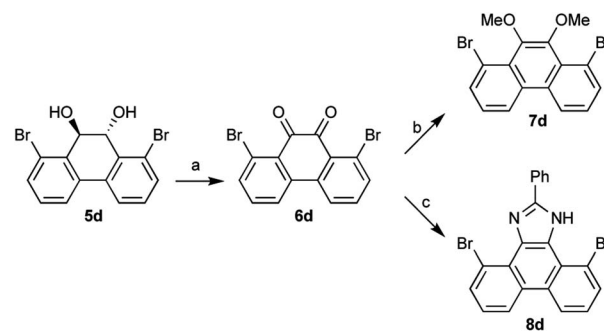
We further explored an intramolecular coupling of 1,1'-biphenyl-2,2'-dicarbaldehyde (**4a**), *ortho*-substituted 3,3'-dihalogenated derivatives **4b–4d** and 3,3'-dimethoxy derivative **4e**, which could be useful for syntheses of *ortho*-substituted phenanthrene derivatives (Table 3). The intramolecular reaction was conducted in 0.2 M for 24 h owing to the low solubility of **4** in CPME and the lower reactivity than that of the intermolecular reaction. While the coupling product **5a** was formed in 29% yield, the coupling of halogenated derivatives gave better yields, 53% (**5b**), 79% (**5c**), and 77% (**5d**), respectively. Methoxy derivative **5e** was also obtained in 65% yield. It seems that the intermolecular coupling caused the low yield of **5a** owing to the less steric hindrance. Only *trans* isomers were formed for **5c–d** and a small amount of *cis* isomers were generated for **5a** and **5b** (*trans* : *cis* = 10 : 1), which were determined by ^1H NMR spectra. Again, this method was found to be suitable for the coupling of *ortho*-substituted derivatives.

According to the related previous reports,^{4,5} a pyridine-boryl radical formed from the pyridine catalyst **2d** and B_2pin_2 could generate a ketyl radical of arylaldehydes **1** or **4**. The radical reaction process was confirmed by the reaction of **1a** with **2d** and B_2pin_2 in the presence of TEMPO (1.0 equiv.), which recovered **1a** in 97% yield. Two plausible reaction mechanisms are conceivable for the carbon–carbon bond formation after generation of the ketyl radical, which is the coupling of two ketyl radicals or the addition of ketyl radical to an aldehyde followed by one-electron reduction with a pyridine-boryl radical.

Table 3 Intramolecular coupling of biphenyldicarbaldehydes^a



^a Reaction conditions: **4** (0.20 mmol), **2d** (0.040 mmol), B_2pin_2 (0.28 mmol), CPME (1.0 mL). Isolated yield. ^b *trans* : *cis* = 10 : 1.



Scheme 2 Conversion to 1,8-dibromophenanthrene derivatives. Reaction conditions: (a) PCC, SiO_2 , 1,2-dichloroethane, reflux, 12 h, 53%; (b) dimethyl sulfate, TBAB, sodium dithionite, THF/ H_2O , rt, 15 min, 60%; (c) benzaldehyde, NH_4OAc , sulfamic acid, EtOH, 12 h, reflux, 77%.

The diols **3** and **5** can be derivatized to benzil and phenanthrene-9,10-diones. Thus, 1,8-dibromo-9,10-dihydrophenanthrene-9,10-diol **5d** was converted to phenanthrene-9,10-dione **6d**, which was further derivatized to 9,10-dimethoxyphenanthrene **7d** (ref. 7) and phenanthro[9,10-*d*]imidazole **8d** (ref. 8) (Scheme 2). These 1,8-substituted phenanthrene derivatives are expected to serve as new building blocks for drug candidates having phenanthrene structures.⁹ Phenanthrene derivatives are also useful in many organic materials such as liquid crystals, fluorophores, redox materials, and nanostructures.¹⁰ Since materials with 1,8-substituted phenanthrene derivatives have not been developed yet, in contrast to widely utilized 2,7- or 3,6-substituted derivatives, these 1,8-substituted derivatives will be useful for the development of new organic materials.

In summary, we established the metal-free thermal pinacol coupling of arylaldehydes by *t*-butyl isonicotinate as the catalyst and bis(pinacolato)diboron as the co-reducing agent. The reaction was effective for the coupling of arylaldehydes with various functional groups, particularly *ortho*-substituted arylaldehydes. The obtained 1,2-diarylethane-1,2-diols and dihydrophenanthrene-9,10-diols are expected to be useful building blocks to develop new drug candidates as well as organic materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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