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A convenient pinacol coupling of diaryl ketones with B_2pin_2 *via* pyridine catalysis†

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A convenient, pyridine-boryl radical-mediated pinacol coupling of diaryl ketones is developed. In contrast to the conventional pinacol coupling that requires sensitive reducing metal, the current method employs a stable diboron reagent and pyridine Lewis base catalyst for the generation of a ketyl radical. The newly developed process is operationally simple, and the desired diols are produced with excellent efficiency in up to 99% yield within 1 hour. The superior reactivity of diaryl ketone was observed over monoaryl carbonyl compounds and analyzed by DFT calculations, which suggests the necessity of both aromatic rings for the maximum stabilization of the transition states.

Pinacol coupling is a valuable reaction that provides a 1,2-diol from two carbonyl compounds *via* the connection of two electrophilic positions, and the reaction has been employed as a key step in natural product synthesis.[1] The reaction mechanism is straightforward. An electron is added to a carbonyl group to form a ketyl radical which then dimerizes to afford a 1,2-diol. Traditionally, the reactive ketyl radical intermediate is generated by low valent metals such as Zn, Ti, Mg, Al/Hg, Sm, In, *etc*. (Fig. 1a).[2] Although this method has been constantly improved, it still has drawbacks including the requirement of highly reactive metallic reducing agents under harsh reaction conditions. Moreover, because of the easily oxidizable nature of the metal reagents, an additional activation process is often necessary for the removal of metal oxide on the surface before use.[3] Recently, new pinacol coupling methods that do not require low valent reducing metals were developed. For example, pinacol coupling has been successfully conducted under photochemical conditions.[4] Through the action of the photoredox catalyst, the single electron reduction of carbonyl compounds was realized in the presence of an amine reductant under visible light. A completely metal-free pinacol coupling has also been reported by the groups of Khaliullin and C.-J. Li.[5] In this method, hydrazine functions as both a reductant and a hydrogen source *via* light-induced hydrogen atom transfer (HAT) under UV irradiation. In both cases, mild reaction conditions could be achieved by harnessing the reducing power from light energy.

For the past few years, chemistry exploiting a diboron-Lewis base complex has emerged.[6] It is known that upon association of a diboron with an appropriate Lewis base such as pyridines

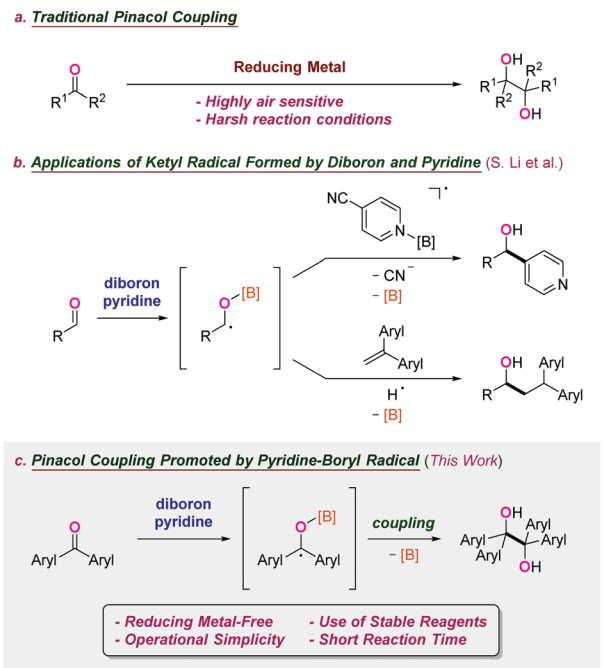

Fig. 1 Pyridine-boryl radical-promoted ketyl radical formation and proposed application to pinacol coupling.

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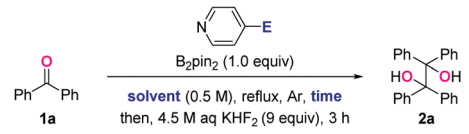
containing electron-withdrawing substituents, the B–B bond is weakened and cleaved in a homolytic manner.[7] The convenient formation of the boryl radical with reagents that are easy to handle as well as its persistent property attracted attention from the synthetic organic community and consequently has brought the development of various organic reactions. Among them, the transformations utilizing the ketyl radical formation from carbonyl compounds with a diboron–pyridine complex are noteworthy. The S. Li group developed reductive C–C bond formations of carbonyl compounds with pyridine or alkene by utilizing a single electron transfer (SET) reactivity of the pyridine-boryl radical (Fig. 1b).[8] Both 1,2-pyridylation of ketones and 1,4-pyridylation of enones were accomplished *via* the substitution reaction between ketyl radical boronate and 4-cyanopyridine-boryl radical complex.[8a,b] Similarly, the alkylation of aliphatic aldehydes with *gem*-diarylethylene proceeds in the presence of diboron and a 4-(4-cyanophenyl)pyridine catalyst (Fig. 1c).[8c] Interestingly, pinacol coupling reactivity has not been observed even though the ketyl radical intermediate is present in these reductive C–C bond formation reactions. Whereas the reductive coupling of imine has been successfully promoted by the diboron–pyridine complex,[9] the related reactivity of ketone or aldehyde has not been described to date. Herein, we report the development of a new pinacol coupling method that does not require the use of a low valent metal by taking advantage of the pyridine-boryl radical as a ketyl radical generator.

To probe pinacol coupling reactivity, the initial reaction conditions survey was performed with benzophenone (**1a**) because diaryl ketone is expected to form a stable ketyl radical. These reactions were conducted with 1.0 equivalent of B_2pin_2 and a catalytic amount of electron-deficient pyridine in refluxing $PhCF_3$ (Table 1).[6f,g] Gratifyingly, in the presence of 0.5 equiv of 4-cyanopyridine,[10] benzopinacol (**2a**) was produced in 72% yield in 1 hour after deborylative workup with 4.5 M aq. KHF_2 (entry 1).[11] Such high reactivity is notable because the previously reported transformations of ketyl radicals derived from diboron–pyridine complexes generally require more than 24 hours.[8] Subsequently, the examination of other pyridine Lewis bases revealed that the *para* substituent of pyridine has a significant influence on the reaction yield (entries 2 and 3).[12] From the reaction with 4-phenylpyridine, **2a** was obtained in a drastically decreased 14% yield (entry 2). On the other hand, methyl isonicotinate (4-carbomethoxypyridine) afforded **2a** in an improved 89% yield (entry 3). Then, the solvent was briefly screened with 1,4-dioxane and methyl *tert*-butyl ether, which are typically employed in the boryl radical chemistry (entries 4 and 5). In 1,4-dioxane, **2a** was formed in 90% yield, which is as high as the yield in $PhCF_3$ (entry 4). In contrast, the reaction was slow in *t*-BuOMe. **2a** was produced in only 54% yield, and *ca.* 23% of the unreacted starting material (**1a**) was recovered (entry 5). With the two efficient solvents, $PhCF_3$ and 1,4-dioxane, the amount of methyl isonicotinate was reduced to 0.2 equivalent (entries 6 and 7). The high reactivity was maintained, and **2a** was obtained in a slightly improved 95% yield in both cases. Further reduction of the catalyst loading led to a small attenuation of the yield even after a longer reaction time (entry 8). Lastly, the reaction time was investigated (entries 9 and 10). A small amount of unreacted starting material remained after 0.5 hours although the isolated yield was still high (entry 9), and no further improvement was observed in 2 hours (entry 10). Therefore, the reaction time of 1 hour was found to be optimal. When the reaction was conducted at room temperature, only 30% of **2a** was produced in 48 hours (entry 11). As expected, the reaction did not proceed either in the absence of a pyridine catalyst (entry 12) or in the presence of a radical scavenger (entry 13).

Table 1 Optimization of pyridine-boryl radical-promoted coupling of benzophenone[a]

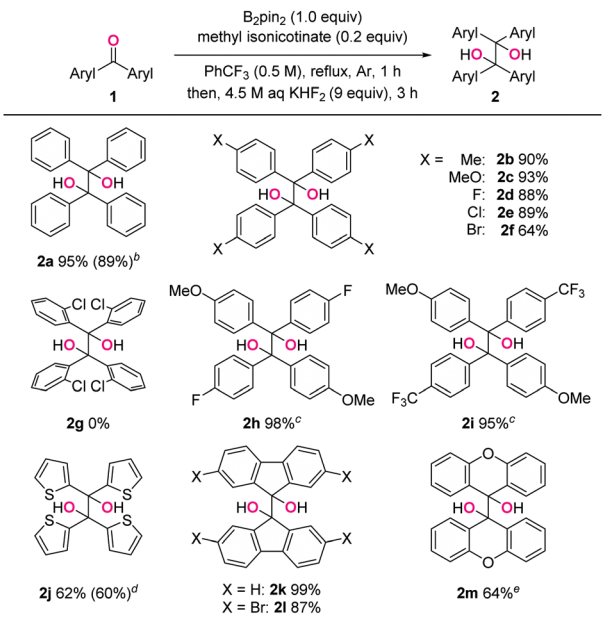


Entry	E	Equiv.	Solvent	Time (h)	Yield[b] (%)
1	CN	0.5	$PhCF_3$	1	72
2	Ph	0.5	$PhCF_3$	1	14
3	CO_2Me	0.5	$PhCF_3$	1	89
4	CO_2Me	0.5	1,4-Dioxane	1	90
5	CO_2Me	0.5	*t*-BuOMe	1	54
6	CO_2Me	0.2	$PhCF_3$	1	95
7	CO_2Me	0.2	1,4-Dioxane	1	95
8	CO_2Me	0.1	$PhCF_3$	3	92
9	CO_2Me	0.2	$PhCF_3$	0.5	93
10	CO_2Me	0.2	$PhCF_3$	2	95
11[c]	CO_2Me	0.2	$PhCF_3$	48	30
12[d]	—	—	$PhCF_3$	1	0
13[e]	CO_2Me	0.2	$PhCF_3$	1	0

[a] Reaction conditions: **1a** (1.0 mmol), B_2pin_2 (1.0 mmol), and pyridine Lewis base in solvent (1 mL). [b] Isolated yields after column chromatography. [c] At room temperature. [d] Without pyridine Lewis base. [e] With 2.2 equiv. of TEMPO.

With the optimal reaction conditions in hand, a range of diaryl ketones were surveyed (Table 2). Consistently high reactivity was observed regardless of the electronic property of benzophenone derivatives. With 4,4′-dimethylbenzophenone (**1b**), the corresponding diol **2b** was obtained in 90% yield. Also, highly electron-rich 4,4′-dimethoxybenzophenone (**1c**) afforded **2c** in 93% yield. From electron-poor substrates such as 4,4′-difluoro-, 4,4′-dichloro-, and 4,4′-dibromobenzophenone (**1d–f**), the coupling products **2d**, **2e**, and **2f** were formed in 88%, 89%, and 64% yields, respectively. However, *ortho*-substitution was not tolerated as the reaction of 2,2′-dichlorobenzophenone (**1g**) did not take place at all. When electronically unsymmetrical substrates such as **1h** and **1i** were employed, the coupling products (**2h** and **2i**) were obtained in 98% and 95% yields, respectively, as a *ca.* 6 : 4 mixture of diastereomers in both cases. Thus, it appears that the electronic differentiation of two aryl rings has a negligible influence on the diastereoselectivity. A heteroaromatic substrate was also examined. With di-2-thienyl ketone (**1j**), **2j** was obtained in moderate yield (62%), and no improvement was observed when conducted in 1,4-dioxane (60%). Additionally, the pinacol coupling was investigated with fused aromatic ketones. In the cases of 9-fluorenone (**1k**) and 2,7-dibromo-9-fluorenone (**1l**), **2k** and **2l** were afforded in 99% and 87% yields, respectively. The reactivity of xanthone (**1m**) was also

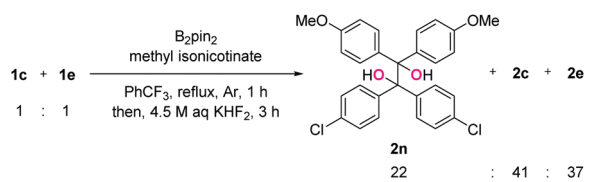
Table 2 Scope of pyridine-boryl radical-promoted pinacol coupling of diaryl ketones[a]



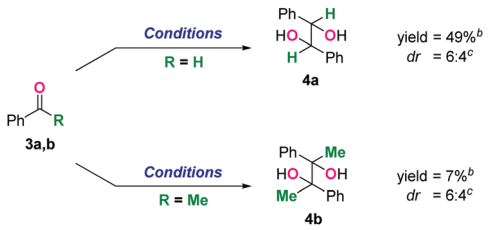
[a] Reaction conditions: **1** (1.0 mmol), B_2pin_2 (1.0 mmol), and methyl isonicotinate (0.2 mmol) in $PhCF_3$ (1 mL). Isolated yield after column chromatography. [b] 10.0 mmol scale. Isolated yield after recrystallization. [c] *ca.* 6 : 4 dr. [d] In 1,4-dioxane. [e] After multiple column chromatography.

comparable, producing **2m** in high conversion. However, **2m** could be isolated only in 64% yield after multiple chromatographic separations because of its instability on silica gel. This newly developed process is easily scalable. In a 10.0 mmol (1.83 g) scale, **2a** was obtained in 89% (1.62 g) isolated yield after recrystallization. Furthermore, heterocoupling was attempted with two electronically complementary substrates, **1c** and **1e** (Scheme 1). Unfortunately, homocoupling was more preferred than the heterocoupling, providing **2n** : **2c** : **2e** with a 22 : 41 : 37 ratio in 92% combined yield. This tendency is understandable because the difference between SOMO energy states of the reacting partners is greater in heterocoupling.

The pinacol coupling was also examined with monoaryl carbonyl compounds in the hope of expanding the substrate scope (Scheme 2). In these cases with the unsymmetrical substrates, diastereoselectivity is of concern in addition to reactivity. The coupling of benzaldehyde (**3a**) was much slower than the reaction of benzophenone (**1a**), and **4a** was produced in 49% yield even after 48 h. Moreover, low diastereomeric preference was observed (6 : 4 dr). Acetophenone (**4a**) remained



Scheme 1 Examination of hetero–pinacol coupling.



Scheme 2 Attempts at boryl radical-promoted pinacol coupling of monoaryl substrates[a] ([a]Reaction conditions: **3** (1.0 mmol), B_2pin_2 (1.0 mmol), and methyl isonicotinate (0.2 mmol) in refluxing $PhCF_3$ (1 mL) for 48 h. [b] Isolated yield after column chromatography. [c] Analyzed by ^1H NMR spectroscopy.)

mostly unreacted, affording only a small amount of **4b** in 7% yield and again with low 6 : 4 dr.

To gain insight into the superior pinacol coupling reactivity of benzophenone over other aromatic carbonyl compounds, DFT calculations were performed for the ketyl radical formation of benzophenone and acetophenone with 4-cyanopyridine-Bpin radical species at the UM06-2X/6-31G(d,p) level of theory (Fig. 2).[13–16] During the initial association of benzophenone and the pyridine-boryl radical (**TS-1**) as well as the subsequent dissociation of pyridine (**TS-2**), both phenyl groups of benzophenone contribute to the stability of the transition states simultaneously. While one phenyl ring aligns with the pyridine ring to

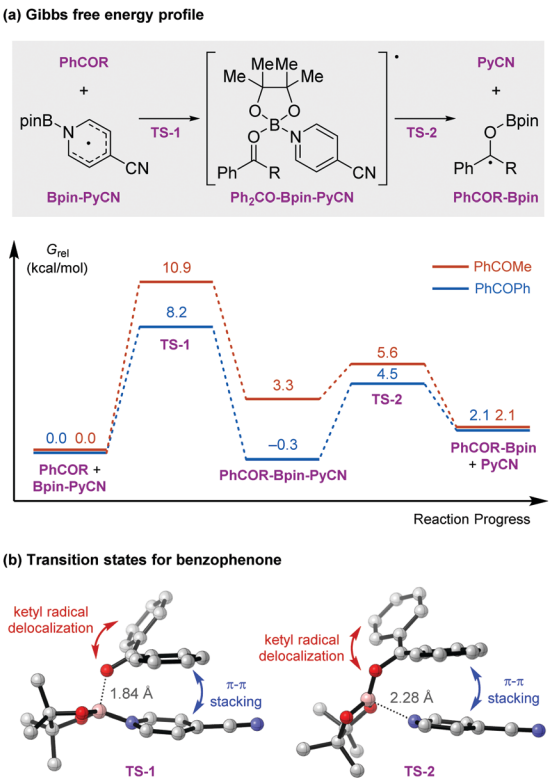


Fig. 2 DFT calculations of ketyl radical formation (UM06-2X/6-31G(d,p)): (a) Gibbs free energy profile (red: acetophenone, blue: benzophenone), and (b) transition states for benzophenone. Hydrogens are omitted for clarity.

have a π–π stacking interaction, the other phenyl ring adopts almost coplanar conformation with the carbonyl group to delocalize the ketyl radical. Thus, the stabilizing effects are maximized when both phenyl rings are present, which explains the high efficiency of the pinacol coupling of benzophenone. (See the ESI† for the comparison with isomeric transition structures that lack the π–π stacking interaction.) Accordingly, higher activation energy is required for the ketyl radical formation of acetophenone which has only one phenyl ring.

In summary, a convenient pinacol coupling of diaryl ketones was developed *via* the combined use of B_2pin_2 and a catalytic amount of methyl isonicotinate for the formation of the ketyl radical intermediate. In this new process, the use of sensitive reducing metal reagents and an additional pre-activation step are avoided. The remarkable efficiency of the current method was demonstrated by the short reaction time (1 hour) as well as the high chemical yield (up to 99%). The superior performance of diaryl ketones over monoaryl substrates was rationalized by the DFT calculations, and it was found that both phenyl groups of benzophenone contribute to the stability of the transition states. Further efforts on reaction scope expansion are currently ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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10 B_2pin_2-mediated reductive coupling of carbonyl compounds with 4-cyanopyridine has been reported (ref. 8a and b). However, such reactivity was not observed under our conditions.

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12 The unpaired electron of the pyridine-boryl radical is known to delocalize over the pyridine aromatic ring. Thus, pyridines with extended conjugation have been typically employed in the pyridine-boryl radical chemistry. See ref. 6*e*.

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