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Photoactivation of Hydrazones for the Synthesis of Diarylalkanes and Trialkylmethylboronates: The Key Role Played by Soluble Base

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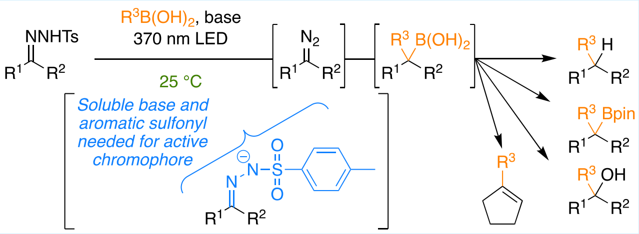
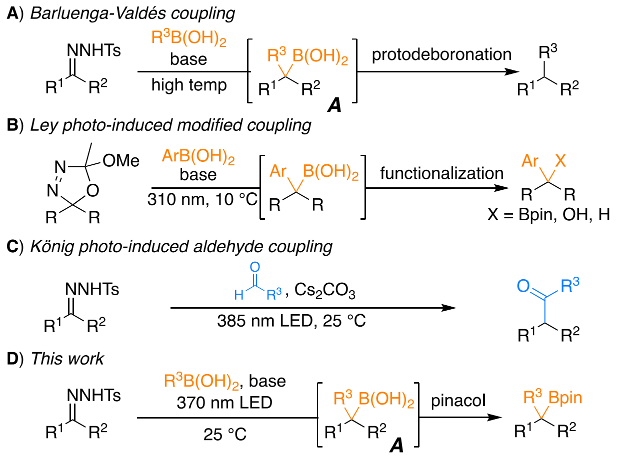
ABSTRACT: The synthesis of diaryl alkanes and tertiary organoboronates via Barluenga coupling at room temperature occurred via photoactivated conversion of aryl sulfonyl hydrazones to diazo compounds in the presence of soluble bases. The combination of arylsulfonyl hydrazone and a soluble base is necessary to provide a near-UV chromophore. Using aromatic hydrazones and aromatic boronic acids resulted in rapid deboronation because of the instability of dibenzylic boron intermediates. Alkyl hydrazones allowed the isolation of derivatives of the tertiary boronate.



Boron-containing organic compounds are synthetically useful in many transformations and as potential drug candidates.[1,2] While the use of boron compounds in organometallic methodologies such as Suzuki−Miyaura coupling[3] has been well-established, metal-free couplings have also been investigated. In 2009, Barluenga and Valdés reported the use of boronic acids and hydrazones to construct C−C bonds at high temperature (Scheme 1A).[4] However, some sensitive substrates and boronic acids are incompatible with this process due to thermal instability.[5] Additionally, after C−C bond formation, organoboron intermediate **A** underwent spontaneous protodeboronation and lost the potential for further exploitation of the C−B bond. To avoid elevated temperatures, the Ley group[6] used a 310 nm UV lamp to fragment oxadiazolines to form diazo compounds in situ for further reaction with aromatic boronic acids (Scheme 1B). In 2022, the König group reported a milder method for the formation of diazo compounds from hydrazones by using near-UV light in the presence of Cs_2CO_3. Aldehydes were used as electrophiles to construct homologous products (Scheme 1C).[7] Despite these notable advancements, several limitations and disadvantages remained to be addressed: 1) harsh reaction conditions, including high temperatures, leading to the decomposition of some substrates or 2) the need for UV light sources and the synthesis of oxadiazolines. Inspired by König's work, we envisioned the use of boronic acids instead of aldehydes in pursuit of a photoactivated version of the Barluenga coupling that enables further functionalization of **A**. Notably, as we were completing these efforts, a parallel approach was reported by Plaza and Valdés.[8,9] This work (Scheme 1D) corroborates that effort, provides additional substrate examples, delineates the limits of the method's effectiveness, and provides essential data from control experiments to understand the requirements of the photoactivation.

Scheme 1. Approaches to the Barluenga Coupling Reaction



To test the hypothesis that an ambient temperature reaction would provide a greater substrate scope and the ability to intercept **A**, methylphenyl tosyl hydrazone (**1**) and 4-methoxyphenyl boronic acid were reacted with Cs_2CO_3 under the irradiation of a 370 nm LED at room temperature. The reductive coupling product **3** was observed in a 21% NMR yield in toluene (Table 1, entry 1). However, no boronated

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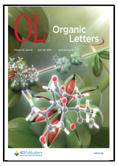

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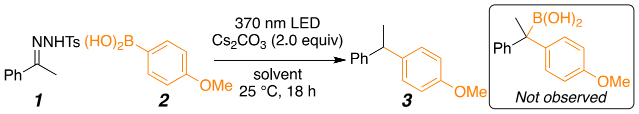
Table 1. Optimization of Diarylethane Formation



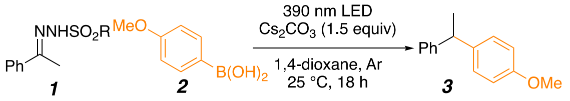
entry	RB(OH)$_2$ equiv	solvent (M)	yield (%)[a]
1	1.5	PhMe (0.1)	21
2	1.5	PhCF$_3$ (0.1)	32
3	1.5	MeCN (0.1)	12
4	1.5	THF (0.1)	40
5	1.5	CHCl$_3$ (0.05)	50
6[b]	1.5	EtOAc	56
7	1.5	1,4-dioxane (0.05)	83 (73)[c]
8	1.5	1,4-dioxane (0.05)	63[d]
9[e]	3.0	1,4-dioxane (0.05)	(87)[c]
10[e]	3.0	1,4-dioxane (0.1)	52 (55)[c]

[a] CH$_2$Br$_2$ (1 equiv) was used as an internal standard for yield determination via ^{1}H NMR. [b] Methyl-4-nitrobenzoate used as an internal ^{1}H NMR standard. [c] Isolated yield in parentheses. [d] Reaction performed while exposed to the ambient atmosphere. [e] 3.0 equiv of Cs$_2$CO$_3$ used.

intermediate was observed in this reaction. It is plausible that the transient diarylmethyl boronic acids rapidly underwent protodeboronation. Nevertheless, it is noteworthy that diarylmethane and ethane compounds possess synthetic utility and have found applications as drug candidates.[10,11] Consequently, the optimization of diarylalkane synthesis was pursued. The use of trifluorotoluene, acetonitrile, tetrahydrofuran, and chloroform did not provide a significant improvement (entries 2−5). Fortunately, diaryl **3** was formed in 83% NMR yield (73% isolated yield) when using 1,4-dioxane (entry 6). Increasing the quantities of boronic acid and base from 1.5 to 3.0 equiv provided up to 87% isolated yield (entry 8), but increasing the concentration from 0.05 to 0.1 M drastically reduced the yield to 55% (entry 9).

Next, we investigated the effect of different sulfonyl groups on the conversion of the hydrazone to a diazoalkane. Utilizing a *p*-toluyl sulfonyl as the leaving group resulted in a commendable 73% yield (Table 2, entry 1), while transforming the toluene methyl group to a *t*-butyl group or increasing steric pressure, as found in a mesityl sulfonyl group, led to a somewhat reduced yield (entries 2 and 3). However, *p*-nitrophenyl sulfonyl groups produced no reaction, presumably due to issues with greatly decreased solubility (entry 4). Importantly, mesyl hydrazone gave no reaction because it lacked a chromophore for the 390 nm LED illumination (entry 5). The mesyl hydrazone was competent for Barluenga coupling, though, as heating it to 110 °C in the presence of **2** did provide **3** in 73% yield via thermal activation.[12,13]

Table 2. Screen of Hydrazone Sulfonyl Groups



entry	R	isolated yield (%)
1	*p*-toluyl	73
2	*p*-*t*-BuC$_6$H$_4$	65
3	mesityl	67
4[a]	*p*-NO$_2$C$_6$H$_4$	no reaction
5	Me	no reaction

[a] 2.0 equiv of Cs$_2$CO$_3$ was used.

We also explored the impact of different light sources on the reaction.[12] Interestingly, the use of blue light with a wavelength of 456 nm resulted in no reaction, while near-UV (370 nm) or violet (390 nm) light sources proved to be effective in yielding the desired product. Furthermore, white light from a compact fluorescent bulb, which encompasses a broader spectrum that includes the violet light range, generated the desired product, albeit in decreased amounts. These results could be explained by the light absorption of the hydrazone in the presence of a variety of additives (Figure 1). An insoluble inorganic base, K$_2$CO$_3$, did not induce any change in the spectrum. Mixing **1a** and Cs$_2$CO$_3$ in 1,4-dioxane showed a red shift of around 70 nm, which corresponded to König's observations.[6,13] However, the addition of a soluble organic base, DBU, provided a very similar shift to that of Cs$_2$CO$_3$ as Plaza and Valdés reported.[8] The strength of the base is important, as Hunig's base provided no shift on its own. Cs$^+$ alone is not responsible for the red shift, as CsClO$_4$, while soluble, did not appreciably alter the absorbance. Together these data support the hypothesis that a soluble base is necessary for the shift in the hydrazone's absorbance into the near-UV region and that an aryl sulfonyl is needed to provide enough conjugation to absorb a photon in that frequency range.

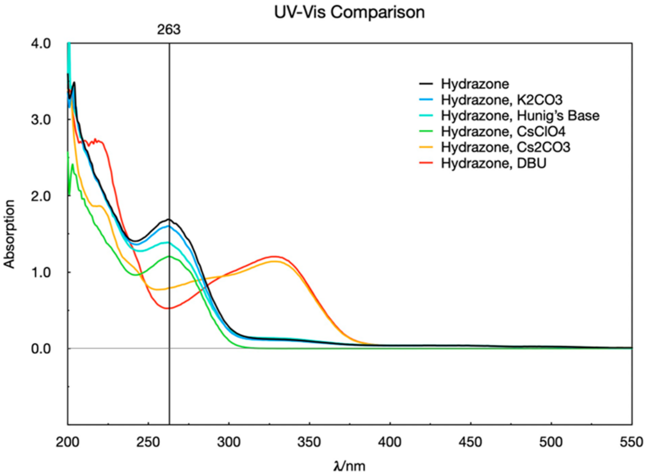


Figure 1. Absorption of hydrazone with additives shows a soluble base-induced shift. Hydrazones were present at 0.0001 M, with 2 equiv of additives in MeCN as the solvent.

Using the most effective reaction conditions, a variety of boronic acids and hydrazones were examined to form diarylalkyl products. Boronic acids with electron-donating groups such as OMe, N(Me)$_2$, and CH$_3$ gave diaryl alkanes in acceptable yields (**3a**−**3e**, Figure 2), while boronic acids with electron-withdrawing groups such as CF$_3$ resulted in no reaction (**3f**). Poor results were also seen when using a heteroaromatic boronic acid (e.g., **3g**), presumably due to the sluggishness of the 1,2-shift during the reaction for electron-deficient heteroaromatics or the presence of a Lewis basic nitrogen. Changing the aromatic hydrazone substituent to 4-methoxyphenyl or 2-thienyl generated the corresponding diaryl alkanes in good yield (**3h**, **3i**). Changing the hydrazone methyl to hydrogen or a cyclic system provided the expected products in good yields (**3j**−**3l**). We note the correspondence of these

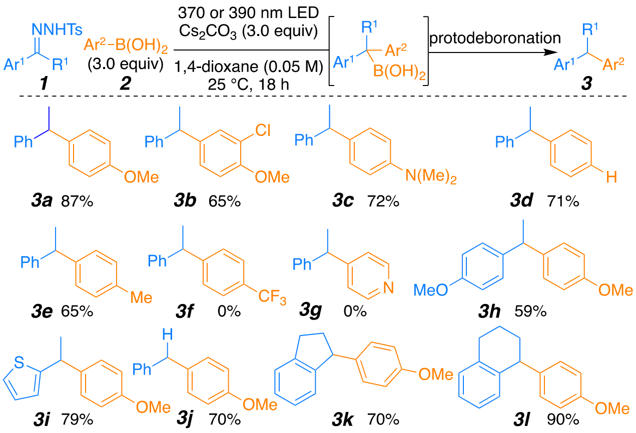
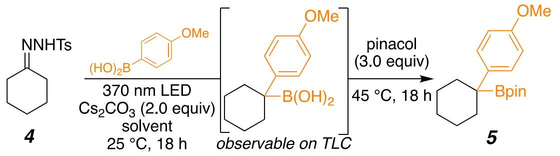


Figure 2. Diarylalkane scope. Yields are the averages of at least two trials.

results to published efforts.[8,9] It is also important to note that while neutral aromatic boronic acids were functional (see **3d**), electron-deficient aryl boronic acids were not. Additionally, a functional group tolerance screen[14] showed that Lewis basic functionality had significant incompatibility with the reaction.[12]

After the synthesis of diaryl alkanes, we moved our attention back to boronated intermediates obtainable from alkyl–aryl systems. However, when cyclohexyl hydrazone was used under the optimized conditions, no expected product formed (Table 3, entry 1). Consequently, reoptimization for the alkyl–aryl system was explored. No significant improvement occurred using nonpolar solvents or some polar solvents such as DMF and DMA (entries 2–7). Interestingly, the use of acetonitrile and ethyl acetate as solvents improved the NMR yield to 70 and 72%, respectively (entries 8 and 9). These compounds augment the substrate scope for the photoactivated Barluenga coupling for hydrazones. Use of 390 nm light did not promote the coupling in these less-conjugated hydrazones.

Table 3. Optimization of Monoaryl Boronate Formation



entry	$RB(OH)_2$ equiv	solvent (M)	NMR yield (%)[a]
1	2.0	1,4-dioxane (0.05)	trace
2	2.0	PhMe (0.1)	(6)[b]
3	2.0	$CHCl_3$ (0.1)	3
4	2.0	CH_2Cl_2 (0.1)	29
5	2.0	THF (0.1)	11
6	2.0	DMF (0.1)	trace
7	3.0[c]	DMA (0.2)	trace
8	2.0	MeCN (0.1)	70 (54)[b]
9	2.0	EtOAc (0.1)	72

[a] CH_2Br_2 was used as an internal standard for NMR yield. [b] Isolated yield. [c] 3.0 equiv of Cs_2CO_3 and 5.0 equiv of pinacol were used.

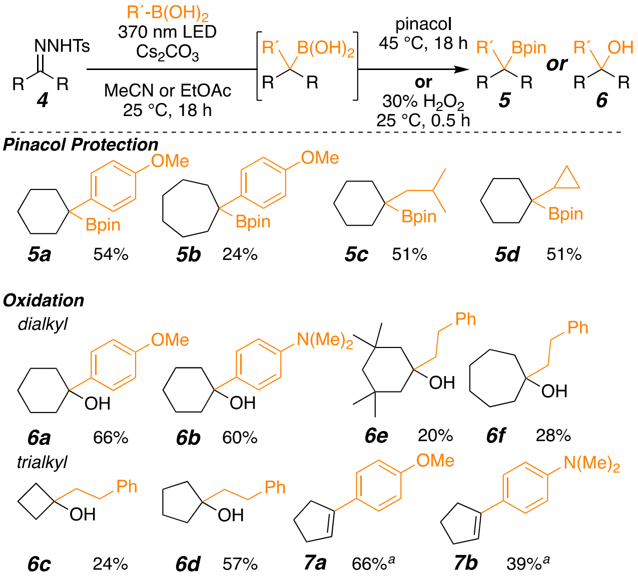


Figure 3. Monoaryl and all alkyl boronate-derived products. [a] indicates treatment with 1.0 equiv of TFA after oxidation was complete.

Versatile transformations of the tertiary boronic acid products were examined (Figure 3). Esterification with pinacol generated Bpin **5a** in 54% yield. Oxidation of the boronic acid intermediates generated tertiary alcohol **6a** in 66% yield. To further investigate the tolerances of this transformation, we then turned our attention to alkyl boronic acids to produce all alkyl products. Though the 1,2-shift necessary for C–C bond formation is slower for alkyl than for aryl groups, the cyclopropyl and alkyl nucleophiles led to the anticipated trialkyl boronic acid intermediates. Pinacol protection formed the boronic esters in moderate to useful yields (**5a**–**5d**). In addition to isolating tertiary alcohols **6a**–**6f** from peroxide-based oxidation, cyclic arylalkenes **7** could be produced by adding a small amount of TFA to the reaction mixture once complete, generating these products directly from hydrazones and boronic acids in a single procedure.

In conclusion, the synthesis of diaryl alkanes and tertiary alkyl organoboronates has been made possible at room temperature via photoactivated conversion of aryl sulfonyl hydrazones to diazo compounds with soluble bases. A soluble base is needed for an absorbance shift of tosyl hydrazones into the near-UV region. The role of Cs^+ in solubilizing an inorganic base has been clarified in this work, along with the structure of the chromophore involved in photon absorbance, suggesting that at least partial deprotonation of an arylsulfonyl hydrazone is necessary for the photoreaction. Using aromatic hydrazones and aromatic boronic acids resulted in rapid deboronation because of the instability of dibenzylic boron intermediates. On the other hand, alkyl hydrazones allowed the isolation of the tertiary pinacolate boronates (after ester formation) or alcohols (after oxidation) in good yields.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c00873.

Complete experimental procedures and compound characterization data (PDF)

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Author Contributions

P.-K.P.: Investigation, data acquisition, writing−original draft, and conceptualization. C.P.D. and Z.D.: Investigation, data acquisition, writing−review and editing, and conceptualization. J.A.M: funding acquisition, project administration, writing−review and editing, and conceptualization.

Author Contributions

§P.-K.P., C.P.D., and Z.D. contributed equally.

Notes

The authors declare no competing financial interest.

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