Organic LETTERS

Letter

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Development of the Direct Suzuki–Miyaura Cross-Coupling of Primary *B*-Alkyl MIDA-boronates and Aryl Bromides

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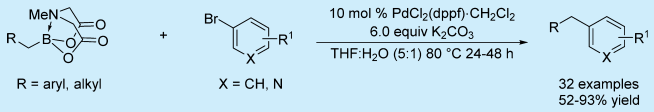
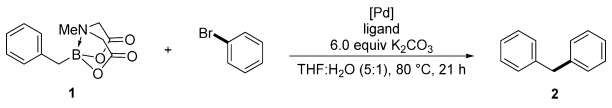
Supporting Information

ABSTRACT: The development of a palladium-catalyzed sp^3–sp^2 Suzuki–Miyaura cross-coupling of *B*-alkyl-*N*-methyliminodiacetyl (*B*-alkyl MIDA) boronates and (hetero)aryl bromides is reported. This transformation is tolerant of a variety of functional groups (F, NO_2, CN, Cl, $COCH_3$, and CHO). *B*-Alkyl MIDA boronates allow an efficient cross-coupling reaction directed toward the synthesis of unsymmetrical methylene diaryls as well as alkylated arenes in good to excellent yields.



The high functional group tolerance,[1] stability,[2] and accessibility of boronic acids[3,4] have made the Suzuki–Miyaura reaction a potent tool in the synthesis of a wide range of challenging targets.[5] There has been comprehensive work on the development of an efficient sp^2–sp^2 Suzuki–Miyaura cross-coupling reaction;[6] however, there have been far fewer reports on sp^3–sp^2 or sp^3–sp^3 variants.[3,7] *B*-Alkyl-9-BBN derivatives are the most commonly employed reagents for sp^3–sp^2 Suzuki–Miyaura cross-couplings.[2,3] However, difficulties with isolation and functional group incompatibility of *B*-alkyl-9-BBN reagents limit their widespread use.[3a,8,9]

Table 1. Optimization of Reaction Conditions



1 2

entry	[Pd] (mol %)	ligand (mol %)	% conversion[a]	% yield[a]	% selectivity[b]
1	$Pd(OAc)_2$ (10)	PPh_3 (20)	73	42	58
2	$Pd(OAc)_2$ (10)	S-Phos (20)	81	24	30
3	$Pd(PPh_3)_4$ (10)		99	49	50
4	$PdCl_2$ (10)	dppf (20)	71	25	35
5	none		0	0	0
6[c]	PdCl(dppf)·CH_2Cl_2 (10)		63	39	62
7[d]	PdCl(dppf)·CH_2Cl_2 (10)		60	55	92
8	PdCl(dppf)·CH_2Cl_2 (10)		99	89	89
9[e]	PdCl(dppf)·CH_2Cl_2 (10)		60	30	50

[a]Yields obtained by GC vs calibrated internal standard (naphthalene). [b]% selectivity = (% yield/% conversion) × 100. [c]3.0 equiv of K_2CO_3 was used. [d]Reagent-grade THF and distilled H_2O used. [e]Toluene was used in place of THF.

In contrast to the challenges associated with manipulation of *B*-alkyl-9-BBN reagents, most *B*-alkyl boronic acids are stable under ambient conditions and can be isolated through crystallization or chromatography.[10] However, boronic acids give rise to side reactions (e.g., protodeborylation and β-hydride elimination) under Suzuki–Miyaura conditions, which is why superstoichiometric loadings are often required.[4,9,11] Tetrahedral boronates inhibit the undesired deborylation by coordinative saturation of the normally vacant p-orbital of boron. The most effective tetrahedral boronates that inhibit the undesired decomposition pathways are the potassium trifluoroborates (RBF_3K) and *N*-methyliminodiacetyl boronates (RB[MIDA]).[12]

Primary and secondary sp^3-RBF_3K species have been successfully applied in the Suzuki–Miyaura reaction with various electrophilic partners,[13] whereas sp^3-MIDA boronates have remained underdeveloped with pinene-derived iminodiacetic acid (PIDA) boronates as notable exceptions.[14] Herein, we demonstrate that primary sp^3-MIDA boronates successfully participate in the Suzuki–Miyaura cross-coupling forming unsymmetrical methylene diaryls and alkylated arenes which are important structural units found in a number of pharmaceutically relevant compounds.[15]

B-Benzyl MIDA boronate **1** and bromobenzene served as prototypical coupling partners. A variety of palladium catalysts and ligands were screened, and their cross-coupling perfomance was measured via internally calibrated gas chromatography (Table 1).

Moderate to excellent conversion ratios were observed in every example. However, the selectivity of the reaction was found to vary. The dialkylbiarylphosphine ligand S-Phos,[16] in combination with $Pd(OAc)_2$, performed poorly in the coupling reaction, providing only 24% yield and 36% selectivity[17] for the desired cross-coupling product (entry 2).[18] $Pd(PPh_3)_4$ afforded

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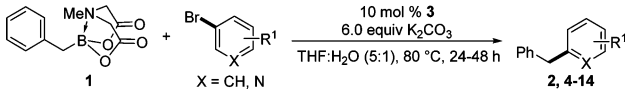
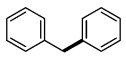
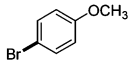
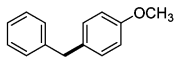
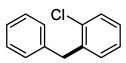
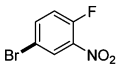
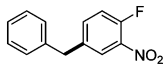
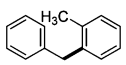
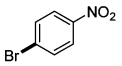
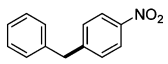
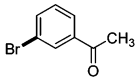
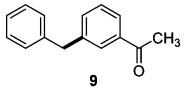
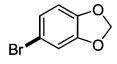
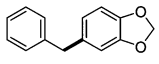
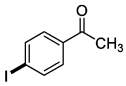
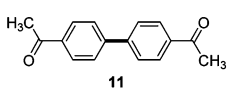
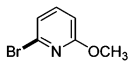
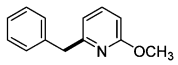
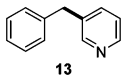
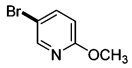
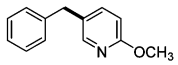
Table 2. Suzuki–Miyaura Cross-Coupling of 1[a]



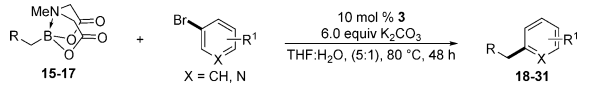
entry	arylBr	product	% yield
1		 **2**	77
2[b]		 **4**	74
3		 **5**	85
4		 **6**	84
5[b]		 **7**	77
6		 **8**	68
7		 **9**	93
8[b]		 **10**	72
9[c]		 **11**	41
10[d]		 **12**	52
11[d]		 **13**	78
12[d]		 **14**	67

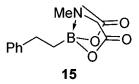
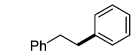
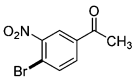
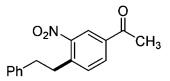
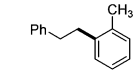
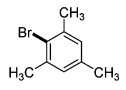
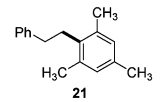
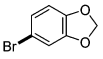
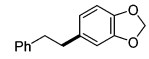
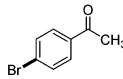
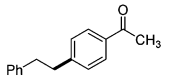
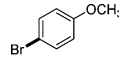
[a]All reactions performed with 1.1 equiv of **1** and 1.0 equiv of arylBr. [b]48 h. [c]No cross-coupled product was observed. [d]1.3 equiv of **1** was used.

high conversion but afforded only 50% selectivity for diphenylmethane **2** (entry 3). The facile oxidative addition of $Pd(OAc)_2$/S-Phos and $Pd(PPh_3)_4$ to the C–Br bond of bromobenzene resulted in more deleterious side reactions, including protodehalogenation, that afforded a reduced assay yield. Commercially available $PdCl_2(dppf)\cdot CH_2Cl_2$ (**3**, entry 8) proved to be the optimal catalyst, delivering excellent conversion and yield after 21 h (entry 8).[19] High selectivity for the desired product could be due to the slower rate of oxidative addition as compared to $Pd(PPh_3)_4$ and $Pd(OAc)_2$/S-Phos.[20] The efficiency of **3** in the presence of other bases was also tested to uncover the optimal set of reaction conditions.[1,20] A screen of inorganic bases confirmed K_2CO_3 to be optimal for this method (see the Supporting Information).[21−23]

We then sought to expand the scope of aryl halide partners. As illustrated in Table 2, the cross-coupling of **1** with a number of aryl bromides resulted in the desired benzylated arenes in good yields. The electronic nature of the aryl bromides had an impact on the overall performance of the cross-coupling reaction. Electron-poor aryl bromides afforded higher yields after 24 h, whereas electron-rich bromides required 48 h to proceed to completion (entries 6 and 7). In addition, bromopyridines (entries 10−12) required extended reaction

Table 3. Cross-Coupling of Unfunctionalized Primary MIDA Boronates[a]



entry	MIDA boronate	arylBr	product	% yield
1	 **15**		 **18**	77
2	**15**		 **19**	78
3	**15**		 **20**	83
4	**15**		 **21**	73
5[b]	**15**		 **22**	71
6	**15**		 **23**	92
7[b]	**15**		**24**	54
8	**15**		**25**	78
9[d]	**15**		**26**	54
10	**16**		**27**	69
11	**16**		**28**	91
12[c]	**16**		**29**	67
13	**17**		**30**	79
14	**17**		**31**	82

[a]All reactions performed with 1.1 equiv of MIDA boronate and 1.0 equiv of arylBr. [b]90 h. [c]90% conversion. [d]1.5 equiv of **15**.

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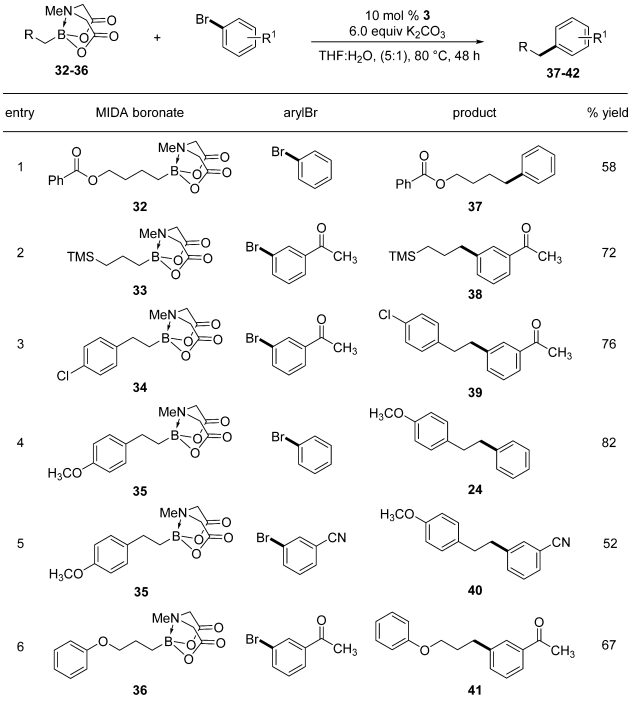
Table 4. Cross-Coupling of Functionalized Primary MIDA Boronates[a]



[a]All reactions performed with 1.1 equiv of MIDA boronate and 1.0 equiv of arylBr.

times and increased loading of **1**. The requirement for the higher loading of **1** can be attributed to the coordination of the Lewis basic pyridine to the Pd-center.[18c]

The nature of the halide also proved to be crucial to the outcome of the cross-coupling reaction. Aryl chlorides were unreactive under our reaction conditions, resulting in the recovery of starting material. This observation is corroborated by the finding that bromo-2-chlorobenzene undergoes cross-coupling selectively at the bromide position in high yield (Table 2, entry 3).[24] Aryl iodides proved to be extremely reactive, producing the undesired homocoupled product in 41% yield with no desired cross-coupled product observed (Table 2, entry 9). Therefore, the reactivity trend is I > Br ≫ Cl, which is similar to that observed for potassium trifluoroborates.

Other nonactivated alkyl MIDA boronates were tested with various coupling partners. The cross-coupling reaction of unactivated primary alkyl MIDA boronates (**15**–**17**) with aryl bromides was found to require extended reaction times (48 h). Even upon prolonged exposure, the desired alkylated products were obtained in good yields. The diminished reactivity of *B*-*n*-alkyl MIDA boronates (**15**–**17**) is consistent with their reduced transmetalation potential (e.g., **1**).[5,20b,25]

We have also evaluated several primary MIDA boronates (**32**–**36**) containing alkyl ether, aryl ether, ester, trialkylsilyl, and aryl chloride functional groups.[26] These functionalized MIDA boronates were found to be effective cross-coupling partners with aryl bromides, delivering the respective alkylated arenes in good yields. The ester containing MIDA boronate **32** chemoselectively cross-coupled with bromobenzene without any hydrolysis byproduct.

In summary, we have demonstrated the use of primary *B*-alkyl-MIDA boronates in intermolecular sp^3–sp^2 Suzuki–Miyaura cross-coupling with (hetero)aryl bromides. This development has allowed the efficient synthesis of unsymmetrical methylene diaryls and alkylated arenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and physical properties of compounds (^{1}H, ^{11}B, ^{13}C, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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