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N-Arylated Sulfoximines as Cross-Coupling Building Blocks

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Abstract. The application of borylated *N*-aryl sulfoximines as newly designed synthetic building blocks in Suzuki-type cross coupling reactions offers rapid access to a wide range of *N*-biaryl derivatives with potential relevance for medicinal chemistry and crop protection in good to excellent yields (up to 98%).

Keywords: building block; MIDA boronate; Miyaura borylation; sulfoximine; Suzuki cross-coupling

In 2011 Roughley and Jordan reported the results of "An Analysis of Reactions Used in the Pursuit of Drug Candidates", and they found that the Suzuki cross-coupling reaction accounted for 40% of all C–C bond forming reactions, thereby being the single most often applied transformation within this category.[1,2] As highlighted by others, Suzuki's method - in conjunction with other metal-catalyzed sp^2-sp^2 couplings - has become so powerful that the number of published "flatland"[3] molecules with relevance for medicinal chemistry has consistently increased during the past decades.[4] In addition to chemical advances, technological progress has also contributed to this development because many of such cross-coupling reactions are amenable to automated parallel synthesis[5] and continuous flow.[6] In all of those processes, "ready-to-couple" molecular building blocks play a central role because they provide rapid access to a large number of derivatives in a most efficient manner. A particularly elegant study along these lines was reported by Burke and co-workers,[7] who demonstrated the use of *N*-methyliminodiacetic acid (MIDA) boronates[8] for the automated synthesis of a large variety of structurally diverse organic small molecules. The high synthetic value of such MIDA boronates and their advantage compared to other boronate esters is a result of their high chemical stability and chemoselectivity[8g], which allow for both an extensive modification of MIDA boronates while leaving the boron-containing site intact as well as boron-selective transformations of polyboron compounds.[8a,9]

In the context of our research program on sulfur chemistry we recently introduced sulfoximidoyl-containing MIDA boronates **1** and demonstrated their cross-coupling potential for providing biaryl sulfoximines with free NH groups.[10-12] The latter products were regarded as analogs of methyl sulfones. Noting the importance of compounds with N-bound polar substituents, we identified MIDA boronates **2** as interesting building blocks.[12] Cross-couplings of such molecules would allow accessing compounds with N-sulfoximidoyl groups, which could prove useful as sulfone amide replacements.[14-16] Considering the pronounced functional group tolerance in Suzuki cross-couplings with MIDA boronates,[17] a late-stage functionalization[18] of promising drug candidates could be envisaged with compounds of type **2**. Our approach towards a range of such building blocks and a summary of their cross-coupling behavior is presented here.

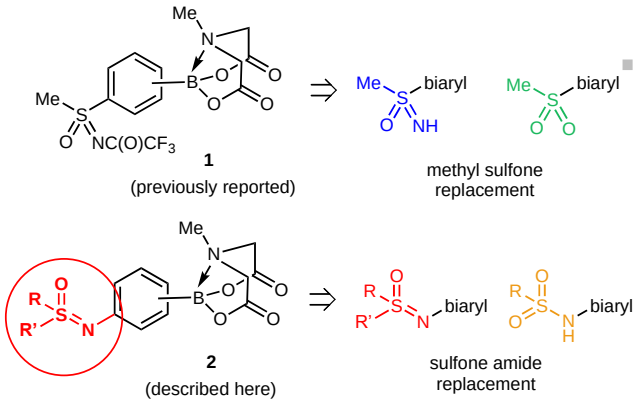

Figure 1. MIDA boronates with sulfoximidoyl substituents.

As first specific target, MIDA boronate **2a** having a *para*-connected N-bound *S*-methyl *S*-phenyl sulfoximidoyl unit was selected. Initial attempts to use standard N-arylation protocols[16] starting from halo-substituted analogs **3** and *N*H-sulfoximine **4a** failed [Scheme 1, (a)]. Neither palladium nor copper or iron catalysis proved effective. Also the second approach, trying to use bisboronic acid ester **5** in combination with **4a** under Chan-Lam coupling conditions[16e,19] remained unsuccessful [Scheme 1, (b)]. Finally, an N-arylation/Miyaura borylation strategy proved applicable [Scheme 1, (c)]. It

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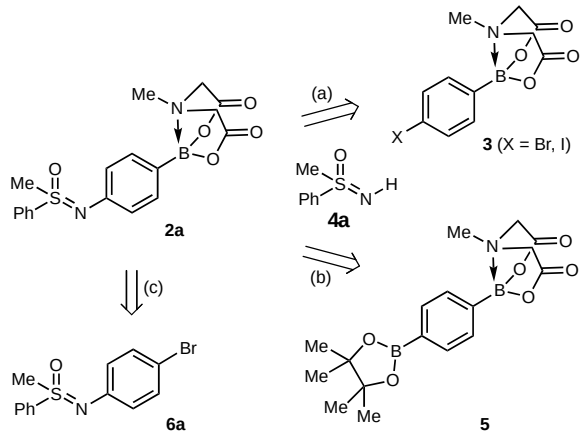
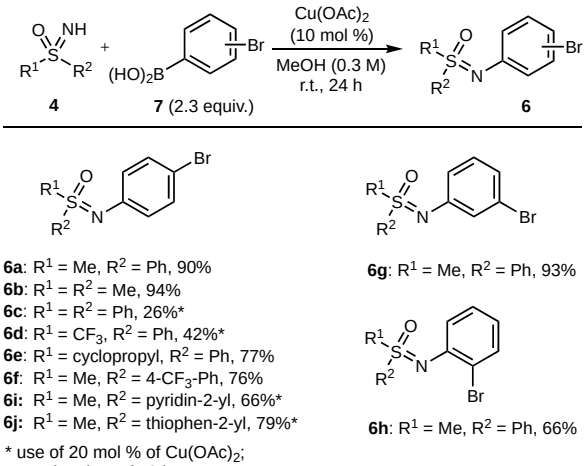
proceeded via *N*-aryl sulfoximine **6a** and involved two sequential metal-catalyzed cross-coupling reactions starting from *N*H-sulfoximine **4a** and 4-bromophenyl boronic acid (**7a**) (for details, see below).[20]



Scheme 1. Strategies for synthesizing MIDA boronate **2a**.

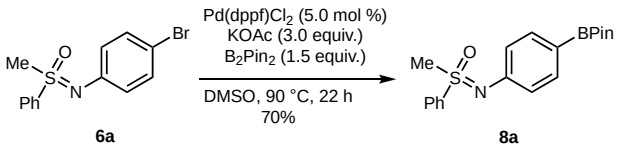
After having established a reaction path towards MIDA boronate **2a**, each synthetic step was reevaluated and generalized by applying substrate variants. First, N-arylations of *N*H-sulfoximines with bromophenyl boronic acids (**7**) were investigated (Scheme 2). Under copper catalysis [with 10 mol % of $Cu(OAc)_2$], the cross coupling of sulfoximine **4a** and **7a** provided **6a** in 90% yield. Also *S*,*S*-dimethyl sulfoximine (**4b**) and **7a** reacted well, leading to **6b** in 94% yield. The analogous coupling of *S*,*S*-diphenyl sulfoximine (**4c**) with **7a** proved challenging, and even with 20 mol % of $Cu(OAc)_2$ and after extending the original 24 h reaction time to 48 h, product **6c** was obtained in only 26% yield. Substituted *S*-alkyl *S*-aryl sulfoximines afforded the corresponding N-arylated products **6d-f** in yields ranging from 42% to 77%. Couplings of **4a** with 3-bromophenyl boronic



Scheme 2. Copper-catalyzed N-arylations of *N*H-sulfoximines **4** with bromophenyl boronic acids **7a-c**.

acid (**7b**) and 2-bromophenyl boronic acid (**7c**) gave **6g** and **6h** in 93% and 66% yield, respectively.

Next, borylations of aryl bromides **6** were studied. Readily available **6a** was used as representative substrate. Under the classical Miyaura conditions with B_2Pin_2 as borylating agent and a palladium catalyst,[21] **8a** was obtained in 70% yield (Scheme 3).



Scheme 3. Palladium-catalyzed borylation of **6a** with B_2Pin_2.

An apparently rapid product degradation and the fact that the conversion of **8a** into **2a** required additional deprotection/protection steps, stimulated the search for alternative pathways. Molander's method with tetrahydroxydiboron [$B_2(OH)_4$] as borylating agent appeared particularly attractive because it directly led to boronic acids, which could further be converted to boronates and related products by reactions with diacids and diols (Table 1).[22] Already the first attempts were successful. Under nickel catalysis and with *N*-methylimidodiacetic acid (**10**, MIDA) as capping agent in the second step, **6a** reacted via boronic acid **9a** to give **2a** in 86% yield (Table 1, entry 1). Lowering the originally used 5 mol % of $NiCl_2$(dppp) (combined with 10 mol % of PPh_3) to 1 mol % of catalyst (with 3 mol % of PPh_3) led to incomplete conversion of **6a**, even after extending the initial reaction time of 3 h to 9 h (Table 1, entry 2). A screening of various palladium catalysts (Table 1, entries 3-8) showed that a combination of Pd(dppf)Cl_2 and XPhos was optimal in terms of catalyst performance and efficiency. Thus, with only 1 mol % of palladium and 3 mol % of ligand, MIDA boronate **2a** was obtained with high purity in 80% yield (Table 1, entry 7).[23] Reacting in-situ formed **9a** with pinacol (**11**) and neopentyl glycol (**12**) afforded the respective boron reagents in yields of 75% and 78%, respectively (Table 1, entries 9 and 10). In particular the former product proved difficult to purify. The attempt to directly prepare the respective BF_3K salt of **9a** was unsuccessful (Table 1, entry 11).

Having established the optimal conditions for the conversion of **6a** into **2a** (Table 1, entry 7), the substrate scope with respect to the substituents on sulfur and the position of the bromo group on the arene was examined. In general, the transformations were smooth, and the corresponding MIDA boronates **2** were obtained in good yields (Scheme 4). The only exception was the reaction sequence starting from *S*,*S*-dimethyl sulfoximine **6b**, which appeared to be hampered by the instability of the respective boronic acid under the conditions of the second step. Consequently, pinacol (**12**) was used instead of

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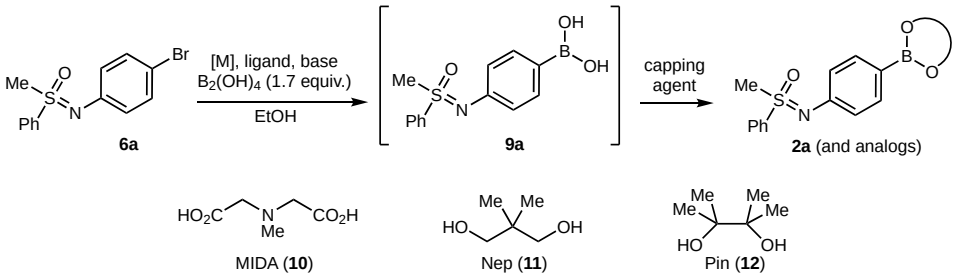
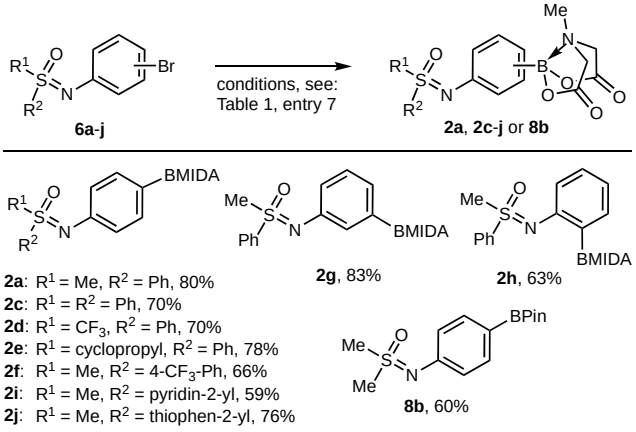
Table 1. Optimization of the conversion of **6a** into **2a** via boronic acid **9a**.



Entry	[M] (mol %)	Ligand (mol %)	Base (equiv.)	*T* [°C]	*t* [h]	Caping agent	Yield [%]
1	$NiCl_2$(dppp) (5.0)	PPh_3 (10)	DIPEA (3.0)	50	3	MIDA[a]	86
2	$NiCl_2$(dppp) (1.0)	PPh_3 (3.0)	DIPEA (3.0)	50	9	MIDA[a]	-[b]
3	$Pd(OAc)_2$ (5.0)	XPhos (15)	KOAc (3.0)	80	16	MIDA[a]	89
4	$Pd_2(dba)_3$ (2.5)	XPhos (15)	KOAc (3.0)	80	14	MIDA[a]	83
5	$Pd(OAc)_2$ (2.5)	XPhos (7.5)	KOAc (3.0)	80	18	MIDA[a]	-[b]
6	Pd(dppf)Cl_2 (2.5)	XPhos (7.5)	KOAc (3.0)	80	18	MIDA[a]	64
7	**Pd(dppf)Cl_2 (1.0)**	**XPhos (3.0)**	**KOAc (3.0)**	**80**	**18**	**MIDA[a]**	**80**
8	$Pd_2(dba)_3$ (0.5)	XPhos (3.0)	KOAc (3.0)	80	18	MIDA[a]	-[b]
9	Pd(dppf)Cl_2 (1.0)	XPhos (3.0)	KOAc (3.0)	80	18	Nep[c,d]	75[e]
10	Pd(dppf)Cl_2 (1.0)	XPhos (3.0)	KOAc (3.0)	80	18	Pin[c,f]	78
11	Pd(dppf)Cl_2 (1.0)	XPhos (3.0)	KOAc (3.0)	80	18	KHF_2[g]	-[e]

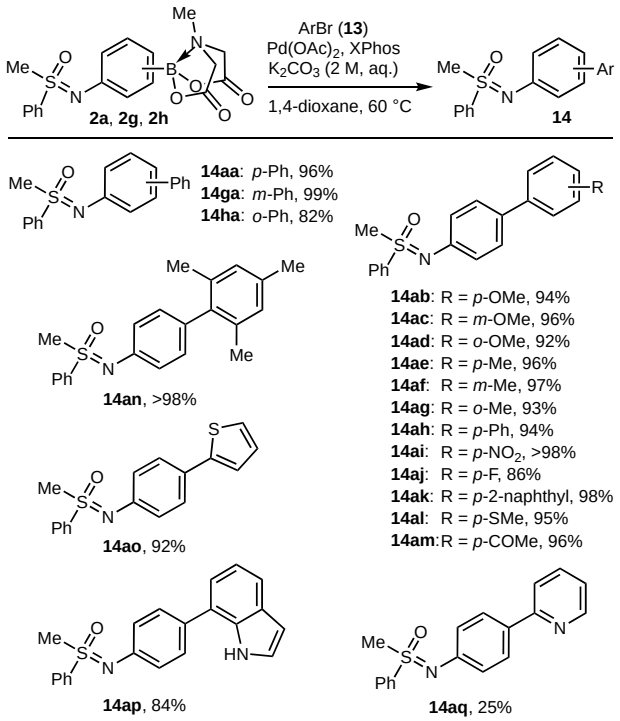
[a] Reaction conditions: MIDA (1.5 equiv.), DMSO, toluene, dean-stark trap, 135 °C, 8 h.
[b] Incomplete conversion.
[c] Reaction conditions: Diol (2.0 equiv.), DCM, r.t.
[d] Nep = neopentyl glycol (**11**).
[e] Difficult purification.
[f] Pin = pinacol (**12**).
[g] Reaction conditions: KHF_2 (3.5 equiv., 4.5 M in H_2O), MeOH, 0 °C.



Scheme 4. Conversions of *N*-aryl sulfoximines **6** into MIDA boronates **2** by palladium-catalyzed borylations with $B_2(OH)_4$ and subsequent ligand exchange with MIDA [or pinacol (**12**) for **8b**].

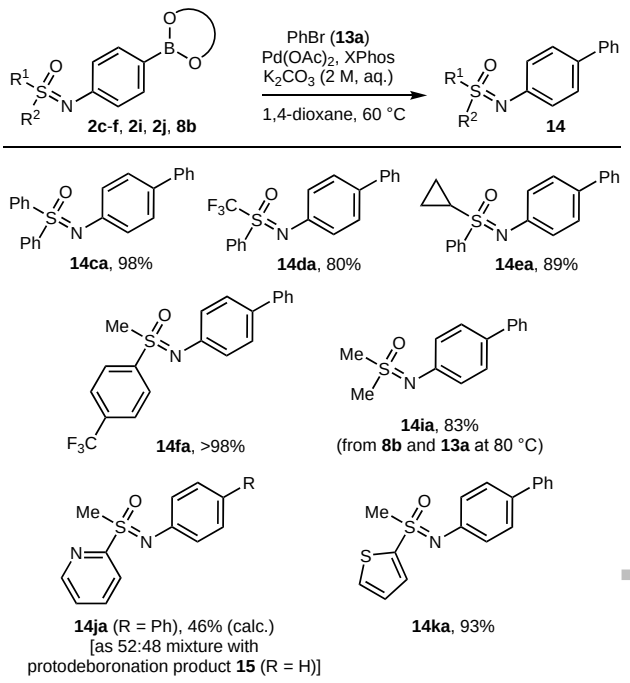
MIDA providing aryl boronic acid pinacol ester **8b** in 60% yield.[13]

The cross-coupling potential of MIDA boronates **2** was investigated next.[17] Scheme 5 summarizes the results obtained by combining **2a**, **2g**, and **2h** with a series of aryl bromides **13** on a 0.2 mmol scale. The catalyst system consisted of $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), K_2CO_3 (5 equiv. as degassed 2 M aq. solution), and 1,4-dioxane, which was kept at 60 °C for 24 h. In general, the yields of the resulting arylated products **14** were high (>90%). Neither steric nor electronic effects were noticable. 2-Bromothiophene (**13o**), 7-bromoindole (**13p**), and 2-bromopyridine (**13q**) were chosen as representative heteroaryl bromides. Whereas in couplings with **2a** the first two compounds provided the corresponding products in high yields (**14ao**: 92% and **14ap**: 84%), the latter afforded **14ap** in only 25% yield. Concomitant, the last reaction led to significant amounts of protodeboronated **2a**, which presumably resulted from an interference of the coupling by coordination of the pyridine nitrogen to the metal catalyst.[8c]



Scheme 5. Cross couplings of MIDA boronates **2a**, **2g**, and **2h** with aryl bromides **13**.

Next, MIDA boronates **2c**-**f**, **2i** and **2j** were applied in Suzuki cross-couplings with boronic acid pinacol ester **8b** aiming to evaluate the effect of the S-substituents on the catalyst efficiency (Scheme 6). Phenyl bromide (**13a**) was selected as representative coupling partner, and the catalyst system was kept identical to the one utilized before (Scheme 5). Also with those boron reagents the transformations proceeded well affording the corresponding products in high yields. Compared to the reactivity of the MIDA boronates, pinacol ester **8b** was less reactive as indicated by the reaction temperature, which needed to be raised from 60 °C to 80 °C for achieving reactivity. Then, however, the yield of the resulting product (**14ia**) was high (83%) as well. Pyridyl-containing MIDA boronate **2i** did not react under the standard conditions. However, by applying a protocol of Burke for the coupling of pyridyl-containing MIDA boronates,[8c] product **14ja** was obtained, albeit only in an amount corresponding to a 46% yield as calculated from the 52:48 mixture with the protodeboronation product *N*-phenyl-*S*-methyl-*S*-(pyridin-2-yl)sulfoximine (**15**).



Scheme 6. Cross couplings of MIDA boronates **2c-f, 2i**, **2j** and boronic acid pinacol ester **8b** with phenyl bromide (**13a**).

In summary, we prepared shelf-stable MIDA boronates with N-bound sulfoximidoyl groups, which can be applied as building blocks in Suzuki-type cross-coupling reactions.[24] We envisage their use in automated parallel synthesis and continuous flow leading to libraries of molecules for high-throughput screenings.

Experimental Section

General method for the synthesis of MIDA boronates 2

N-(Bromophenyl)sulfoximine **6** (1.00 mmol), $Pd(dppf)Cl_2$ (7.32 mg, 0.01 mmol, 1.0 mol %), XPhos (14.3 mg, 0.03 mmol, 3.0 mol %), $B_2(OH)_4$ (152.00 mg, 1.70 mmol, 1.7 equiv.) and KOAc (294.00 mg, 3.00 mmol, 3.0 equiv.) were placed in a dry Schlenk tube equipped with a magnetic stirring bar and dissolved in absolute EtOH (6.6 mL). The reaction mixture was purged with argon for 10 min. before the tube was sealed and heated at 80 °C for 18 h. After this time, full conversion of the starting material was observed (as monitored by TLC). The reaction mixture was cooled to r.t., filtered over a plug of celite (eluting with 100 mL of EtOAc), and the filtrate was evaporated under reduced pressure. The residues were suspended in EtOAc (25 mL) and 1 M aqueous HCl (25 mL). The organic layer was separated and washed with brine. The aqueous layers were extracted with EtOAc (3 x 25 mL each). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting boronic acid **9** was suspended in toluene (42 mL) and DMSO (8.4 mL) and MIDA (**10**, 221 mg, 1.50 mmol, 1.5 equiv.) was added. The resulting mixture was fitted to a dean-stark trap and refluxed at 135 °C for 8 h. Removal of the solvents under reduced pressure afforded MIDA boronate **2**, which was purified by FCC.

General Method for the synthesis of N-arylated sulfoximines 14

In a Schlenk tube equipped with a magnetic stirring bar boronate **2** (0.220 mmol, 1.1 equiv.), $Pd(OAc)_2$ (2.25 mg, 10.0 µmol, 5.0 mol %) XPhos (9.53 mg, 20.0 µmol, 10 mol %) and the - if solid - aryl bromide **13** (0.200 mmol) were suspended in 1,4-dioxane (2.4 mL). (A liquid aryl bromide **13** was added by using a syringe after the tube was sealed.) The tube was placed under argon and sealed with a rubber septum. The mixture was stirred at r.t. for 10 min., and then a 2 M aqueous degassed K_2CO_3 solution (0.500 mL, 1.00 mmol, 5.0 equiv.) was added by syringe, and the mixture was heated at 60 °C for 24 h. After cooling to r.t., the solvents were removed under reduced pressure and the residue was directly subjected to purification by FCC affording N-arylated sulfoximine **14**.

Acknowledgements

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[23] Under these conditions, the use of the analogous aryl iodide of **6a** (with I instead of Br; compound **6i**) led to **2a** in a yield of 60%. Applying the corresponding aryl chloride (**6a** with Cl instead of Br; compound **6j**) resulted in incomplete conversion.

[24] Here, all applied chiral sulfoximines were racemic. For well-established synthetic routes towards enantiopure substrates, which should lead to optically active products, see: S. Dong, M. Frings, H. Cheng, J. Wen, D. Zhang, G. Raabe, C. Bolm, *J. Am. Chem. Soc.* **2016**, *138*, 2166–2169 and references therein.

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N-Arylated Sulfoximines as Cross-Coupling Building Blocks

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