

Manganese-Catalyzed Borylation of Unactivated Alkyl Chlorides

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S Supporting Information

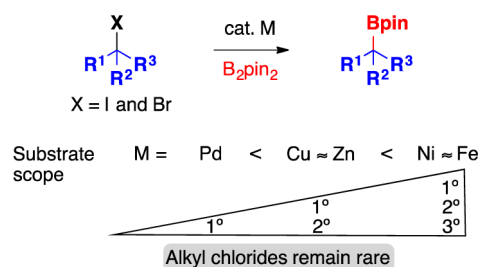
ABSTRACT: The use of low-cost manganese(II) bromide (MnBr_2) and tetramethylethylenediamine (TMEDA) catalyzes the cross coupling of (bis)pinacolato-diboron with a wide range of alkyl halides, demonstrating the first manganese-catalyzed coupling with alkyl electrophiles. This method allows access to primary, secondary, and tertiary boronic esters from the parent chlorides, which were previously inaccessible as coupling partners. The reaction proceeds in high yield with as little as 1000 ppm catalyst loading, while 5 mol % can provide high yields in as little as 30 min. Finally, radical-clock experiments revealed that at 0 °C direct borylation outcompetes alternative radical processes, thereby providing synthetically useful, temperature-controlled reaction outcomes.

Manganese salts represent a particularly attractive option for transition metal catalysis since manganese is one of the most abundant, nontoxic transition metals in the earth's crust.¹ Although manganese has received attention recently for facile C–H activation² and its use in the production of antihypertensive drug irbesartan,³ manganese-catalyzed cross-coupling reactions remain woefully underdeveloped relative to later base metal catalysts such as iron, cobalt, nickel, and copper.^{1a} Manganese bromide can function as the precatalyst for the coupling of aryl or styrenyl iodides with aryl or alkynylstannanes.⁴ For the coupling of aryl halides with Grignard reagents, the aryl halides must be deactivated with electron-withdrawing groups in the *ortho* or *para* positions.⁵ Aryl Grignard reagents also react with 2-chloroaryl ketones in the presence of manganese chloride to afford the corresponding *ortho*-substituted arylketones in good yields without Grignard addition to the ketone.⁶ Vinyl halides couple stereospecifically with aryl Grignard reagents to afford the cross-coupled products in good yield.⁷ Likewise, chloroenynes and chlorodienes couple stereoselectively with alkylmagnesium reagents with a Mn/DMPU-based system.⁸ Manganese can also catalyze carbon–heteroatom bond formation as in the coupling of aryl iodides and thiols.⁹ In all of these examples, however, the electrophile is an sp^2 -hybridized carbon. *To date, manganese-catalyzed coupling of simple alkyl halides has gone undiscovered.* Here, we show manganese(II) salts can function as highly active, mild precatalysts for the borylation of alkyl halides, including chlorides.

With the ubiquity of the Suzuki–Miyaura reaction, aryl boronic acids and esters constitute the foundation of critical building blocks for organic synthesis. With the development of alkyl Suzuki variants,¹⁰ alkyl boronic acids and esters represent

an emerging class of important reagents. As such, new methods for the synthesis of alkyl boronic esters have proven a popular venue for exploring novel transition metal-catalyzed cross-coupling technology (Scheme 1). In the past few years, a

Scheme 1. Current State of Miyaura-Type Borylation of Alkyl Halides



number of examples have emerged employing Pd,¹¹ Ni,^{11b,12} Cu,¹³ Zn,¹⁴ and Fe.¹⁵ The large number of examples in such a short span highlights the critical need and difficulty of creating a general catalytic system. For example, Pd systems function only with primary bromides.^{11a} Copper systems function well with primary and secondary bromides, but only two secondary chloride substrates have been reported^{13a} that do not require in situ Finklestein with tetrabutylammonium iodide (TBAI).^{13b} The Zn-catalyzed borylation allows coupling with primary and secondary iodides and bromides, but only one tertiary substrate, 1-bromoadamantane, was reported.¹⁴ To date, the Ni- and Fe-catalyzed borylation of alkyl bromides and iodides offer the most general strategies for the creation of alkyl boronic esters, allowing access to a range of primary, secondary, and tertiary boronic esters (Scheme 1). However, the direct borylation of unactivated alkyl chlorides remains an unsolved problem. Here, we report a manganese system capable of borylating a wide range of alkyl halides, including unactivated primary, secondary, and tertiary chlorides.

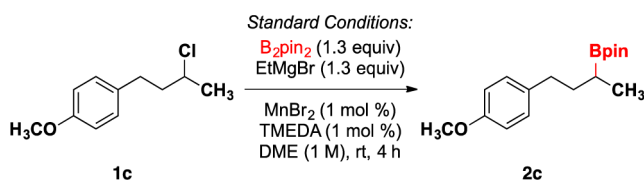
Cognizant of the low reactivity of both Ni and Fe systems toward the borylation of alkyl chlorides, we set out to find a system that worked generally across all alkyl halides. Based on the fact that only starting alkyl chloride remains when using the reported Ni¹² or Fe^{15a} systems, the C–Cl bond cleavage step (or oxidative addition) appeared problematic. We hypothesized that by moving to a “harder” metal, perhaps the enhanced M–Cl bond strength would lead to productive C–Cl bond scission. To test this hypothesis, we moved from Fe to Mn. Strikingly, by replacing 10 mol % Fe(acac)₃ with 5 mol % MnBr₂·4H₂O

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under our previously disclosed conditions,^{15a} the reaction furnished the borylated product in 96% yield. The near-quantitative yield of the Mn-catalyzed example prompted the exploration of the Mn-source, solvent, ligand, and EtMgBr/ B_2pin_2 equivalents [see Supporting Information (SI)]. The reaction proceeds with only a slight excess (1.3 equiv) of EtMgBr/ B_2pin_2 and 1 mol % $MnBr_2$ /TMEDA (entry 1, Table 1). While all Mn salts examined proved competent in the

Table 1. Reaction Optimization



entry	deviation from standard conditions	yield ^a
1	none	88% ^b
2	24 h	89%
3	5% $MnBr_2$ /TMEDA	86%
4	5% $MnBr_2$ /TMEDA, 1.7 equiv of EtMgBr	71%
5	THF, 24 h	60%
6	1.2/1.2 equiv of EtMgBr/ B_2pin_2	78%
7	PhMgBr instead of EtMgBr	0%
8	no TMEDA	2%
9	5% $MnBr_2$ /dppf	0%
10	no $MnBr_2$	0%
11	$MnBr_2 \cdot 4H_2O$ used	69% ^b

^aYield determined by GC. ^bIsolated yield.

reaction (with $MnBr_2$ performing the best), ligands other than TMEDA resulted in substantially reduced yields (entries 8–9, Table 1). Interestingly, employing tetrahydrofuran (THF) as the solvent resulted in a limited catalyst lifetime when compared to dimethoxyethane (entry 5, Table 1 and SI).

Next, the substrate scope of the reaction was examined (Table 2). Since previous methods function well with alkyl iodides and bromides, our primary interest was the reaction of alkyl chlorides, examples of which remain rare and structurally limited.^{13a,15a} Strikingly, the borylation of alkyl chlorides proceeds in short reaction times at room temperature for primary (1a, 1i, 1k, 1u–1v; Table 2), secondary (1c, 1n, 1o, 1q; Table 2), and tertiary chlorides (1f, 1h, 1m; Table 2). Base-sensitive chloride 1u produces borylated product 2u in 81% yield with no elimination detected. Our prior disclosure on iron-catalyzed borylation offered the lone example of the reaction with a tertiary chloride,^{15a} but the reaction proceeded in a meager 6% yield. Both neomenthyl chloride 1n and menthyl chloride 1o furnish the more stable equatorial borylation product 2n in 78% yield with an 81:19 dr and 59% yield with an 88:12 dr, respectively, while *exo*-2-chloronorbornane 1p and *exo*-2-bromonorbornane 1q favor the *exo* product 2p in near-identical ratios in 83% and 79% yields, respectively. Diboration of geminal (1w–1y) dihalides proceeds smoothly to furnish the bisborylated products (2w and 2y).¹⁶ Satisfyingly, the synthetically useful bis[(pinacolato)-boryl]methane 2y was constructed in good yield using cheap and readily available reagent-grade dichloromethane.

Increasing the scale of the reaction 10-fold to 5.0 mmol scale furnished 2c in 81% yield, which is comparable to our 0.5 mmol reactions (Table 2). With solubility concerns regarding $MnBr_2$ in DME, we sought a highly soluble Mn/TMEDA complex we

Table 2. Substrate Scope of the Borylation Reaction^a

Reaction scheme: $1a-1y + B_2pin_2$ (1.3 equiv) + EtMgBr (1.3 equiv) $\xrightarrow{MnBr_2$ (1 mol %), TMEDA (1 mol %), DME (1 M), rt, 4 h} $2a-2y$

Starting Material	Product	Starting Material	Product	Starting Material	Product
1a	59% (X = Cl)	1c	88% (X = Cl)	1f	71% (X = Cl)
1b	75% (X = Br)	1d	91% (X = Br)	1g	83% (X = Br)
1e	68% (X = I)	1i	58% ^b (X = Cl)	1k	14% ^b (X = Cl)
1h	83% (X = Cl)	1j	60% (X = Br)	1l	64% (X = Br)
1m	65% (X = Cl) 2:1 eq:ax	1n	78% (X = ax-Cl) 81:19 dr	1p	83% (X = <i>exo</i> -Cl) 86:14 dr
1o	59% (X = eq-Cl) 88:12 dr	1q	79% (X = <i>exo</i> -Br) 87:13 dr	1r	76% (X = Br)
1s	66% (X = Br) (lin:cyc=3:1)	1u	81% (X = Cl)	1v	76% ^c (X = Cl)
1w	60% ^d (X = Cl)	1y	64% ^d (X = Cl)	1x	51% ^d (X = Br)

Gram Scale: 81% w/1c

^aIsolated yield. ^b5% Mn/TMEDA loading, 2.5 equiv each of B_2pin_2 /EtMgBr. ^c0.5 M concentration. ^d2.3 equiv each of B_2pin_2 /EtMgBr.

could easily employ in our catalyst loading studies. Employing $Mn(hfacac)_2(tmeda)$ ¹⁷ as the precatalyst, the reaction proceeds in 80% yield with 1000 ppm catalyst loading, albeit with a 24-h reaction time (entry 1, Table 3). Conversely, one can obtain 78% of desired borylated product 2c (at 80% conversion) starting from the parent chloride after only 30 min at room temperature with 5 mol % catalyst loading (entry 3, Table 3). Consequently, this transformation represents an obvious

Table 3. Effect of Catalyst Loading

Reaction scheme: $1c + B_2pin_2$ (1.3 equiv) + EtMgBr (1.3 equiv) $\xrightarrow{MnBr_2$ (X mol %), TMEDA (X mol %), DME (1 M), rt} $2c$

entry	Mn/TMEDA %	time	yield ^a
1 ^b	0.1%	24 h	80%
2	1%	4 h	88%
3	5%	0.5 h	78%

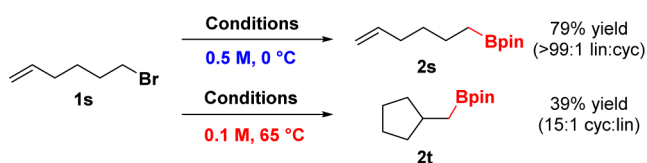
^aYield determined by GC using dodecane as an internal standard.

^b $Mn(hfacac)_2(tmeda)$ complex used.

starting point for both process and medicinal chemists seeking alkyl boronic esters.

At this point in the investigation, little is known about the mechanism of the reaction. For example, when an enantio-enriched secondary chloride (>99% ee) was subjected to the standard reaction conditions, only racemic product is obtained, thereby suggesting a stepwise, radical oxidative addition (see SI). The intermediacy of alkyl radicals was further tested in a series of radical-trap experiments. When 6-bromo-1-hexene (**1s**) was subjected to the reaction conditions, we isolated 66% of a 3:1 mixture of direct borylation product **2s** to ring-closed product **2t** (Scheme 2). The preference for **2s** offers a new

Scheme 2. Controlling Linear vs Cyclized Product with Temperature^a

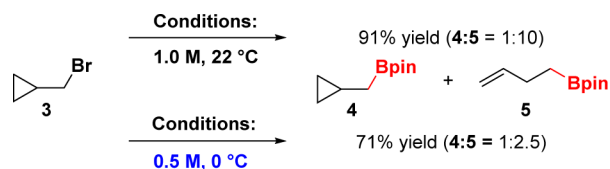


^aConditions: 5% MnBr₂, 5% TMEDA, 1.3 equiv of EtMgBr/B₂pin₂, DME, 4 h.

entry to such systems since all previous methods form ring-closed product **2t**.^{11b,13b,14,15} Amazingly, reducing the temperature to 0 °C produced direct borylation product **2s** as the sole product in 79% yield, providing the first example of **2s** being formed via transition metal-catalyzed borylation. Likewise, increasing the reaction temperature to 65 °C reversed the selectivity to produce the cyclized product **2t** in 37% yield with 2% direct borylation (Scheme 2). The fact that 5-exo ring closure is slower than radical recombination with the metal implies a close association of the metal with the resulting radical formed during oxidative addition. Specifically, radical recombination with Mn occurs at a rate $>1.0 \times 10^5/s$ at 0 °C.¹⁸ Since small temperature differences have little effect on the rate of 5-exo-dig radical cyclization,¹⁹ the predominance of product at 65 °C is likely due to solvation of the radicals during the oxidative addition. Such an event might also explain the compromised yield at this temperature. This example offers the first report on the use of temperature to effect a switch in selectivity in radical-based transition metal chemistry.

The unusual selectivity of 6-bromo-1-hexene (**1s**) prompted the examination of another radical probe, (bromomethyl)cyclopropane (**3**). At room temperature, **3** produced a 10:1 mixture of opened product **5** and unopened cyclopropyl product **4** in 91% yield (Scheme 3). Conducting the reaction at 0 °C more than doubled the amount of cyclopropylmethyl boronate **4**, providing a 1:2.5 ratio of **4** to **5** (Scheme 3). This

Scheme 3. Radical Clock Demonstrates Rapid, Radical Oxidative Addition^a

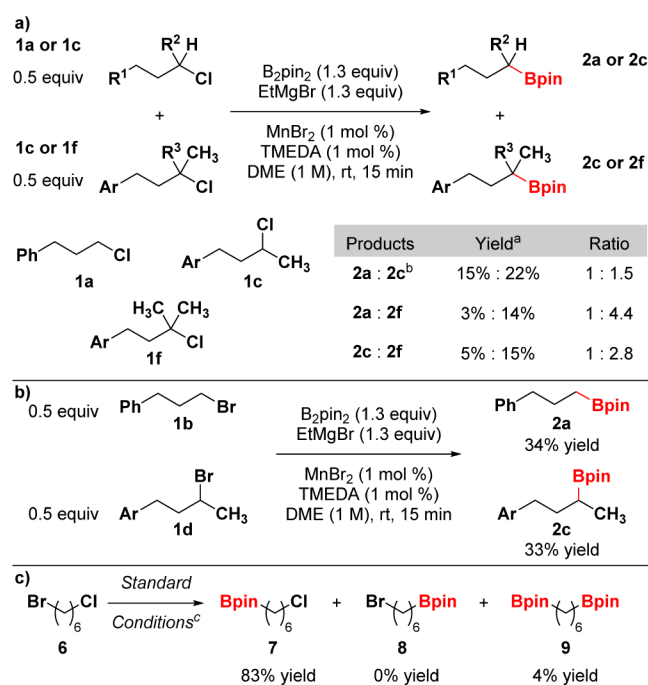


^aConditions: 5% MnBr₂, 5% TMEDA, 1.3 equiv of EtMgBr/B₂pin₂, DME, 4 h.

experiment provides access to cyclopropylmethyl boronate **4** from (bromomethyl)cyclopropane for the first time. Moreover, this substrate allows us to refine the rate of radical recombination with the metal to approximately $1 \times 10^8/s$.¹⁸

Based on the rapid oxidative addition observed in the radical-trap experiments (Schemes 2-3), we performed a series of competition experiments. Similar to the Ni-catalyzed borylation, we find that increasing the substitution at the halide increases the rate of reaction.¹² The competition among primary, secondary, and tertiary chlorides reveals rates where $1^\circ < 2^\circ < 3^\circ$ ($k_{rel} = 1:2.5:4.5$), thereby supporting the intermediacy of alkyl radicals if radical formation is involved in the turnover-limiting step (Scheme 4a).²⁰ The equivalent competition

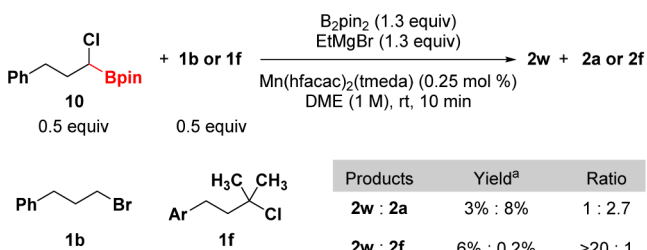
Scheme 4. Competition Experiments^{a,b,c}



^aYield determined by GC using dodecane as an internal standard. ^bReaction time = 45 min. ^cWith 2.6 equiv of B₂pin₂/EtMgBr yields are 40% (**7**), 0% (**8**), 43% (**9**) after 4 h reaction time. Ar = 4-methoxyphenyl.

experiments between primary and secondary bromides, however, reveal no clear preference between the two, suggesting a shift in the turnover-limiting step for alkyl bromides (Scheme 4b). The competition between a primary bromide and a primary chloride using 1-bromo-6-chlorohexane (**6**), however, produced borylation predominantly at the primary bromide to form monoborylated product **7** with some additional coupling at the primary chloride to form **9** (Scheme 4c).

We also observed interesting rate effects with the borylation of geminal dihalides **1w–1y**. Even under standard conditions where there is an excess of reactive halide relative to EtMgBr and B₂pin₂, we only ever detected trace amounts of the monoborylated products, suggesting that a geminal Bpin enhances the rate of borylation for the chloride. The competition between the geminal chloro-boryl substrate **10** and either a primary bromide (**1b**) or tertiary chloride (**1f**) shows that the rate is much more similar to that of alkyl bromides (Scheme 5). The increased rate could be due to an

Scheme 5. α -Boryl Substitution Enhances Reaction Rate^a

^aYield determined by GC using dodecane as an internal standard. Ar = 4-methoxyphenyl.

increase in the stability of the intermediate radical. It has been shown that a neighboring boron atom can offer significant radical stability on the order of 14.5 kcal/mol.²¹

In summary, we created a mild, low-cost reaction system for the general borylation of alkyl halides. The reaction generally proceeds in high yields with exceptional substrate scope. Consequently, the reaction should be the first choice for those seeking to borylate alkyl halides. The target reaction also offers the first synthetically useful control over direct borylation vs radical ring-closing or ring-opening reactions using temperature. Further efforts will be directed toward understanding the reaction mechanism of this interesting transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03157.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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