Micellar Catalysis

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An Improved System for the Aqueous Lipshutz–Negishi Cross-Coupling of Alkyl Halides with Aryl Electrophiles

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Abstract: *The development of a palladacyclic precatalyst supported by a new biaryl(dialkyl)phosphine ligand (VPhos) in combination with octanoic acid/sodium octanoate as a simple and effective surfactant system provided an improved catalyst system for the rapid construction of a broad spectrum of alkylated scaffolds from alkyl zinc reagents generated in situ.*

Convenient methods for the preparation of heteroarenes appended with saturated heterocycles are increasingly important in the pharmaceutical industry, particularly in medicinal chemistry. In many research areas, the installation of non-aromatic heterocycles is used to survey binding-pocket interactions and build a structure–activity relationship (SAR). Several advanced clinical candidates and drugs possessing these scaffolds have been shown to offer improved prospects for clinical survival, possibly linked to reduced receptor promiscuity and improved physiochemical properties.[1] The availability of a general process to readily couple a variety of non-aromatic heterocycles to heteroarenes would enable the rapid construction of candidate molecules and expedite the search for therapeutic agents.

The transition-metal-catalyzed cross-coupling of secondary alkyl organometallic reagents, R–M (R = *sec*-alkyl, M = B, Zn, Sn, Mg), is a useful method for attaching saturated heterocycles onto hetero(aryl) halides.[2–6] However, there are few general procedures that enable this approach and utilize shelf-stable precursors. The most popular alkyl nucleophiles used in cross-coupling reactions, alkyl boronates and alkyl zinc reagents, have drawbacks for use in a drug-discovery setting. Alkyl boronic acids, trifluoroboronates, and *N*-methyliminodiacetic acid (MIDA) boronates are shelf-stable, but their slow rate of alkyl transfer and/or often facile protodeboronation in aqueous media limits their utility.[7] In contrast, secondary alkyl zinc reagents undergo more rapid transmetalation but suffer from limited bench-top stability and often must be prepared immediately before use.[8] Despite these issues, nickel- and palladium-catalyzed cross-coupling reactions with secondary alkyl nucleophiles have found significant success.[3–6] However, there is still a need for generally more effective and convenient methods.

An alternative and direct strategy for constructing $C(sp^3)$–$C(sp^2)$ carbon–carbon bonds is the coupling of aryl and alkyl halides via aliphatic zinc intermediates that are generated in situ. By the use of shelf-stable alkyl halides, this approach obviates the need to preform and/or store organozinc reagents and is thus more amenable to parallel synthesis. The research groups of Weix, Gong, and Molander have described important nickel-catalyzed versions of this process.[9] Our study, however, was inspired by the pioneering efforts of Lipshutz and co-workers, in which alkyl zinc reagents were generated in situ and successfully cross-coupled with aryl bromides under micellar conditions with a palladium catalyst.[10] One drawback is that competitive reduction of the aryl halide was often observed, and a significant excess of the alkyl halide was required to suppress this side reaction. Furthermore, despite a generally broad reaction scope, few non-aromatic heterocyclic halides or (hetero)aryl chlorides were evaluated in detail in these studies.

A plausible representation of the catalytic cycle of a palladium-catalyzed alkyl–aryl reductive coupling reaction and potential undesired pathways is shown in Scheme 1 a. The catalytic cycle operates by the oxidative addition of aryl halide **1**, followed by transmetalation of the alkyl zinc species **3**, which is generated in situ from an aliphatic halide **2**, and reductive elimination from the resulting intermediate complex **B** to deliver the desired sp^3–sp^2 cross-coupled product **4**. Nonproductive β-hydride elimination from palladium(II) intermediate **B** would generate complex **C**. Species **C** could form isomerized product **5** after further migratory insertion and reductive elimination from intermediate **D**, or produce reduced arene **6** by direct reductive elimination.

Importantly, the transmetalation of **3** with **A** must be faster than the protonation of organozinc species **3** by water. Likewise, the oxidative addition of aryl halide **1** must be faster than the reaction of **1** with zinc (Scheme 1 b). Therefore, to limit these side reactions and provide the desired product in high yield, the catalyst must display high turnover frequency (TOF). Palladium precatalysts developed in our laboratory reliably and efficiently generate monoligated palladium intermediates, L_1Pd^0, which undergo rapid oxidative addition with aryl halides.[11] We felt that these precatalysts could serve as an effective system to control the unwanted reduction of the aryl halide by zinc. We have also demonstrated that, with an appropriate ligand, $C(sp^3)$–$C(sp^2)$ Negishi coupling reactions of preformed secondary alkyl zinc reagents with heteroaryl bromides proceed with excellent levels of regioselectivity.[4b,c] We wondered whether our broadly applicable

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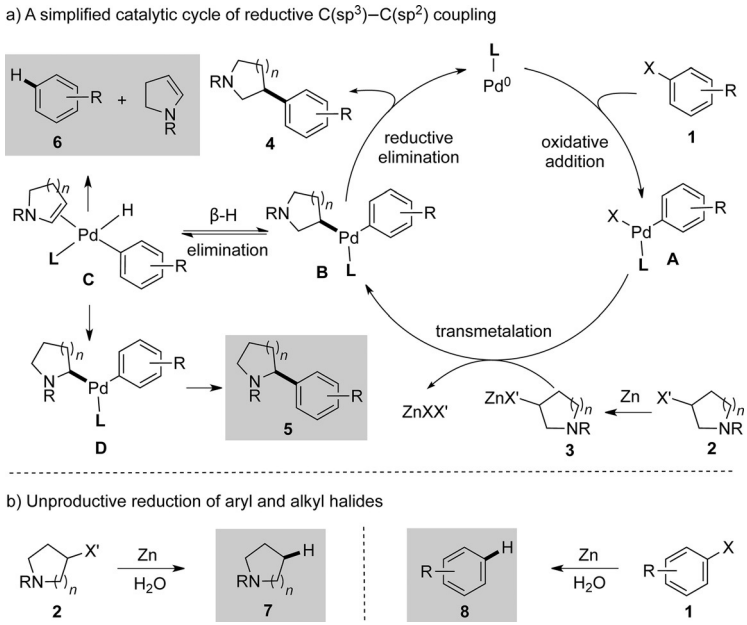


Scheme 1. a) Schematic representation of sp^3–sp^2 coupling of a generic non-aromatic heterocyclic zinc reagent and b) potential associated side reactions.

catalysts could be employed for the direct coupling of (hetero)aryl halides with alkyl zinc species generated in situ.

We began our study by evaluating a series of known biaryl(dialkyl)phosphine-based palladium precatalysts and anionic surfactants for the coupling of 4-chloroanisole (**9a**) and 4-bromotetrahydropyran (**10**). Owing to the ease in their removal from the reaction mixture, we primarily focused on long-chain fatty acids, and from a preliminary screen, we found that octanoic acid was an effective surfactant for this transformation. We have previously demonstrated that SPhos (**L1**), RuPhos (**L2**), and CPhos (**L3**) were useful supporting ligands for Suzuki and Negishi reactions of aryl chlorides with secondary alkyl nucleophiles.[4b,c,12] However, employment of the corresponding precatalysts **P1**–**P3** under these conditions afforded the coupling product **11a** in modest yield along with a significant amount of unreacted **9a** and anisole (Scheme 2, entries 1–3). Although the highest cross-coupling yield was observed with XPhos-based precatalyst **P4**, a substantial fraction of the product was an isomerized product (entry 4). The CPhos-based precatalyst **P3** provided the desired product for the reaction of the electron-rich aryl chloride **9a** in poor yield. However, precatalyst **P5**, based on a hybrid ligand **L5** that bears features of both CPhos (an *ortho*-NMe_2 group) and SPhos (an *ortho*-OMe group), provided a significant amount of the cross-coupled product with no isomerized-product formation. Thus, the properties of both of these ligands seemed to be incorporated in the hybrid **L5**: good reactivity towards electron-rich aryl chlorides and good regioselectivity.

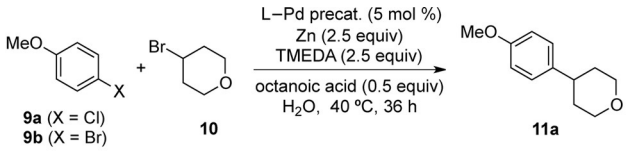
Given this result, we hypothesized that a precatalyst derived from a hybrid ligand possessing similarities with XPhos and SPhos might provide the product of the reaction in Scheme 2 both in high yield and with a good level of regioselectivity. Thus, we combined a bulky *ortho* substituent (as on the bottom ring of XPhos) with the *ortho*-OMe group from the bottom ring of SPhos to arrive at the new ligand VPhos (**L6**).[13] The use of the VPhos precatalyst **P6** in the test reaction led to a substantial improvement in the yield, and no product resulting from isomerization was observed (entry 6). The less challenging aryl bromide **9b** (entry 7) was also accommodated well by the catalyst/surfactant system, and was converted into **11a** in slightly higher yield.

The conditions that we developed are operationally simple, requiring neither the use of a glovebox nor any special order of reagent addition. In the workup, octanoic acid could be removed by simply washing with a base (0.3 M aqueous NaOH). Other long-chain acid surfactants were examined, but none were as effective as octanoic acid (Scheme 2, entries 9–12). The use of precatalyst [$PdCl_2$-$(AmPhos)_2$] (**P7**), which has previously been shown to be an excellent catalyst for this process with aryl bromides, afforded no detectable cross-coupled product under these conditions with **9a** (entry 8).[9a]

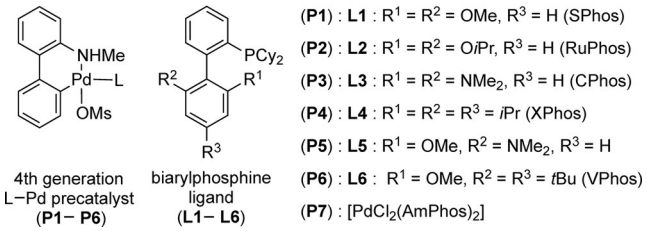
We next examined the scope of the combination of 4-bromotetrahydropyran (**10**) with other (hetero)aryl halides with the optimized catalyst and surfactant system (Scheme 3). Electron-rich, electron-deficient, and electron-neutral aryl chlorides and bromides were efficiently coupled with only 1.5 equivalents of **10** in excellent yields with no isomerized-product formation detected (products **11a–d**). Simple heterocyclic bromides, such as a pyridine (product **11e**), an indole (product **11f**), an azaindole (product **11g**), and a nitrogen-rich pyrrolopyrimidine (product **11h**), were all coupled in moderate to good yields and with a high level of regioselectivity.[14]

Next, we examined other saturated heterocyclic bromides (*N*-Boc-4-bromopiperidine (**12**), *N*-Boc-3-bromopyrrolidine (**13**), *N*-Boc-3-bromoazetidine (**14**), and 3-bromooxetane (**15**)) as coupling partners. For these substrates, the use of octanoic acid as the surfactant resulted in low yields with significant amounts of reduction of both the alkyl and aryl halide. We suspected that either the zinc-insertion process for these alkyl bromides was relatively fast as compared with that for **10**, or that the corresponding alkyl zinc species underwent faster protonation by water. The use of less zinc and/or TMEDA did not lead to an improvement. However, changing the surfactant from octanoic acid to a mixture of sodium octanoate and either 1-octanol or methyl octanoate with sodium chloride as an additive significantly improved the yield of the desired products.[15] These modified conditions enabled the coupling of alkyl halides **12**–**15** with a variety of (hetero)aryl electrophiles (Scheme 4). Several simple aryl bromides were coupled with *N*-Boc-4-bromopiperidine (**12**) in good yields (Scheme 4a, products **16a–c**). Aryl triflates were also efficiently cross-coupled under these conditions (products **16d**,**e**), as were heteroaryl halides (products **16f–h**).

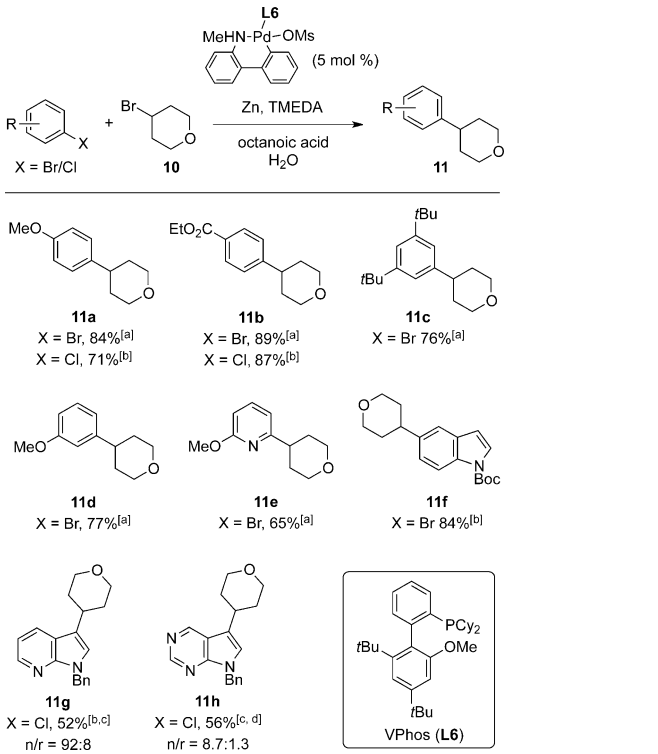
A similar trend in reactivity was observed for *N*-Boc-3-bromopyrrolidine (**13**) and *N*-Boc-3-bromoazetidine (**14**) (Scheme 4b,c). A wide array of electronically and sterically challenging aryl bromides and chlorides (products **17a**, **17b**,



Entry	9a/9b	Surfactant	Pd precat.	Yield [%][a]	ArH [%][a]
1	**9a**	octanoic acid	**P1**	56	14
2	**9a**	octanoic acid	**P2**	54	33
3	**9a**	octanoic acid	**P3**	trace	–
4	**9a**	octanoic acid	**P4**	79[b]	10
5	**9a**	octanoic acid	**P5**	60	14
6	**9a**	octanoic acid	**P6**	76	18
7[c]	**9b**	octanoic acid	**P6**	84[d]	6
8[c]	**9a**	octanoic acid	**P7**	0	–
9[c]	**9b**	myristic acid	**P6**	62	7
10[c]	**9b**	palmitic acid	**P6**	80	7
11[c]	**9b**	steric acid	**P6**	28	9
12[c]	**9b**	SDS	**P6**	0	8



Scheme 2. Effect of ligand structure on the sp^3–sp^2 reductive coupling of non-aromatic heterocyclic bromide **10** and aryl halide **9a**/**9b**. Reaction conditions: 4-chloroanisole (0.2 mmol), 4-bromotetrahydropyran (0.3 mmol), Pd precatalyst (0.01 mmol), Zn (0.5 mmol), TMEDA (0.5 mmol), octanoic acid (0.1 mmol), H_2O (0.3 M). [a] Yields were determined by GC analysis with 1,3,5-trimethoxybenzene as an internal standard. [b] n/r = 7.6:2.4 (n = normal product, r = rearranged product); the n/r ratio was determined by GC analysis. [c] The reaction temperature was 35 °C. [d] Yield of the isolated product from a reaction on a 1 mmol scale. The reaction was carried out with 1 mmol of octanoic acid and 3 mmol of TMEDA. SDS = sodium dodecyl sulfate, TMEDA = tetramethylethylenediamine.



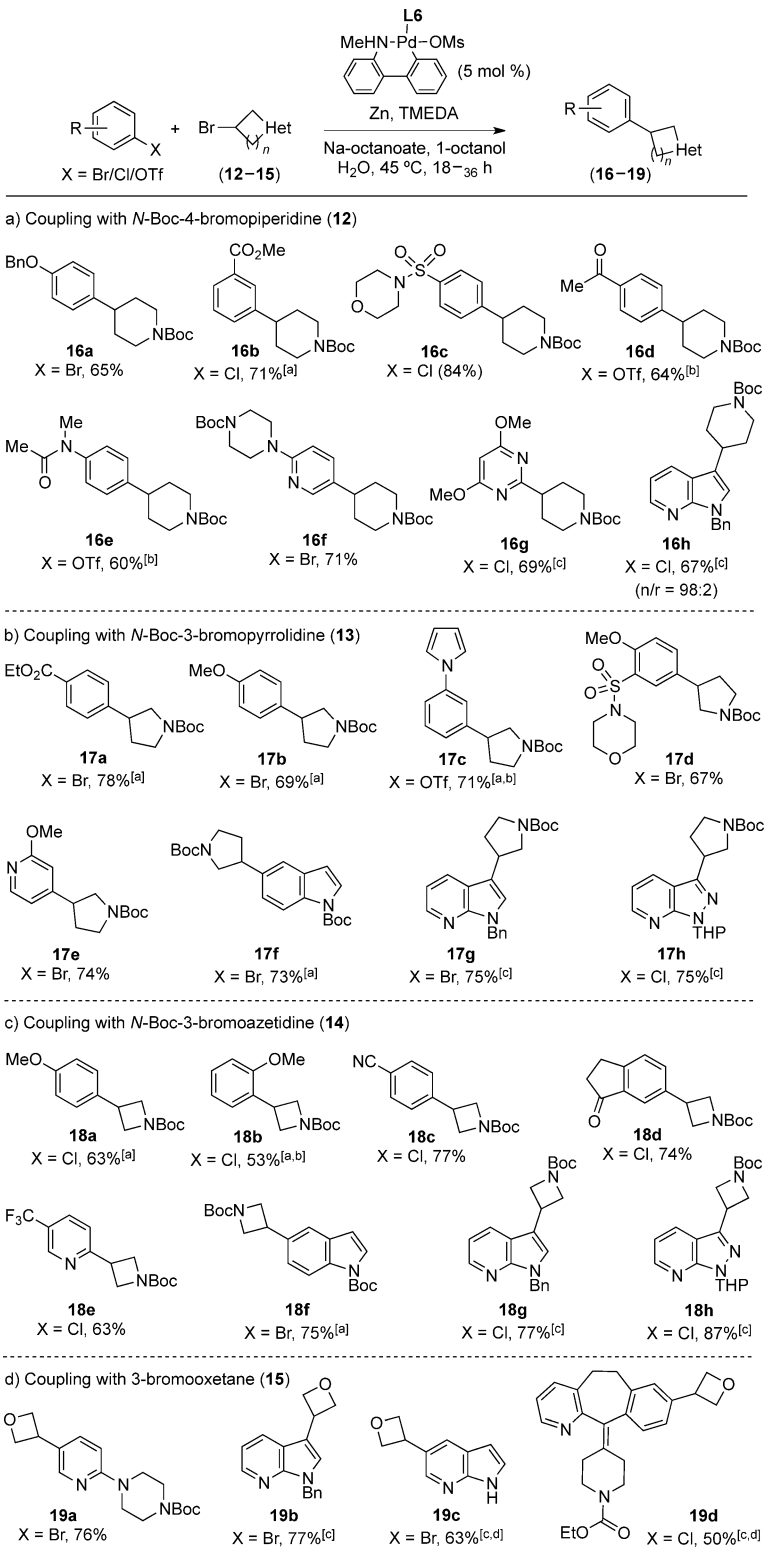
Scheme 3. Scope of the coupling reaction of aryl halides with 4-bromotetrahydropyran (**10**). Reaction conditions: aryl halide (1.0 mmol), **10** (1.5 mmol), Zn (2.5 mmol), TMEDA (3.0 mmol), Pd precatalyst (0.05 mmol), octanoic acid (1.0 mmol), H_2O (3.3 mL). [a] The reaction temperature was 40 °C. [b] The reaction temperature was 45 °C. [c] Reaction conditions: aryl halide (1.0 mmol), **10** (2.0 mmol), Zn (2.5 mmol), TMEDA (2.5 mmol), Pd precatalyst (0.07 mmol), sodium octanoate (1.0 mmol), methyl octanoate (1.0 mmol). [d] The reaction temperature was 60 °C. The n/r ratio (n = normal product, r = rearranged product) was determined by GC and ^{1}H NMR analysis of the crude reaction mixture. Bn = benzyl, Cy = cyclohexyl, Ms = methanesulfonyl.

18a, **18b**), along with an aryl triflate (product **17c**), afforded the desired products in good yields. Sulfonamide (product **17d**), nitrile (product **18c**), and ketone functional groups (product **18d**) were all compatible with the micellar conditions. A variety of heterocyclic scaffolds, including simple pyridines (products **17e, 18e**), an indole (products **17f, 18f**), an azaindole (products **17g, 18g**), and a heteroatom-rich pyrazolo[3,4-*b*]pyridine (products **17h, 18h**), were efficiently cross-coupled without the formation of observable regioisomeric products, thus showcasing the efficacy of this method for the preparation of complex heterocycles.

Finally, we demonstrated that 3-bromooxetane could also be employed in cross-coupling reactions under these conditions (Scheme 4d). In this case, several heteroaryl halides (products **19a–c**), including the histamine antagonist loratidine (product **19d**), underwent clean coupling, thus demonstrating the utility of this method for the late-stage modification of biologically active compounds. Notably, the current micellar reaction conditions facilitated the Negishi coupling without substantial quenching of the alkyl zinc intermediates generated in situ, even at the higher temperature (70 °C) required for producing **19c**[16] and **19d** in good yields.

We note that this process is not without limitations. Several of the non-aromatic heterocyclic bromides that we examined (*N*-Boc-3-bromopiperidine, 3-bromotetrahydropyran, and 3-bromotetrahydrofuran) were converted into the desired products in only low yields under the optimized conditions.[17]

In summary, we have developed a new hybrid VPhos-supported palladium precatalyst that incorporates the structural elements of existing ligands, thus resulting in an improved activity profile for the reductive coupling of several non-aromatic heterocyclic alkyl bromides. We have also found the simple, inexpensive and easily removable combination of octanoic acid/sodium octanoate is an efficient surfactant system for this micelle-enhanced Negishi coupling. This new catalyst and new surfactant system allowed the $C(sp^3)$–$C(sp^2)$ cross-coupling of a broad spectrum of electronically differentiated (hetero)aryl halides with as little as 1.5 equivalents of a variety of non-aromatic heterocyclic



Scheme 4. Cross-coupling of non-aromatic heterocyclic bromides. Reaction conditions: Aryl halide (1.0 mmol), alkyl halide (1.5 mmol), Zn (2.5 mmol), TMEDA (2.5 mmol), Pd precatalyst (0.05 mmol), sodium octanoate (0.5 mmol), 1-octanol (1.5 mmol), H_2O (3.3 mL). [a] Methyl octanoate (1.0 mmol) was used instead of 1-octanol. [b] The reaction temperature was 55 °C. [c] Reaction conditions: aryl halide (1.0 mmol), alkyl halide (2.0 mmol), Zn (3.0 mmol), TMEDA (3.0 mmol), Pd precatalyst (0.05 mmol), sodium octanoate (1.0 mmol), 1-octanol (2.0 mmol), NaCl (3.0 mmol). [d] The reaction temperature was 70 °C. The n/r ratio was determined by ^{1}H NMR and HPLC–MS analysis of the crude reaction mixture. THP = tetrahydropyranyl, Tf = trifluoromethanesulfonyl.

bromides in good yields. This operationally simple methodology, which uses shelf-stable aryl and alkyl halides as coupling partners, should enable straightforward access to functionally diverse sets of sp^3–sp^2 cross-coupled products and be readily translated to parallel synthesis efforts in drug-discovery settings.

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[13] Owing to the commercial availability of the starting 3,5-di-*tert*-butylphenol and ease of the synthesis of VPhos, we decided to use a *t*Bu group on the lower ring of the biaryl backbone instead of an *i*Pr group. See the Supporting Information for the synthesis of VPhos.

[14] For the reactions to form **11g** and **11h**, a mixture of sodium octanoate and methyl octanoate provided better yields than octanoic acid (see the discussion in the subsequent text and Ref. [15]).

[15] It appears that the corresponding alkyl zinc species generated from these bromides might be more polar than **10** and react with the aqueous medium. A mixture of sodium octanoate and 1-octanol/methyl octanoate might shield these alkyl zinc species from the aqueous phase by swelling the micelle core (hydrocarbon phase). A similar effect was also noticed by Lipshutz and co-workers (Ref. [10d,e]).

[16] The cross-coupling reaction to give **19c** resulted in the deprotection of the azaindole scaffold (removal of the Boc group).

[17] The zincation of these alkyl bromides appears to be slow, as the majority of the alkyl bromide substrate was recovered at the end of the reaction. The product of reduction of the aryl halide was also observed as a result of competitive zinc insertion.

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