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Complete List of Authors:	Liang, Yongqi; Shanghai University, Department of Chemistry Ma, Yilin; Shanghai University, Department of Chemistry Zhou, Wei ; Shanghai University Cui, Yongmei; Shanghai University, Department of Chemistry Szostak, Michal; Rutgers University, Chemistry Liu, Chengwei; Shanghai University, Department of Chemistry

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COMMUNICATION

Samarium Diiodide/Samarium-Mediated Direct Deoxygenative Hydroborylation of Ketones with Hydroborane Esters

Yongqi Liang,^a Yilin Ma,^a Wei Zhou,^a Yongmei Cui,^{*a} Michal Szostak^{*b} and Chengwei Liu^{*a}

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A direct deoxygenative hydroborylation of ketones with hydroborane ester promoted by a combination of samarium diiodide, samarium and nickel has been developed. In this method, secondary alkyl borate esters are synthesized from unactivated ketones with hydroborane esters in one step. Broad substrate scope and excellent selectivity for C=O cleavage has been demonstrated. This approach represents a general method for the construction of versatile secondary alkyl borate esters from unactivated ketones.

Secondary alkyl borate esters are versatile building blocks for organic synthesis, which can be easily converted into other useful architectures, such as secondary alkyl alcohols, secondary alkyl amines, trialkylmethanes, and arylmethanes.¹ Although the synthetic methods of aryl borate esters have become mature with the development of transition-metal-catalyzed cross-coupling reactions,² the synthesis of alkyl borate esters, especially the synthesis of secondary alkyl borate esters, faces many challenges.³

Simultaneously, ketones are naturally present in nature, and the advantages of ketones include ready availability, stability, and non-toxicity. Due to their unique carbonyl containing characteristics, ketones are classically used in nucleophilic addition reactions as electrophilic partners.⁴ The specific addition process involves nucleophiles being added to the electrophilic carbon atom of the carbonyl group, while hydrogen or other atoms are appended at the oxygen of the carbonyl group. In the classical nucleophilic addition, the C=O double bond of the carbonyl group becomes C–O single bond, converting a π bond into a σ bond, and the oxygen of the carbonyl group is not removed. In fact, the activation energy of the C=O double bond of carbonyl group is very high, rendering the scission of the C=O double bond of ketones and thus deoxygenative functionalization of the carbonyl group a

formidable challenge.

The development of synthetic methods for the assembly of secondary alkyl borate esters directly from ketones is significant. In this field, several indirect conversion methods from ketones to secondary alkyl borate esters have been disclosed.^{5–6} In 2016, Tortosa group developed a copper-catalyzed borylative aromatization of *p*-quinone methides to generate secondary alkyl borate esters.⁵ This method does not directly activate the carbonyl group, but rather functionalizes the C–H bond of olefin at the *para* position of carbonyl group. Another indirect method by Zhu group is to first activate ketones into diazomethanes, and then achieve the enantioselective conversion of diazomethanes to secondary alkyl borate esters under transition-metal-catalysis (Figure 1A).⁶ In 2018, Liu research group developed a copper-catalyzed hydroborylation of ketones, and this transformation involves diboration of ketone carbonyl groups, which are then reduced by external hydride source to deliver secondary alkyl borate esters (Figure 1B).⁷ In 2020, Li group reported a metal-free deoxygenative borylation of ketones using activated aromatic diboron reagents, and the reaction process includes diboration of the carbonyl group, protodeboronation using water, and trans-esterification using alcohols (Figure 1C).⁸ Moreover, some deoxygenative difunctionalizations of ketones have also been disclosed.^{9–10}

Samarium diiodide is a powerful single electron transfer reagent.^{11–25} Since its discovery in 1977 by Kagan,^{11,12} samarium diiodide has gradually become one of the most popular single electron transfer reagents in organic laboratories.^{13–15} Unsaturated organic compounds can easily be reduced by samarium diiodide, such as olefins,¹⁶ nitriles,¹⁷ carboxylic acids,¹⁸ esters,¹⁹ and amides.²⁰ In addition, samarium diiodide can also promote diverse cyclization reactions of various compounds.^{21–23} Recently, An group achieved samarium diiodide-mediated diverse synthesis of deuterated compounds.^{24–25} Furthermore, Ogawa, Wang and other groups developed samarium diiodide-mediated direct deoxygenative functionalization of amides.^{26–32} Recently, electrochemical synthesis methods have also been applied to deoxygenative borylation of ketones or aldehydes, demonstrating excellent functional group tolerance and substrate universality.³³ Since

^a A Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China. E-mail: liuchengwei@shu.edu.cn; liuchengwei2024@163.com ymcui@shu.edu.cn. Group website: https://www.x-mol.com/groups/chengwei_liu

^b Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, USA. E-mail: michal.szostak@rutgers.edu; Group website: <https://szostakgroup.com>

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the carbonyl group of amides could be deoxygenated under the induction of samarium diiodide, we were keen to investigate whether samarium diiodide can also achieve the direct deoxygenative functionalization of ketones. With this hypothesis in mind, a preliminary exploration was conducted, and to our delight, the SmI_2/Sm -mediated deoxygenative functionalization of ketones was achieved.

In this communication, a novel samarium diiodide/samarium/nickel promoted direct deoxygenative hydroborylation of ketones is reported. The significant features of this method include: (1) the first general and practical direct deoxygenative borylation of ketones with hydroborane esters has been developed; (2) the cleavage of a π bond and the formation of a σ bond has been achieved simultaneously; (3) secondary alkyl borate esters are synthesized directly from unactivated ketones and hydroborane esters in one step; (4) broad substrate scope and excellent selectivity demonstrate a reliable and efficient pathway for deoxygenative borylation of ketones.

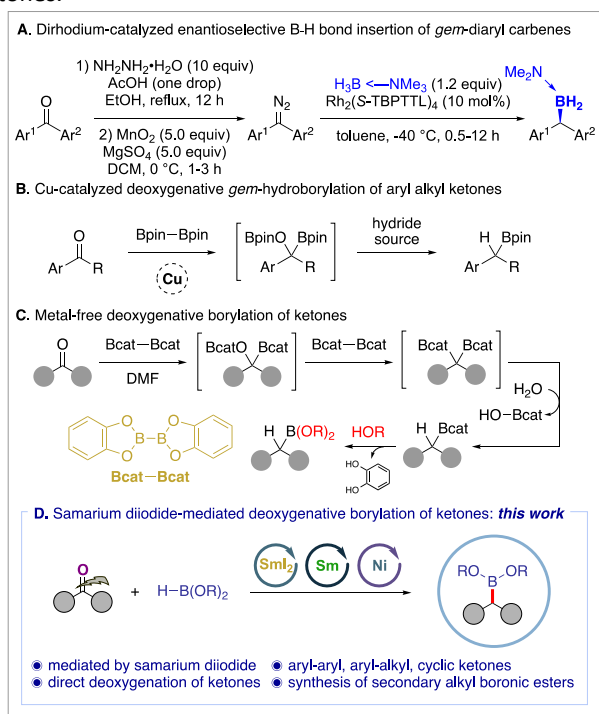


Figure 1 Direct deoxygenative borylation of ketones.

The samarium diiodide/samarium-mediated direct deoxygenative borylation of ketones was first investigated using benzophenone (**1a**) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2a**) as model substrates (Table 1). Based on our research experience in the deoxygenative functionalization of amides, CuI was first selected as an additive to promote this reaction. As shown in the Table 1, the base-free conditions were first attempted, and the results showed that only 15% yield was obtained without base (entry 1). Next, different bases were screened (entries 2-14), including organic and inorganic bases, and the results showed that KOt-Bu was the optimal base for this transformation (entry 14). Encouraged by the success, 8 different types of metal additives were next screened (entries

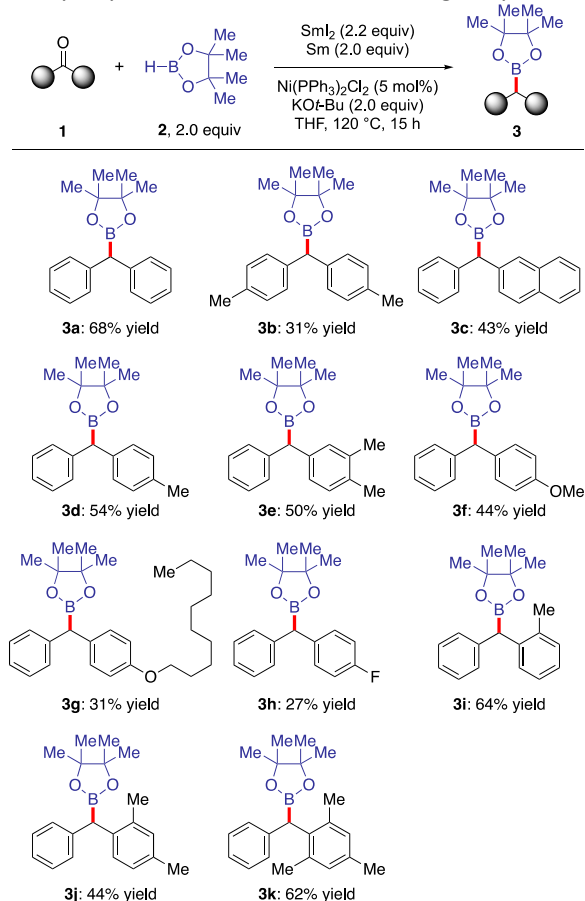
14-21), and the experimental results showed that nickel exhibited better catalytic ability than copper or other catalysts (entry 21). Therefore, different nickel catalysts have been tested (entries 22-28), and the results showed that $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ is the optimal catalyst for this reaction. Next, the amount of hydroborane ester was screened, and we found that the reaction yield decreased with the increase of the amount of hydroborane ester (entries 29-31). Therefore, we maintained the 1:2 stoichiometry of hydroborane ester. Next, we established that even if the amount of SmI_2 was increased to 4 equivalents, the reaction yield was not significantly improved (entry 32), thus we maintained the original stoichiometry of SmI_2 . Furthermore, we are curious whether the amount of nickel catalyst could affect the outcome of the reaction, thus relevant experiments have been attempted. Interestingly, the reaction yield decreased with the increase of the amount of nickel catalyst (entries 33-35). Finally, control experiments (entries 36-37), showed that the reaction could not occur without the addition of SmI_2 or Sm, indicating that both SmI_2 and Sm were essential for the reaction, as expected for the generation of Sm-carbene.²⁶⁻²⁸

Table 1. Summary of Optimization Studies.^a

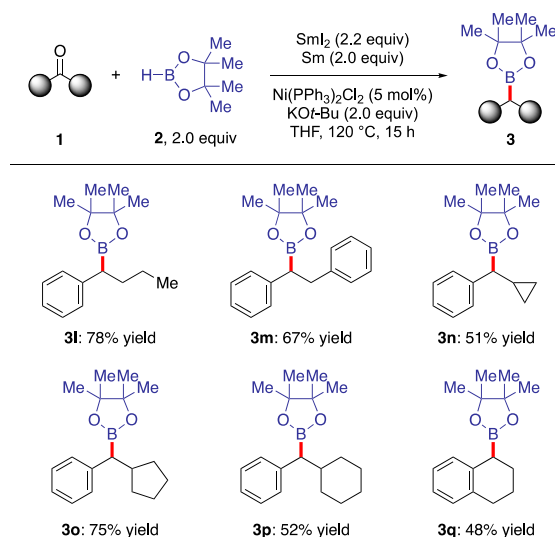
entry	catalyst (mol%)	additive	Yield(%)
1	CuI (10)		15
2	CuI (10)	DMAP	<2
3	CuI (10)	Na_2CO_3	22
4	CuI (10)	K_2CO_3	23
5	CuI (10)	Cs_2CO_3	17
6	CuI (10)	K_3PO_4	20
7	CuI (10)	NaOAc	<2
8	CuI (10)	KOAc	<2
9	CuI (10)	NaOH	<2
10	CuI (10)	KOH	<2
11	CuI (10)	KF	<2
12	CuI (10)	LiOt-Bu	<2
13	CuI (10)	NaOt-Bu	36
14	CuI (10)	KOt-Bu	45
15	AgBF_4 (10)	KOt-Bu	11
16	NaBF_4 (10)	KOt-Bu	3
17	CoI_2 (10)	KOt-Bu	14
18	FeCl_3 (10)	KOt-Bu	16
19	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	35
20	$\text{Rh}(\text{PPh}_3)_3\text{Cl}$ (2)	KOt-Bu	22
21	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	68
22	$\text{Ni}(\text{PCy}_3)_2\text{Cl}_2$ (5)	KOt-Bu	10
23	$\text{Ni}(\text{dppe})\text{Cl}_2$ (5)	KOt-Bu	30
24	$\text{Ni}(\text{dppp})\text{Cl}_2$ (5)	KOt-Bu	18
25	$\text{Ni}(\text{dppf})\text{Cl}_2$ (5)	KOt-Bu	28
26	NiCl_2 (5)	KOt-Bu	7
27	NiI_2 (5)	KOt-Bu	37
28	$\text{Ni}(\text{acac})_2$ (5)	KOt-Bu	<1
29 ^b	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	63
30 ^c	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	59
31 ^d	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	45
32 ^e	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	70
33	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	57
34	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	51
35	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	44
36 ^f	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	<2
37 ^g	$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ (5)	KOt-Bu	<2

^aConditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (2.0 equiv), SmI₂ (2.2 equiv), Sm (2.0 equiv), additive (2-10 mol%), base (2.0 equiv), THF, 120 °C, 15 h; ^b**2a** (3.0 equiv); ^c**2a** (4.0 equiv); ^d**2a** (5.0 equiv); ^eSmI₂ (4.0 equiv); ^fwithout SmI₂; ^gwithout Sm.

With the optimal conditions in hand, the substrate scope of diaryl ketones in this transformation was next investigated (Scheme 1). To our delight, the ketone substrates bearing electron-neutral (**3a-3e**), electron-rich (**3f-3g**), and electron-deficient (**3h**) substituents are well compatible with this method. Furthermore, even challenging sterically-hindered ketones (**3i-3k**) could also be tolerated to deliver the desired secondary alkyl borate esters in moderate to good yields.



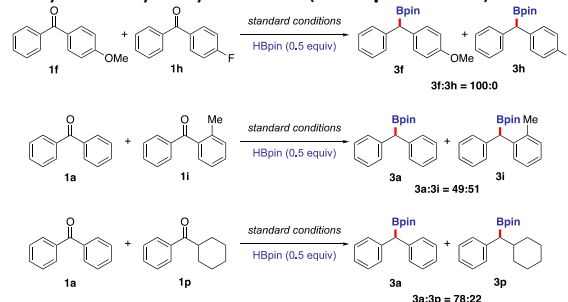
Scheme 1. Substrate Scope of Diaryl Ketones.



Scheme 2. Substrate Scope of Aryl Alkyl Ketones.

Moreover, substrate scope of aryl alkyl ketones for this transformation was also investigated as shown in Scheme 2. Pleasingly, we found that this method is broadly compatible with various aryl alkyl ketones, such as 1-phenylbutan-1-one (**3l**), 1,2-diphenylethan-1-one (**3m**), cyclopropyl(phenyl)methanone (**3n**), cyclopentyl(phenyl)methanone (**3o**), cyclohexyl(phenyl)methanone (**3p**), and 3,4-dihydronaphthalen-1(2H)-one (**3q**). At this stage, diaryl ketones containing strongly electron-withdrawing groups, such as CF₃ or CN, are not tolerated due to competing carbonyl reduction. Likewise, dialkyl ketones are competitively reduced to alcohols. A representative example of an α,β -unsaturated ketone was tested, and no desired deoxygenative product was detected.

In order to better understand the mechanism of this method, a series of competition experiments were performed (Scheme 3). The control experiments showed that electron-rich ketones are significantly more reactive than electron-deficient substrates (4-OMe : 4-F = >98 : 2), as expected from the stabilization of Sm-carbene. Furthermore, there is no difference between unsubstituted ketones and sterically hindered substrates (2-H : 2-Me = 49 : 51). Interestingly, the experimental results also indicated that diaryl ketones exhibit higher reactivity than aryl alkyl ketones (**3a** : **3p** = 78 : 22).



Scheme 3. Competition Experiments.

The proposed mechanism is shown in Figure 2. This mechanism is based on the previous literature, which confirmed the presence of carbene by insertion/cyclization pathways.²⁶⁻²⁸

At present, the carbene intermediate has been too challenging to isolate. First, SmI_2 -mediated SET reductive activation of the ketone $\text{C}=\text{O}$ group generates ketyl radical **1-1**, which is then further reduced by Sm/SmI_2 couple to give intermediate **1-2**. Subsequently, α -elimination generates samarium(III) oxide and Sm -carbene intermediate **1-3**.³⁴ Simultaneously, nickel catalyst reacts with KOt-Bu to form $\text{M}(\text{Ot-Bu})_n$, which then intercepts the Sm -carbene intermediate **1-3** to form nickel-carbene **1-4**. Coordination of hydroborane with metal-carbene **1-4** forms intermediate **2-1**. Hydrogen migration and reductive elimination generates the desired secondary alkyl borate ester.

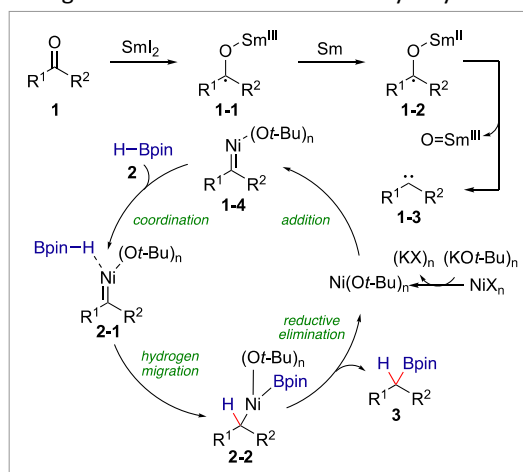


Figure 2. Proposed mechanism.

In conclusion, we have reported a novel $\text{SmI}_2/\text{Sm}/\text{Ni}$ -promoted direct deoxygenative hydroborylation of ketones to generate secondary alkyl borate esters, which represents the first lanthanide-mediated direct deoxygenative hydroborylation of ketones with hydroborane esters. In this method, the cleavage of a π bond and the formation of a σ bond has been achieved simultaneously. Broad substrate scope and good functional group tolerance demonstrate that this is a reliable and efficient approach for deoxygenative hydroborylation of ketones. This method for synthesizing valuable secondary alkyl borate esters is expected to be useful in both academic and industrial arenas.

Conflicts of interest

There are no conflicts to declare.

Data availability

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

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Data Availability Statement

The data underlying this study are available in the published article and its Electronic Supplementary Information (ESI). The Electronic Supplementary Information is available free of charge on the RSC Publications website.