

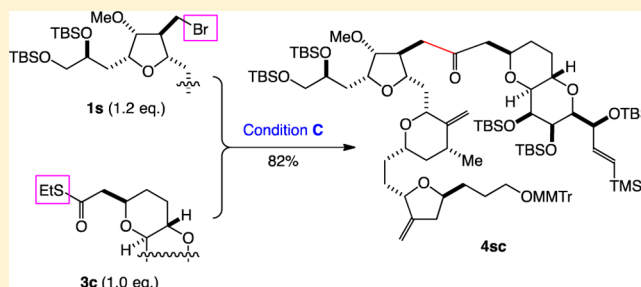
One-Pot Ketone Synthesis with Alkylzinc Halides Prepared from Alkyl Halides via a Single Electron Transfer (SET) Process: New Extension of Fukuyama Ketone Synthesis

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S Supporting Information

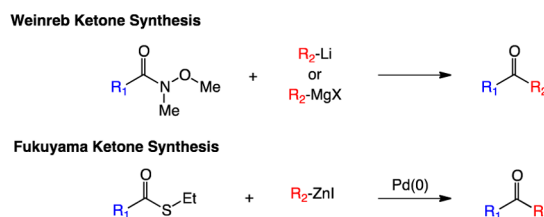
ABSTRACT: One-pot ketone synthesis has been developed with in situ activation of alkyl halides to alkylzinc halides in the presence of thioesters and Pd-catalyst. The new method provides us with a reliable option for a coupling at a late stage in a convergent synthesis of complex molecules, with use of a near 1:1 molar ratio of coupling partners. First, two facile, orthogonal methods have been developed for preparation of alkylzinc halides: (1) direct insertion of zinc dust to 1°- and 2°-alkyl halides in the presence of LiI in DMI and (2) early transition-metal assisted activation of alkyl halides via a single electron transfer (SET) process. CrCl₂ has been found as an unprecedented, inevitable mediator for preparation of alkylzinc halides from alkyl halides, where CrCl₂ likely functions to trap R·, generated via a SET process, and transfer it to Zn(II) to form RZnX. In addition to a commonly used CoPc, a new radical initiator NbCpCl₄ has been discovered through the study. Second, with use of the two orthogonal methods, three sets of coupling conditions have been developed to complete one-pot ketone synthesis, with Condition A (Pd₂dba₃, PR₃, Zn, LiI, TESCl, DMI), Condition B (A + CrCl₂), and Condition C (B + NbCpCl₄ or CoPc) being useful for simple linear and α -substituted substrates, simple linear and β -substituted substrates, and complex substrates, respectively. Condition C is applicable to the broadest range of substrates. Overall, one-pot ketone synthesis gives excellent yields, with good functional group tolerance. Controlled formation of alkylzinc halides by a combination of CrCl₂ and NbCpCl₄ or CoPc is crucial for its application to complex substrates. Interestingly, one-pot ketone synthesis does not suffer from the chemical instability due to the inevitable radical pathway(s), for example a 1,5-H shift. Notably, even with the increase in molecular size, no significant decrease in coupling efficiency has been noticed. To illustrate the synthetic value at a late stage in a complex molecule synthesis, ketone **4sc**, containing all the carbons of Eribulin, has been synthesized from **1s** and **3c**.



INTRODUCTION

Ketone is one of the most important functional groups in organic chemistry, as it not only is widely found in natural/man-made products but also is a versatile synthetic intermediate to other functionalities. Over the past several decades, impressive progress has been made to achieve a ketone synthesis with high selectivity and efficiency. The Weinreb amide is recognized as the method of choice for monoaddition of an organometallic reagent, i.e., organolithium or Grignard reagent, and the reliability and effectiveness of Weinreb ketone synthesis have been demonstrated for a wide range of substrates (Scheme 1).¹ However, there are limitations in functional group tolerance with an organolithium or Grignard reagent. In that respect, we should note Knochel's work to prepare Grignard reagents under mild conditions.² In contrast, a transition-metal-catalyzed ketone synthesis, represented by Fukuyama ketone synthesis, has advantages, because it does not require a strongly basic and nucleophilic reagent (Scheme 1).^{3,4} The effectiveness of Fukuyama ketone synthesis has been demonstrated for a variety of substrates, even in an industrial scale.⁵ However, our literature survey reveals that this method

Scheme 1. Weinreb and Fukuyama Ketone Syntheses



has been used for relatively small nucleophiles (often excess equivalents), thereby hinting at a potential issue in its use at a late stage in a multistep synthesis of complex molecules. In addition, preparation of an organometallic reagent is often cumbersome for complex substrates and their stability might become problematic during preparation.

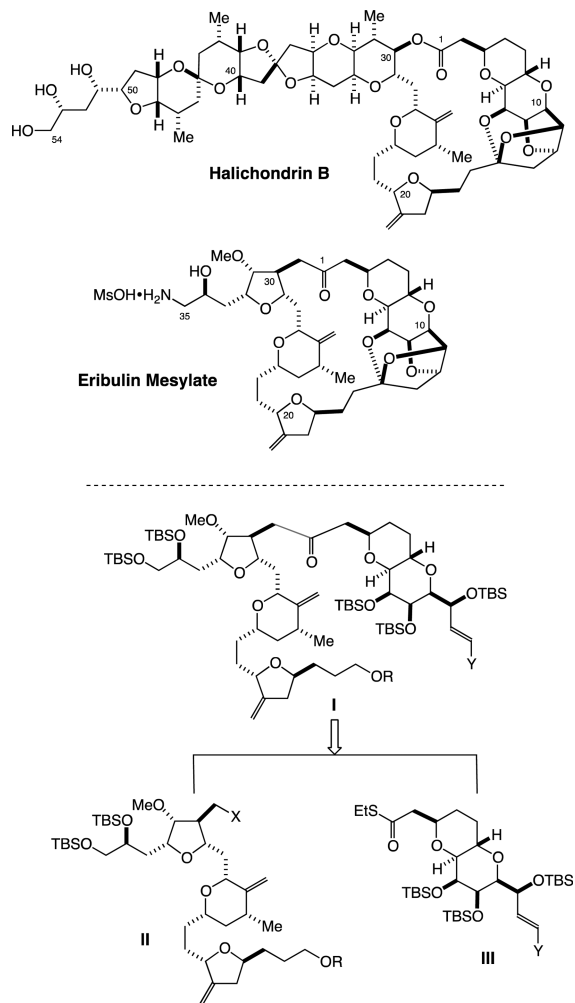
Related to the synthesis of Eribulin,^{6,7} a totally synthetic anticancer drug developed through structure modification of

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the right half of the marine natural product halichondrin B, we have become interested in the possibility of synthesizing ketone I or its synthetic equivalent via a coupling of two advanced building blocks II and III in one step (Scheme 2). This

Scheme 2. Structure of Halichondrin B and Eribulin Mesylate and Retrosynthesis



retrosynthesis is attractive because of its high degree of convergency. In order to realize the proposed synthesis efficiently, however, we need a ketone synthesis with good functional-group tolerance, desirably with use of a 1:1 molar ratio of coupling partners. In our analysis, none of the known ketone synthesis satisfactorily meets with our need, and we began our work. To achieve this goal, we considered the possibility of modifying Fukuyama ketone synthesis to a one-pot synthesis, which could be achieved by generating an alkylzinc species from an alkyl halide in the presence of a thioester and a Pd-catalyst. Interestingly, Ni-mediated one-pot ketone syntheses from alkyl halides and acid derivatives are known,⁸ but they have not been used at a late stage in a convergent synthesis of complex molecules. Here, we would like to report a highly efficient one-pot ketone synthesis by using alkylzinc halides prepared from alkyl halides via direct Zn-insertion or a SET process, followed by Pd-catalyzed coupling with a thioester. This method has a few appealing features, including (1) excellent functional group tolerance; (2) excellent

coupling efficiency with use of a near 1:1 molar ratio of coupling partners; and (3) experimental convenience.

RESULTS AND DISCUSSION

A. Activation of Alkyl Halides via Direct Zn Insertion and Single Electron Transfer. Fukuyama ketone synthesis is generally considered to involve three distinct steps: (1) oxidative addition of a Pd(0)-catalyst to a thioester, (2) transmetalation from a preprepared alkylzinc halide to the resultant Pd(II) species, and (3) reductive elimination leading to a ketone and simultaneously regenerating the Pd(0)-catalyst.^{4c} In order to achieve the proposed one-pot ketone synthesis, we first searched for a method to prepare alkylzinc halides from alkyl halides.

We should note that there might be an additional benefit in one-pot ketone synthesis. Alkylzinc halides are known to exhibit a radical character;⁹ for example, a trace amount of oxygen was suggested to break down alkylzinc halides to alkyl radicals,¹⁰ thereby hinting at a potential issue; namely, some alkylzinc halides might suffer from the chemical instability due to the inevitable radical pathway(s), for example a 1,5-H shift. By adjusting the rate of alkylzinc-halide generation relative to the rate of Zn → Pd transmetalation, one could imagine the possibility of avoiding accumulation of generated alkylzinc halides so that such an inherent problem might be suppressed or eliminated. Thus, one-pot ketone synthesis could allow us to expand the substrate scope in Fukuyama ketone synthesis and, at the same time, minimize the waste of organozinc species.

The direct insertion of zinc into alkyl halides could give the simplest solution for preparation of alkylzinc halides. However, this process is known to be relatively inefficient with commercially available zinc.¹¹ Several methods for activating nonactivated alkyl halides with zinc have been developed, including preactivation of zinc,¹² Rieke-zinc,¹³ and Zn/I₂/DMA/70 °C.¹⁴ Recently, Knochel reported LiCl-acceleration of zinc insertion to alkyl halides, to form organozinc halides (Zn/LiCl/THF/50 °C, and Mg/ZnCl₂/LiCl/THF).¹⁵ To the best of our knowledge, however, these methods have not yet been tested for preparation of highly functionalized and/or sterically demanding alkylzinc halides.

To prepare alkylzinc halides in situ, we planned to study two methods: (1) direct insertion of zinc dust to alkyl halides and (2) early transition-metal assisted alkyl halide activation via a SET process.¹⁶ Although alkyl-halide activation by early transition metals such as CoPc or Fe(acac)₃ is well established, preparation of alkylzinc halides via a SET process has not been demonstrated thus far. Nonetheless, we believe its feasibility, because this process is effective to generate alkylchromium intermediates from alkyl halides for the Co/Cr- and Fe/Cr-mediated couplings.¹⁷

At the onset, we decided to use alkyl bromides, instead of the corresponding alkyl iodides, considering the fact that alkyl bromides generally tolerate better in various organic transformations than alkyl iodides do. Later, we found that the best activation condition utilizes LiI so that alkyl bromides are transformed to the corresponding alkyl iodides in situ. For the screening, we chose a linear-chain alkyl bromide **1a**, as well as β- and α-methyl substituted bromides **1b,c**. Experimentally, **1a–c** were subjected to the specified conditions and the extent of Zn-activation was estimated from the product distribution after aqueous workup (Table 1). For these experiments, commercial zinc dust was used without any pretreatment.¹⁸

Table 1. Activation of Alkyl Halides to Alkylzinc Halides^a

$\text{TBDPSO-CH}_2\text{-CH(R}^1\text{)-CH(R}^2\text{)-X} \xrightarrow[\text{solvent (C = 0.4 M), rt, 16 h}]{\text{Zn dust (excess)}} \text{TBDPSO-CH}_2\text{-CH(R}^1\text{)-CH(R}^2\text{)-H}$

1a-c **2a-c**

a-series: R¹ = R² = H
b-series: R¹ = H; R² = Me
c-series: R¹ = Me; R² = H

entry	R ¹	R ²	X	solvent	additive (equiv)	RH/RBr/RI ^b
1	H	H	Br	THF	LiI (1.0)	3/1/0
2	H	H	Br	DMI ^c	LiI (1.0)	1/0/0
3	H	H	Br	DMI	LiBr (1.0)	1/9/0
4	H	H	Br	DMI	LiCl (1.0)	0/1/0
5	H	Me	Br	DMI ^d	LiI (1.0)	1/0/0
6	H	Me	Br	DMI	LiI (0.5)	1/60/10
7	H	Me	I	DMI	none	1/0/18
8	H	Me	Cl	DMI	LiI (1.0)	NR
9	H	Me	Br	DMI	LiI (0.5)/ TESCl (1.5)	6/1/0
10	H	Me	Br	DMI	CoPc (0.1)	1/0/0
11	H	Me	Br	DMI	NbCpCl ₄ (0.1)	8/1/0
12	Me	H	Br	DMI	LiI (1.0)	1/1/0
13	Me	H	I	DMI	LiI (0.5)	1/0/0
14	Me	H	Br	DMI	CoPc (0.1)	1/0/0
15	Me	H	Br	DMI	NbCpCl ₄ (0.1)	1/0/0

^aUnless indicated, the reactions were run with **1** (0.04 mmol), Zn(0) (>5 equiv), and an additive(s) in solvent (0.4 M) at rt in a glovebox.

^bProduct distribution was estimated from ¹H NMR of crude products.

^cFull conversion was achieved in other aprotic polar solvents such as DMA and NMP. ^d**2b** was not formed in DMA or NMP. Abbreviation: DMI = 1,3-dimethyl-2-imidazolidinone; DMA = *N,N*-dimethylacetamide; NMP = *N*-methyl-2-pyrrolidone; CoPc = Cobalt(II) phthalocyanine; NbCpCl₄ = cyclopentadienylniobium(V) tetrachloride; NR = no reaction.

We first studied direct insertion of zinc dust to alkyl bromides. Activation of linear-chain bromide **1a** was uneventfully observed. Namely, in the presence of LiI,¹⁹ zinc insertion smoothly took place at room temperature in aprotic polar solvents such as 1,3-dimethyl-2-imidazolidinone (DMI), *N,N*-dimethylacetamide (DMA), and *N*-methyl-2-pyrrolidone (NMP) (entry 2). Even in THF, zinc insertion was observed, although it was significantly slower (entry 1). On the basis of two pieces of literature information, the observed results were not totally surprising. First, polar solvents such as DMA, HMPA, and DMF are known to facilitate Zn insertion, although harsher conditions (heating and ultrasound) are usually employed.^{19,20} Second, lithium salts are known to exhibit a significant accelerating effect for Zn insertion.¹⁵ Interestingly, for activation of **1a** at room temperature, LiBr and LiCl were found to be much less effective than LiI (entries 3 and 4). We assume that LiI plays two roles, i.e., in situ formation of the iodide corresponding to **1a** and Zn insertion acceleration by lithium salt.

Contrary to **1a**, activation of β -substituted bromide **1b** was challenging. We eventually found that DMI (solvent) and LiI (additive, 1 equiv) are a special combination which effectively achieves zinc insertion at room temperature (entry 5). Interestingly, zinc insertion was not detected in other aprotic polar solvents such as DMA and NMP under the same conditions. In order to gain structure information on the “alkylzinc halide” prepared under the conditions of entry 5, we used electrospray-ionization negative-ion mass spectroscopy,

thereby demonstrating that the major species present in the solution corresponded to the expected alkylzinc halides.¹⁸

Overall, these results indicate that the Zn-insertion involves: (1) alkyl bromide **1a** is first converted to the corresponding iodide and (2) lithium iodide or bromide accelerates Zn-insertion to the resultant alkyl iodide. Experimental results given under entries 3–5, 7, and 8 support the first step. However, mechanistic insight into the remarkable acceleration effect observed with LiI in DMI is not clear at this time.

A decrease in the amount of LiI from 1.0 to 0.5 equiv caused a sharp drop in activation (entry 6 vs 5). Intriguingly, addition of TESCl restored smooth zinc insertion (entry 9). We would speculate that the major role of TESCl is cleaning the surface of commercial zinc dust.

As mentioned above, we were interested in the possibility of generating alkylzinc species via a SET process. Uneventfully, we found that a radical initiator CoPc activated **1b** without assistance of LiI (Table 1, entry 10). Interestingly, we found that NbCpCl₄ was also an effective initiator (entry 11). Our literature search revealed that low-valent niobium is used for radical-based transition metal catalyzed reactions,²¹ but not for alkyl-halide activation thus far. Nonetheless, we suggest that the low-valent niobium, generated by reduction of NbCpCl₄ with Zn in situ, works as a radical initiator. We should add that NbCpCl₄ appears to be a slower initiator than CoPc, which might be an advantage for one-pot Pd-catalyzed ketone synthesis with use of a 1:1 molar ratio of alkyl bromide and thioester for the reason mentioned above.

We should point out that these experiments showed that **1b** was activated with CoPc and NbCpCl₄, but did not establish that the resultant product(s) was alkylzinc halides required for the following Pd-mediated coupling. As a matter of fact, we will discuss that this activation did not yield alkylzinc halides usable for the Pd-mediated coupling.

α -Substituted bromide **1c** (X = Br) was found to behave as predicted on the basis of the results observed on **1a,b**. Direct zinc insertion to **1c** with X = Br was sluggish (entry 12 vs entries 2 and 5), which was expected because of the slower rate of Br \rightarrow I displacement. Indeed, facile activation of **1c** (X = I) was observed (entry 13).²² SET activation behaviors of **1c** were found almost identical to those observed for **1b** (entries 14 and 15 vs entries 10 and 11).

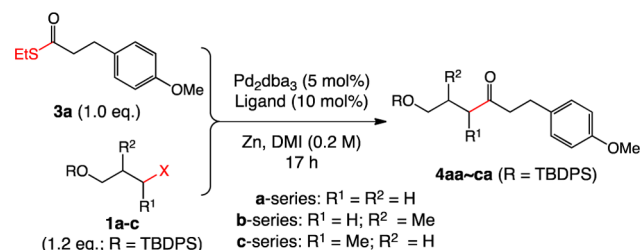
Before shifting our focus to the carbon–carbon bond-forming step, we tested the stability of alkylzinc halide, prepared via direct Zn-insertion of an alkyl bromide at room temperature, thereby demonstrating that it is stable at room temperature at least for 2 weeks.²³

B. One Pot Ketone Synthesis from Alkyl Halides and Thioesters. Fukuyama ketone synthesis has a number of appealing aspects, including the nearly neutral conditions employed for coupling alkylzinc halides with thioesters with excellent functional group compatibility. To the best of our knowledge, however, its application is limited to relatively small nucleophiles thus far. We envisioned that in situ preparation of alkylzinc halides could allow us to achieve Fukuyama ketone synthesis in one pot, thereby not only giving experimental convenience but also adding a new dimension in organic synthesis. We are particularly interested in the possibility of employing one-pot ketone synthesis at a late stage in a convergent synthesis of complex molecules. For this reason, we aim toward one-pot ketone synthesis, which should meet with several criteria including the synthetic efficiency, the functional

group tolerance, and the use of a near 1:1 molar ratio of coupling partners.

With two orthogonal methods for activation of alkyl halides with zinc dust at room temperature, we began to study the feasibility of one-pot ketone synthesis. For this study, we chose the coupling of **1a–c** + **3a** → **4aa–ca** (Table 2).

Table 2. One-Pot Ketone Synthesis via in Situ Activation of Alkyl Halides^a



entry	R ¹	R ²	X	ligand	additives (equiv)	4/3 ^b
1	H	H	Br	PPh ₃	LiI (1.0)	1/2.5
2	H	H	Br	PPh ₃	LiI (1.0)/TESCl (1.5)	1.5/1
3	H	H	Br	PCy ₃	LiI (1.0)/TESCl (1.5)	4.3/1
4	H	Me	Br	PCy ₃	LiI (1.0)/TESCl (1.5)	1.1/1
5 ^c	H	Me	Br	PCy ₃	LiI (1.0)/TESCl (1.5)/CrCl ₂ (0.25)	3/1
6	H	Me	Br	PCy ₃	CoPc (0.05)/TESCl (1.5)	0/1 ^d
7	H	Me	Br	PCy ₃	CoPc (0.05)/TESCl (1.5)/CrCl ₂ (0.25)	1/15 ^e
8	H	Me	Br	PCy ₃	NbCpCl ₄ (0.05)/TESCl (1.5)	0/1 ^d
9	H	Me	Br	PCy ₃	NbCpCl ₄ (0.05)/TESCl (1.5)/CrCl ₂ (0.25)	5/1
10	H	Me	I	PCy ₃	LiI (0.6)/TESCl (1.5)	2.6/1
11	H	Me	I	PCy ₃	LiI (0.6)/TESCl (1.5)/CrCl ₂ (0.25)	10/1
12	Me	H	I	PCy ₃	LiI (1.0)/TESCl (1.5)	1.8/1 ^f
13	Me	H	I	PCy ₃	LiI (1.0)/TESCl (1.5)/CrCl ₂ (0.25)	1/1.3
14	Me	H	I	PCy ₃	NbCpCl ₄ (0.02)/TESCl (1.5)	1/1
15	Me	H	I	PCy ₃	NbCpCl ₄ (0.02)/TESCl (1.5)/CrCl ₂ (0.25)	1/3.4

^aConditions: To **1** (0.048 mmol), **3a** (0.04 mmol), and Zn (0) (>5 equiv) was added premixture II-A [0.1 mL, LiI (0.4 M) in DMI] or premixture II-B [0.1 mL, CrCl₂ (0.1 M), LiI (0.4 M) in DMI]. Then, premixture I [0.1 mL, Pd₂dba₃ (0.02 M), Ligand (0.04 M) in DMI], TESCl (1.5 equiv), and additional additive(s) were added to the reaction mixture at rt in a glovebox. ^bRatio was estimated from ¹H NMR of crude products. ^cIn 0.2 mmol scale in DMI (C = 0.4 M) after 1 d, **4ba** was isolated in 95% yield. ^dOnly **2b** and **3a** were detected. ^eFull conversion was achieved after 2 days. ^fFull conversion was obtained when **1c** (2.0 equiv) was used. Abbreviation: Pd₂dba₃ = tris(dibenzylideneacetone)dipalladium(0); PPh₃ = triphenylphosphine; PCy₃ = tricyclohexylphosphine.

Experimentally, palladium catalyst/phosphine ligand and lithium salt, dissolved in DMI separately, were added to substrates and Zn dust, and the product distribution was estimated from ¹H NMR analysis of crude products (Table 2).

Knowing that the activation of bromide **1a** was effectively achieved in DMI in the presence of LiI (Table 1, entry 2), we first tested this condition for one-pot ketone synthesis and succeeded in isolation of the expected ketone **4aa** (Table 2, entry 1). In spite of its modest efficiency, we were pleased with the result, because this experiment demonstrated the feasibility

of one-pot ketone synthesis. Naturally, we were anxious to improve the coupling yield and speculated that the observed modest yield could be attributed to either (1) poor efficiency for zinc insertion and/or (2) poor efficiency for a Pd-mediated carbon–carbon bond-forming step. To address this question, we tested the coupling in the presence of LiI and TESCl (entry 2), cf., entry 9 in Table 1, and found the coupling efficiency was significantly improved, thereby suggesting that the former reason was more likely. In other words, the thioester, Pd-catalyst, and/or phosphorus ligand appeared to slow down the direct Zn-insertion step.

Using 1.0 equiv of LiI and 1.5 equiv of TESCl in DMI, we then optimized the coupling conditions, including the Pd-catalyst²⁴ and phosphorus ligand,²⁵ and eventually found that the phosphorus ligand has a significant effect;²⁶ bulky and electron-rich tricyclohexylphosphine (PCy₃) was found to be best.

Once again, we found that one-pot ketone synthesis from β-branched bromide **1b** was far more challenging than the corresponding nonbranched bromide **1a**. Under the optimized conditions in the nonbranched series, we observed that the coupling of **1b** with **3a** indeed took place, but only in a low efficiency (entry 4).

In a broad sense, Fukuyama ketone synthesis is one of the Pd-mediated cross-couplings. The reaction mechanism for Pd-catalyzed cross-coupling reactions appears to be more complex than the generally accepted catalytic cycle, i.e. oxidative addition, transmetalation, and reductive elimination. For example, Organ showed the involvement of higher-order organozincates in the alkyl–alkyl Negishi cross-coupling; Koszinowski suggested that a less active Zn–Pd dimer could be formed in the Negishi coupling, but lithium salt could prevent the dimerization of Zn–Pd by forming anionic organozincates.^{27,28} With this information, we tested the effect of lithium salt, but found that an increase of lithium salt did not improve the efficiency of **1b** + **3a** → **4ba**.¹⁸ We then conducted an extensive search for a second metal promoter, leading us to discover that CrCl₂ significantly improves the coupling efficiency (entry 5). A similar improvement by CrCl₂ was observed with **1b** (X = I) (entries 10 and 11). We assume that chromium salt might shift the equilibrium toward higher-order organozincates and/or might break Pd–Zn to restore palladium reactivity.

Next, we studied the feasibility of one-pot ketone synthesis with an alkylzinc halide prepared via a SET process. Our first attempt with CoPc (cf., entry 10, Table 1) was disappointing; we could not detect the desired product **4ba** in either the presence or absence of LiI (entry 6). To our delight, we observed that, on addition of 25 mol % CrCl₂, the desired ketone **4ba** was formed with excellent efficiency (entry 7). Interestingly, the same phenomena were observed with NbCpCl₄ (entries 8 and 9). We suggest that CrCl₂ plays a role in trapping the alkyl radical, generated by CoPc or NbCpCl₄, and transferring it to the zinc halide.

The behavior of α-substituted bromide **1c** was intriguing. Based on the steric reason, we anticipated α-substituted halide **1c** to behave similarly to β-substituted bromide **1b** rather than nonsubstituted bromide **1a**. Experimentally, however, the best conditions for **1c** were found to be the best conditions for **1a** (entry 12) rather than the best conditions for **1b** (entry 5). Contrary to **1b**, addition of CrCl₂ gave a negative effect on the coupling efficiency of **1c** (entries 12 vs 13 and 14 vs 15). Furthermore, Zn-activation via SET was less effective than

direct Zn-insertion (entries 12 vs 14, 15). The coupling with isopropyl iodide exhibited the overall profile similar to that with **1c** (Table 4). We speculate that this intriguing observation might relate to the relative stability or reactivity of secondary vs primary alkylchromium halides.²⁹ Obviously, further studies are needed to gain the mechanistic insight for the observed results.

In order to demonstrate that these screening results are translated to a useful synthetic method, we carried out one-pot ketone synthesis **1a–c** + **3a** → **4aa–ca** in a 0.2 mmol scale, to isolate ketone **4aa–ca** in 87% (entry 3), 95% (entry 5), and 93% yields (entry 12), respectively.³⁰

Before shifting our focus to application to complex substrates, we compared the one-step (one-pot) procedure with the two-step procedure in the following section.

C. One-Step vs Two-Step Procedure. Alkylzinc halides prepared via direct zinc insertion are stable at room temperature at least for 2 weeks (vide ante). That observation suggests the possibility of utilizing alkylzinc halides thus prepared for Fukuyama ketone synthesis in a two-step procedure similar to the original Fukuyama protocol. To address this notion, we compared the efficiency of the one-step procedure (one-pot) with that of a two-step procedure.

As an example for the direct zinc insertion method, we chose the coupling **1b** + **3a** → **4ba** (Table 3). We noticed virtually no difference in the overall yield between the one- and two-step procedures, as expected.³¹

Table 3. Comparison of One- vs Two-Step Procedure^a

Alkylzinc halides prepared via direct zinc insertion: 1b + 3a → 4ba	
one-step (one-pot) procedure ^b :	95% isolated yield
two-step procedure 1st step: LiI, Zn followed by 2nd step: CrCl ₂ , Pd ₂ dba ₃ , PCy ₃	91% isolated yield
Alkylzinc halides prepared via a SET process: 1b + 3a → 4ba	
one-step (one-pot) procedure ^c :	96% isolated yield
two-step procedure with CoPc: test #1 1st step: CoPc, Zn followed by 2nd step: CrCl ₂ , Pd ₂ dba ₃ , PCy ₃ , 3a	0% isolated yield
two-step procedure with CoPc: test #2 1st step: CoPc, Zn, CrCl ₂ , followed by 2nd step: Pd ₂ dba ₃ , PCy ₃ , 3a	85% isolated yield
one-step (one-pot) procedure ^d :	95% isolated yield
two-step procedure with NbCpCl ₄ : test #1 1st step: NbCpCl ₄ , Zn followed by 2nd step: CrCl ₂ , Pd ₂ dba ₃ , PCy ₃ , 3a	0% isolated yield
two-step procedure with NbCpCl ₄ : test #2 1st step: NbCpCl ₄ , Zn, CrCl ₂ , followed by 2nd step: Pd ₂ dba ₃ , PCy ₃ , 3a	95% isolated yield

^aOne-pot coupling was carried out under the conditions specified in Table 2 (entries 5, 7, and 9^d). See Supporting Information for more details.

For the study on alkylzinc halides generated via a SET process, we first studied the conditions with CoPc for the coupling **1b** + **3a** → **4ba** (Table 3). As discussed in the preceding section, CrCl₂ plays the key role in achieving an efficient one-pot ketone synthesis of β -substituted bromide **1b**. Then, there are two possibilities in the timing of the addition of this key additive, i.e., addition of CrCl₂ in the first or second step. Experimentally, it was found that its addition in the first

step gave the expected ketone in the yield comparable to that in the one-step procedure, whereas its addition in the second step gave virtually no expected ketone. This experiment established the experimental protocol for preparation of alkylzinc halides with use of a SET process. At the same time, it provided the evidence that CrCl₂ is involved in the process from alkyl halides to the alkylzinc halide. This observation is consistent with the assumption that the role of CrCl₂ is to trap the alkyl radical, generated via a CoPc-mediated SET process, and transmetallate it to Zn(II) to form RZnX.³² In addition, we mention that CrCl₂ may have an additional role as noticed in the coupling under the conditions that included LiI, TESCl, and CrCl₂ (entry 5, Table 2). The overall profile for the coupling with an alkylzinc halide, generated with NbCpCl₄ and zinc dust, is the same as that observed for the coupling with an alkylzinc halide, generated with CoPc.

D. Three Coupling Conditions. As summarized in Table 2, we have developed three different types of coupling conditions for one-pot ketone synthesis (Table 4).³³ We applied these three coupling conditions to arbitrarily chosen substrates, with the hope that this study should demonstrate functional-group tolerance and, at the same time, give a guideline in selecting the coupling conditions for a given substrate.

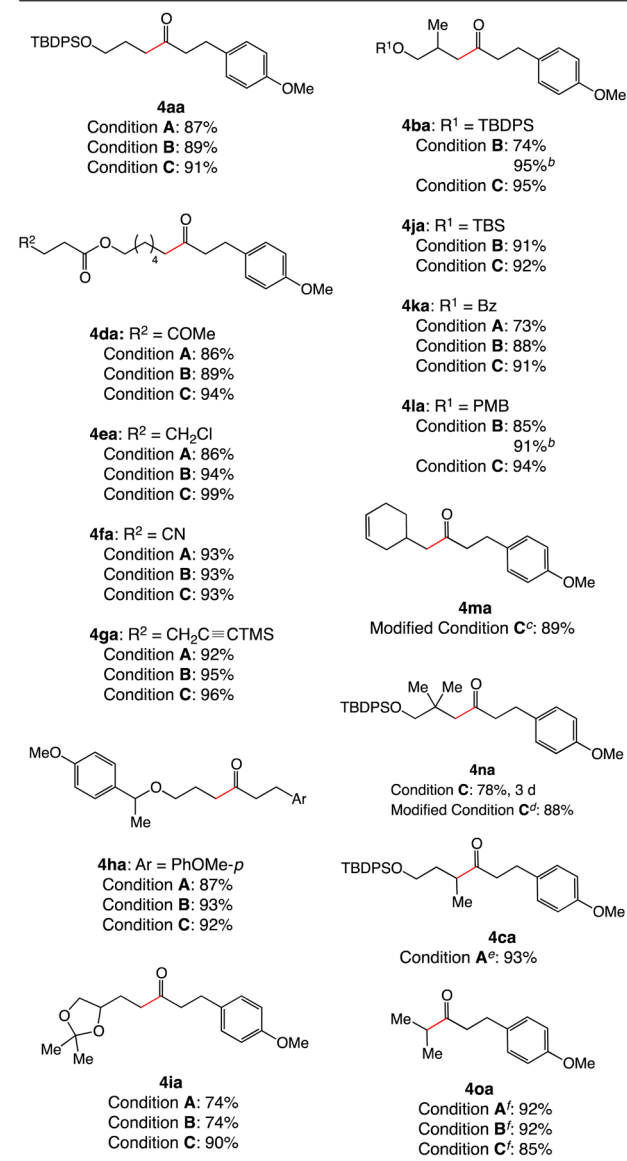
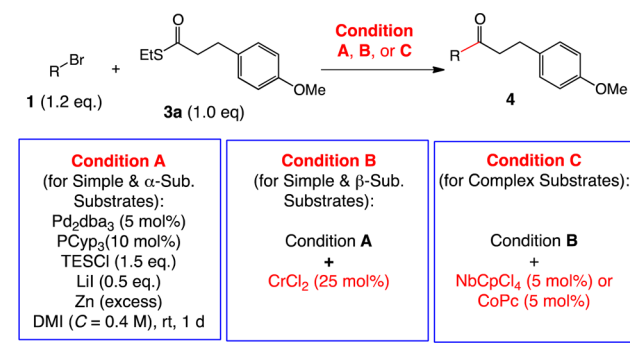
Overall, one-pot ketone synthesis was amazingly effective for all the arbitrarily chosen substrates, and Condition C worked best for the substrates tested, except for α -substituted iodides, cf., **4ca** and **4oa** (Table 4). Thus, with use of Condition C, it can be tested whether one-pot ketone synthesis is applicable to a given substrate. However, in terms of the experimental simplicity and cost-effectiveness, the preference order is obvious: Condition A > Condition B > Condition C. A glance of the results given in Tables 2 and 4 gives a rough guideline for predicting the effectiveness of Conditions A and B for a given substrate. Overall, the effectiveness of Condition A appears to be limited to simple linear and α -substituted alkyl halides, cf., **1a**, **1d–i**, **1c**, and **1o**, whereas Condition B appears to be limited to simple linear and β -substituted alkyl halides, for example **1b** and **1j–n**.

E. Functional Group Tolerance and Limitation. The results given in Table 4 show that common functional groups were well tolerated in one-pot ketone synthesis, including silyl protecting groups, *p*-methoxybenzyl (PMB), acetonide, ester, cyanide, ketone, chloride, olefin, and TMS-protected acetylene.

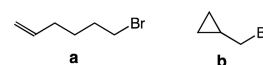
In order to test for leakage of alkyl bromide via a radical process such as a 1,5-H shift, we deliberately chose the alkyl halides leading to **4ha** and **4la**. Even under Condition C, using a SET process for preparation of alkylzinc halides, the reductive radical quenching did not override the desired Pd-catalyzed coupling pathway.

Obviously, several functional groups are not compatible with one-pot ketone synthesis (Figure 1). Due to the well-recognized radical process,^{9,10} bromides **a** and **b** gave the cyclized product and the ring-opened product as the major product, respectively. In addition, some functional groups, including iodo-olefins, do not tolerate under Pd-mediated coupling conditions.

F. Coupling Efficiency vs Molar Ratio of Coupling Partners. Under coupling Condition C, we examined the coupling efficiency vs the molar ratio of coupling partners. For this test, we chose the coupling of **1b** + **3a** → **4ba**, where **4ba** was isolated in 95%, 93%, 88%, 82%, and 87% yields with **1b**:**3a** = 1.2:1.0, 1.1:1.0, 1.0:1.0, 1.0:1.1, and 1.0:1.2, respectively. This

Table 4. One-Pot Ketone Synthesis with Arbitrarily Chosen Nucleophiles^a

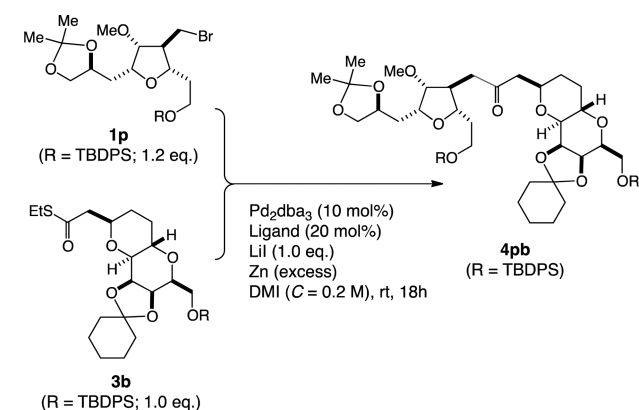
^aThe couplings were done in a scale of **3a** (0.20 mmol) and **1** (0.24 mmol), and the yields are based on chromatographically isolated products.³³ ^bPCy₃ instead of PCyp₃. ^cPd₂dba₃ (10 mol %), PCyp₃ (20 mol %), CrCl₂ (50 mol %), Lil (1 equiv), NbCpCl₄ (10 mol %), DMI (C = 0.4 M). ^dCoPc (5 mol %) instead of NbCpCl₄ (5 mol %). ^e1c (2.0 equiv) and PCy₃ used. ^f1o (1.5 equiv) and PCy₃ used. Abbreviation: PCyp₃ = tricyclopentylphosphine.

**Figure 1. Alkyl bromides do not survive in one-pot ketone synthesis.**

experiment demonstrated that one-pot ketone synthesis is effective even with an ~1:1 molar ratio of coupling partners.

G. Application to Syntheses of Complex Molecules.

Having demonstrated the feasibility of a one-pot ketone synthesis from alkyl halides and thioesters, we moved into the next phase of study, namely a test of the coupling efficiency with both nucleophile and electrophile bearing structure complexity (Table 5). For this test, we chose the coupling of **1p** + **3b** → **4pb** and studied the coupling efficiency under three different types of coupling conditions, i.e., Conditions A–C.

Table 5. One-Pot Ketone Synthesis with Complex Nucleophile and Electrophile^a

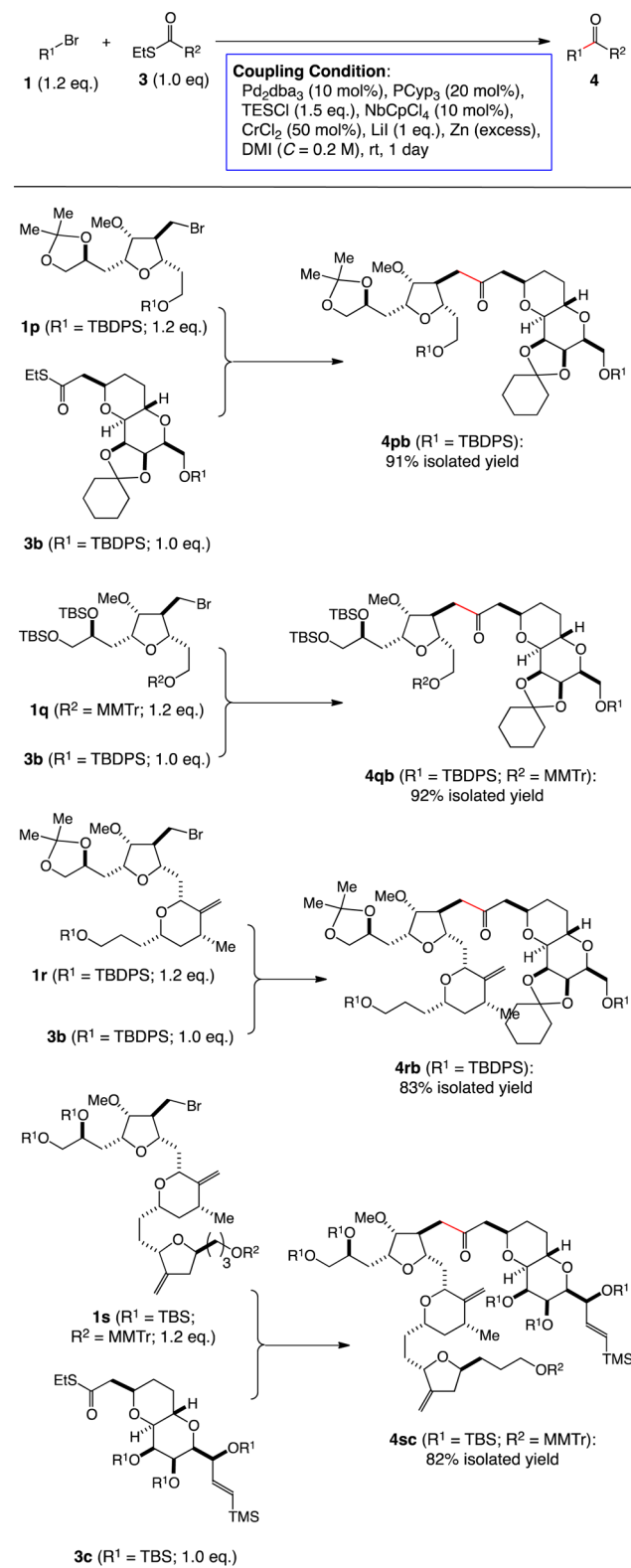
entry	ligand	additives (mol %)	conversion (%)
1	PCy ₃	TESCl (1.5)/CrCl ₂ (0.5)	33
2	PCyp ₃	TESCl (1.5)/CrCl ₂ (0.5)	50
3	PCyp ₃	TESCl (1.5)/CoPc (0.1)/CrCl ₂ (0.5)	60
4	PCyp ₃	TESCl (1.5)/CpNbCl ₄ (0.1)/CrCl ₂ (0.5)	100

^aScreening was done with a scale of **1p** (0.012 mmol) and **3b** (0.010 mmol). Conversion was estimated by crude ¹H NMR.

On the basis of the results summarized in Tables 1 and 2, it was not surprising to observe only a negligible level of conversion under Condition A (data not shown). Even under Condition B, the efficiency of one-pot ketone synthesis was not satisfactory (entry 1). In contrary to (**1a–c** + **3a**)-coupling, tricyclopentylphosphine (PCyp₃) was found to be more effective than tricyclohexylphosphine (PCy₃), presumably due to the steric reason (entry 1 vs 2).

One-pot ketone synthesis under Condition C, particularly with NbCpCl₄, gave a clean, complete conversion to furnish the desired ketone in 91% isolated yield (Table 6). Overall, these observations demonstrated once again that one-pot ketone synthesis via a SET process gives excellent efficiency even for complex substrates.

H. Application to Synthesis of Eribulin. Lastly, we used Eribulin as an example to illustrate that one-pot ketone synthesis is a reliable option for a late stage coupling in a convergent synthesis of complex molecules (Table 6). To our delight, we found no significant difference in coupling efficiency, with the increase in molecular size. It is also worthwhile to point out that even the halides having an allylic

Table 6. Application to Eribulin Synthesis^a

^aCouplings were done in a 0.10 mmol scale, except for **1s** + **3c** → **4sc** in a 0.05 mmol scale. Yields were based on the products isolated by column chromatography.

tertiary hydrogen positioned for the 1,5-H shift did not show obvious leakage through a radical species (**1r**, **1s**). Finally, one-

pot ketone synthesis was successfully applied to a synthesis of ketone **4sc** containing all the carbons of Eribulin.

CONCLUSION

A facile activation of nonactivated 1°- and 2°-alkyl halides was achieved via (1) direct Zn insertion or (2) early transition-metal assisted SET-activation. For alkyl bromides, lithium iodide in DMI was found to be a special combination for efficient insertion of zinc dust into alkyl bromides at room temperature. Mechanistically, alkyl bromides were first transformed to the corresponding alkyl iodides, which then reacted with zinc dust. An orthogonal, unprecedented method was developed, to prepare alkylzinc halides with use of a combination of CoPc or NbCpCl₄ and CrCl₂, where the former serves as a radical initiator whereas the latter serves to trap and transfer the generated radical to zinc halide. Through this study, a new radical initiator, generated from NbCpCl₄ and zinc dust, was discovered.

Combined with the two facile methods for preparation of alkylzinc halides, Fukuyama coupling was then extended to one-pot ketone synthesis from alkyl halides and thioesters. With use of the two orthogonal activation methods, three sets of coupling conditions were developed, with Condition A (Pd₂dba₃, PR₃, Zn, LiI, TESCl, DMI), Condition B (A + CrCl₂), and Condition C (B + NbCpCl₄ or CoPc) being useful for simple linear and α-substituted alkyl halides, simple linear and β-substituted alkyl halides, and complex substrates, respectively. Overall, Condition C was found to be applicable for the broadest range of substrates. All conditions gave an excellent synthetic efficiency, with good functional group tolerance.

Controlled formation of alkylzinc halides by a combination of CrCl₂ and NbCpCl₄ or CoPc was crucial for its application to complex substrates. Interestingly, one-pot ketone synthesis did not suffer from the chemical instability due to the inevitable radical pathway(s), for example a 1,5-H shift. Notably, even with the increase in molecular size, no significant decrease in coupling efficiency was noticed. For these reasons, one-pot ketone synthesis is a reliable option for coupling at a late stage in a convergent synthesis of complex molecules, as exemplified in a synthesis of **4sc** containing all the carbons of Eribulin.

It is worthwhile noting that all the required reagents are commercially available and can be conveniently premixed and stored without loss of activity. We believe that the reported, facile preparation of alkylzinc halides at room temperature will find various applications beyond this work. Extension of one-pot ketone synthesis to an intramolecular setting is in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03897.

Additional data for Tables 1 and 2, experimental procedures, characterization data, and copies of spectra (PDF)

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Notes

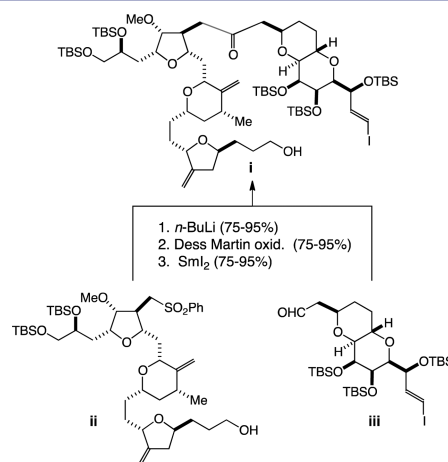
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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(22) Direct insertion of zinc to 2°-alkyl halides compared to 1°-alkyl halides is known to be faster.^{9,11}

(23) The same yield was obtained in the coupling using 2-week old or freshly prepared RZnX in the two-step procedure given in Table 3.

(24) Several Pd catalysts, including Pd/C D1,⁵ were tested, but we found that Pd₂dba₃ was best for screening ligands, although Pd(PCy₃)Cl₂ gave similar results. We thank Dr. Seki for generous donation of various Pd/C.

(25) Other ligands tested included *t*-Bu₃P, SPhos, and PEPPSI-IPr.

(26) Other thioesters, prepared from various ArSH (containing EWG or EDG), CF₃CH₂SH, and MeO₂CCH₂SH, did not give any beneficial impact.

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(30) See Table 4 for more details.

(31) TESCl is not required and can be omitted for two-step procedures.

(32) After step one in the two-step procedures, each supernatant solution was diluted and subjected to ESI mass spectroscopy in negative ionic mode. Besides ZnX₃⁻, RZnX₂⁻ ions were observed at higher *m/z* ratios for following conditions: (1) direct Zn insertion: (Zn, LiI); (2) SET with CrCl₂: (CoPc, Zn, CrCl₂) and (NbCpCl₄, Zn, CrCl₂).¹⁸

(33) In general, tricyclohexylphosphine (PCy₃) is more effective than tricyclopentylphosphine (PCyp₃) for simple substrates (Table S-2)¹⁸ but PCyp₃ was found to be the optimal choice of ligand for complex substrates (Table 5 and 6). Thus, PCyp₃ was used to study functional group tolerance in Table 4. Higher yields were expected with most substrates if PCy₃ was used rather than PCyp₃ as shown with **1b** and **1l**, especially under Condition A.