LETTERS

Fe/Cu-Mediated One-Pot Ketone Synthesis

Vemula Praveen Kumar, Vaddela Sudheer Babu, Kenzo Yahata, and Yoshito Kishi*👳

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

Supporting Information

ABSTRACT: An Fe/Cu-mediated one-pot ketone synthesis was reported. Unlike Ni- and Pd-mediated one-pot ketone syntheses, the reported Fe/Cu-mediated method allowed selective activation and coupling of alkyl iodides over vinyl iodides. The newly developed one-pot ketone synthesis was applied to a synthesis of vinyl iodide/ketone **13**, the left half of halichondrin B, as well as vinyl iodide/ketone **8a**, the C20–C26 building block of halichondrins.



T he addition of organometallic reagents onto carboxylic acids or derivatives gives a simple solution for ketone synthesis. One drawback associated with this method is the fact that desired ketones often react further with organometallic reagents. Weinreb ketone synthesis offers an ingenious solution to overcome this drawback.¹ In recent years, it has been demonstrated that Ni- or Pd-mediated coupling of an activated form of carboxylic acid with an organometallic offers an alternative solution.²

We recently reported a one-pot ketone synthesis with alkylzinc halides, prepared *in situ* from alkyl halides via a single electron transfer (SET) process, and were curious to extend this concept to development of Cu-mediated one-pot ketone synthesis for two reasons.³ First, Cu-mediated one-pot ketone synthesis might exhibit a reactivity profile different from Ni-and/or Pd-mediated one-pot ketone syntheses; for example, the latter methods do not match well with nucleophiles bearing vinyl and/or aryl halides.⁴ Second, it is well recognized that overaddition of organometallic reagents is not the issue for cuprate-based ketone synthesis.⁵ In this letter, we report the development and application of Fe/Cu-mediated one-pot ketone synthesis.

For the feasibility study of the proposed reductive coupling, we chose the substrates shown in Scheme 1, because this pair of





substrates was used for the study on Pd- and Ni-mediated onepot ketone synthesis in this laboratory.^{3,6} The first attempt under the arbitrarily chosen condition [**2a** (5 equiv), **1a** (1 equiv), MnPc (10 mol %), CuCN (1 equiv), LiCl (3 equiv), THF (C = 0.2 M), rt, 6 h] gave **3a** in 35% isolated yield. Being encouraged by this result, we optimized the coupling condition, including (1) radical initiator and loading,⁷ (2) copper source,⁸ (3) LiCl effect,⁹ (4) **1a:2a** molar ratio,¹⁰ (5) reducing metal,¹¹ (6) solvent and concentration,¹² and (7) additives.¹³ Through this study, the conditions that include "**1a** (1.0 equiv), **2a** (3.0 equiv), Fe(TMHD)₃ (10 mol %; **4** in Scheme 2), CuCl₂ (1.0 equiv), Mn (2 equiv), LiCl (3 equiv), DME (*C* 0.4 M), 0 °C, 15 h" were found to be effective for the (**1a** + **2a**)-coupling (76% isolated yield).¹⁴



The scope and limitation of this method was then studied under the conditions of Method A in Scheme 3. Overall, the efficiency of Cu-mediated one-pot ketone synthesis was comparable with that of Pd- and Ni-mediated one-pot ketone syntheses. As expected, however, the Cu-mediated method exhibited an appealing reactivity profile; that is, unlike the Pdand Ni-mediated method, the Cu-mediated method allowed selective activation and coupling of an alkyl iodide over a vinyl or aryl iodide, cf., **1j–m**. Related to the ongoing project, we were interested in this selectivity. In particular, we recognized the possibility of synthesizing **8a**, the C20–C26 building block of halichondrins, via the coupling of **6** with 7.¹⁵

Under the condition of Method A (Scheme 3), the one-pot ketone coupling gave the desired product 8a. However, finetuning was necessary to efficiently perform the coupling. The activation rate of alkyl iodide in 7 was slower than that in the model 1j. With a higher loading of $Fe(TMHD)_3$, the coupling rate was accelerated as expected, but the product was

Received: April 13, 2017

Scheme 3. Scope and Limitation



LiCl (3 equiv), Mn (2.0 equiv), DME (C 0.4 M), 0 °C, 15 h Method B: 2a (1.0 equiv), 1a~q (1.2 equiv), FeBr₂(dppb) (5 mol %), CuCl₂ (1.0 equiv), LiCl (3 equiv), Mn (2.0 equiv), DME (C 0.4 M), 0 °C, 15 h

Method C: 2b (1.2 equiv), 1a~q (1.0 equiv), FeBr₂(dppb) (5 mol %), Cul (1.0 equiv), Cp₂ZrCl₂ (1.0 equiv), LiCl (3 equiv), Mn (2.0 equiv), DME (C 0.4 M), 0 °C, 15 h

A. Steric Effects	Me	Mo. Mo
TBDPSO	TBDPSO	
1a	1b	1c
Method A: 76%	Method A: 74%	Method A: 72%
Method B: 90%	Method B: 86%	Method B: 80%
Method C: 80%	Method C: 78%	Method C: 72%
TBDPSO	TBDPSO	
1d ^{Me}	Mế Me 1e	
Method A: 74%	Method A: no PD	
Method B: 80%	Method B: no PD	
Method C: 74%	Method C: no PD	
B Tolerance with Common	Protecting Groups	

RO L

1b: R = TBDPS	1f: R = TBS	1g: R = Bz	1h: R = THP	1i: R = PMB
Method A: 74%	Method A: 78%	Method A: 81%	Method A: 75%	Method A: 719
Method B: 86%	Method B: 90%	Method B: 90%	Method B: 85%	Method B: 78%
Method C: 78%	Method C: 81%	Method C: 90%	Method C: 80%	Method C: 70%

C. Differentiation from Vinyl and Aryl Halides and Other Groups

		X	
1j: X = I	1I: X = I	1n : X = Cl	1p : X = OH
Method A: 76%	Method A: 75%	Method A : 72%	Method A : 25%
Method B: 86%	Method B: 86%	Method B : 76%	Method B : 36%
Method C: 79%	Method C : 81%	Method C : 70%	R I 1q: R = -C°'C-TES Method A: 75% Method B: 86% Method C: 78%
1k: X = Br	1m : X = Br	1o : X = Br	
Method A: 74%	Method A : 74%	Method A : 15%	
Method B: 85%	Method B : 87%	Method B : 30%	
Method C: 80%	Method C : 80%	Method C : 21%	

accompanied by a small amount of side-product **8b** (X = H).¹⁶ Tuning the Fe(TMHD)₃ loading provided a practical solution to overcome this problem; with 13–15 mol % catalyst, the (6 + 7)-coupling gave the desired ketone **8a** (75% isolated yield), along with a trace amount of **8b** (<1% yield), in 15 g scale experiments (Scheme 4).

Scheme 4. Synthesis of the C20–C26 Building Block of Halichondrins via Fe/Cu-Mediated One-Pot Coupling



Similarly, the Fe/Cu-mediated coupling with the vinyl bromide corresponding to 7 gave the desired product in a comparable yield.

As illustrated in the transformation of $6 + 7 \rightarrow 8a$, the Fe/ Cu-mediated one-pot ketone synthesis, initiated with Fe-(TMHD)₃, exhibited a unique profile of reactivity, which might be difficult to achieve by the Pd- or Ni-mediated one-pot ketone synthesis. Nevertheless, we were anxious to improve one particular aspect of this coupling, i.e., a 3:1 molar ratio of electrophiles and nucleophiles. For the case of (6 + 7)coupling, the unbalanced molar ratio of electrophile and nucleophile was acceptable, because 6 was significantly less expensive than 7. However, it would not be appealing to apply this coupling for the inverse case, i.e., a more expensive electrophile compared to the nucleophile.

It was speculated that some of 6 was wasted during the activation process of the Fe-catalyst; in order for Fe(TMHD)₃ to function as a radical initiator, Fe(III) should be reduced to Fe(II) by Mn metal. The reduction released one molecule of β diketone, which consumed some of 6 in a nonproductive manner. If so, this side reaction could be avoided with use of an Fe(II)-initiator. For this reason, various radical initiators were screened for the Cu-mediated ketone coupling. Among them, FeBr₂·(dppb) was found to promote the (1a + 2a)-coupling well.¹⁷ Through optimization, it was found that the coupling was effectively achieved under the following conditions: FeBr₂. (dppb) (5 mol %), acid chloride (1.0 equiv), iodide (1.2 equiv), $CuCl_2$ (1.0 equiv), LiCl (3 equiv), Mn (2 equiv), DME (C = 0.4 M), 0 °C, 15 h.¹³ Interestingly, FeBr₂ (dppb) gave a better coupling yield than the corresponding FeCl₂ (dppb).¹⁸ Under the optimized condition, the coupling was tested with the molar ratio of 1a/2a being 1.2/1.0 and 1.0/1.2, to give 3a in 90% and 87% isolated yield, respectively. With the 1.2/1.0 molar ratio of nucleophile and electrophile, the coupling efficiency was studied for the substrates listed in Method B in Scheme 3.

The FeBr₂·(dppb) condition was applied for the (6 + 7)coupling, to give **8a** in 72% isolated yield. The coupling yield was further improved up to an 80% yield, by replacing FeBr₂· (dppb) with the FeBr₂-complex prepared from the SciOPPligand, recently reported by Nakamura and co-workers.¹⁹

Phosphine-based FeBr2-catalysts allowed us to efficiently achieve the one-pot ketone synthesis, even with a near 1:1 molar ratio of nucleophiles and electrophiles. Encouraged by this result, we attempted to apply this approach to a synthesis of vinyl iodide 13, the left half in the halichondrin-B series, as well as closely related vinyl iodide 11.²⁰ In the latter series, we were able to prepare the acid chloride and demonstrated that the coupling gave the desired product 11 in 20-25% overall yield from the carboxylic acid.²¹ However, in the former series, we could not prepare the required acid chloride. Overall, because of their instability during preparation and/or coupling, these acid chlorides were not useful for our purpose. Under these circumstances, we focused on a 2-thiopyridine ester as an alternative electrophile, because it proved to be an excellent electrophile in the Zr/Ni-mediated one-pot ketone synthesis.6

With this background, we tested the $(1a + 2b \rightarrow 3a)$ coupling under the conditions of Method B and obtained the desired product in ~15% yield. Being encouraged by this result, we optimized the coupling, thereby revealing that the 2-thiopyridine ester was not stable under the conditions of Method B; namely, 2b rapidly decomposed in the presence of CuCl₂, as anticipated from the literature precedent.²³ However, the 2-thiopyridine ester was found to be stable in the presence of CuI, immediately suggesting the coupling in the presence of CuI, instead of CuCl₂ (Method C). The coupling efficiency under this condition was studied for each substrate listed in Scheme 3.

The Fe/Cu-mediated one-pot ketone synthesis under the conditions of Method C furnished vinyl iodide 13, the left half in the halichondrin-B series, as well as closely related vinyl iodide 11, with a 1.0:1.2 molar ratio of electrophile and nucleophile (Scheme 5). This new synthetic route had a few

Scheme 5. Substrates Used for Feasibility Test of Fe/Cu- or Co/Cu-Mediated Ketone Synthesis



appealing aspects, including (1) a higher degree of convergency and (2) introduction of the C39 vinyl group before the ketone coupling via a standard transformation of terminal acetylene to *trans*-vinyl iodide.²⁴

Finally, the behavior of two commonly used radical probes was tested under the three coupling conditions (Scheme 6). As expected, the observed results indicated that a radical intermediate(s) was involved in all three sets of coupling conditions.

Scheme 6. Substrates Used for Feasibility Test of Fe/Cu- or Co/Cu-Mediated Ketone Synthesis



In summary, an Fe/Cu-mediated one-pot ketone synthesis was reported. Unlike Ni- and Pd-mediated one-pot ketone syntheses, the Fe/Cu-mediated method allows selective activation and coupling of alkyl iodides over vinyl iodides for one-pot ketone synthesis. The newly developed method was applied to a synthesis of vinyl iodide/ketone **13**, the left half of halichondrin B, as well as vinyl iodide/ketone **8a**, the C20–C26 building block of halichondrins.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b01128.

Experimental procedures, characterization data, and copies of spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: kishi@chemistry.harvard.edu.

ORCID [©]

Yoshito Kishi: 0000-0001-5612-350X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Changfeng Huang of this laboratory for his participation in scaling studies on the C20–C26 building block. Financial support from the Eisai USA Foundation is gratefully acknowledged. K.Y. thanks the Naito Foundation for a fellowship.

REFERENCES

(1) Nahm, S.; Weinreb, S. M. Tetrahedron Lett. 1981, 22, 3815.

(2) For a general review on ketone syntheses with organometallics, see: (a) Dieter, R. K. Tetrahedron 1999, 55, 4177. For selected references for metal-catalyzed ketone syntheses, see: Ni/Zn or Mn: (b) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. Chem. Lett. 1981, 10, 531. (c) Wotal, A. C.; Weix, D. J. Org. Lett. 2012, 14, 1476. (d) Wotal, A. C.; Ribson, R. D.; Weix, D. J. Organometallics 2014, 33, 5874. (e) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. Org. Lett. 2012, 14, 3044. (f) Zhao, C.; Jia, X.; Wang, X.; Gong, H. J. Am. Chem. Soc. 2014, 136, 17645 and references cited therein. (g) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. J. Am. Chem. Soc. 2013, 135, 7442. RMgX/Ni: (h) Fiandanese, V.; Marchese, G.; Ronzini, L. Tetrahedron Lett. 1983, 24, 3677. RMgX/Ni and RMgX/Fe: (i) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. Tetrahedron Lett. 1985, 26, 3595 and references cited therein. RZnX/Pd: (j) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. Tetrahedron Lett. 1983, 24, 5181. RSnX₃/Pd: (k) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. Org. Lett. 2003, 5, 3033. RB(OH)₂/Pd: (1) Liebeskind, L. S.; Srogl, J. J. Am. Chem. Soc. 2000, 122, 11260. RSnX₃/Cu: (m) Li, H.; He, A.; Falck, J. R.; Liebeskind, L. S. Org. Lett. 2011, 13, 3682. R₂Zn/Ni: (n) Zhang, Y.; Rovis, T. J. Am. Chem. Soc. 2004, 126, 15964.

(3) Lee, J. H.; Kishi, Y. J. Am. Chem. Soc. 2016, 138, 7178.

(4) In this paper, an alkyl iodide is referred to as a nucleophile, because of its conversion to a nucleophile *in situ*.

(5) For a review, see for example: (a) Knochel, P.; Betzemeier, B. Modern Organocopper Chemistry; Wiley-VCH: 2002. (b) Normant, J. F. Synthesis 1972, 1972, 63. (c) Lipshutz, B. H. Synthesis 1987, 1987, 325. (6) Ai, Y.; Ye, N.; Yahata, K.; Kishi, Y. Submitted for publication.

(7) Relative reactivity of radical initiators tested was roughly in the following order: $Fe(TMHD)_3 > Fe(DBM)_3 > CoPc > Fe(acac)_3 \approx ZnPc > MnPc \approx FePc.$

(8) Several Cu(I) salts were studied: CuCl, CuBr, CuI, CuCN, CuTc gave 62%, 20%, 58%, 12%, and 10% yields, respectively. Also, replacement of Cu(I) salts with Cu(II) salts was tested: CuCl₂ and CuBr₂ yielded **2a** in 76% and 32%, respectively.

(9) LiCl, LiBr, and LiI were tested, thereby showing that 3 equiv of LiCl gave the best result; see Supporting Information for details.

(10) The molar ratios of 1a:2a = 1.0:1.5, 1.0:2.0, 1.0:3.0 were tested. Among them, 1.0:3.0 was found to be the best.

(11) Mn- and Zn-powders were tested; Mn gave better results.

(12) DME gave slightly better results. Other solvents such as DMI, DMA, DMF, and 1,4-dioxane gave only poor-to-low yields. Concentration effects were also studied with C = 0.2, 0.3, and 0.4 M, but no significant difference was noticed. Thus, C = 0.4 M was chosen for the study.

(13) Addition of Cp_2ZrCl_2 , $MnCl_2$, $ZnCl_2$, $MgCl_2$, and $CrCl_2$ resulted in a lower coupling efficiency.

(14) See Supporting Information for details.

(15) Previously, this coupling was done in two steps, i.e., Co/Crmediated coupling, followed by oxidation; (a) Kim, D.-S.; Dong, C.-G.; Kim, J. T.; Guo, H.; Huang, J.; Tiseni, P. S.; Kishi, Y. J. Am. Chem. Soc. 2009, 131, 15636. (b) Dong, C.-G.; Henderson, J. A.; Kaburagi, Y.; Sasaki, T.; Kim, D.-S.; Kim, J. T.; Urabe, D.; Guo, H.; Kishi, Y. J. Am. Chem. Soc. 2009, 131, 15642.

(16) On treatment with the reagent mixture of Method A for 12 h at room temperature, 8a was completely deiodinated, to give 8a.

(17) Phosphine complexes FeBr₂ (dppb), FeCl₂ (dppb), FeBr₂. (dppe), FeCl₂ (dppe), and FeBr₂ (PPh₃)₂ gave product **3a** in 90%, 79%, 54%, 46%, and 48% yield, respectively, under the coupling condition Method B (Scheme 3).

(18) Britovsek, G. J. P.; England, J.; Spitzmesser, S. K.; White, A. J. P.; Williams, D. J. Dalton Trans. 2005, 945 and references cited therein.

(19) FeCl₂(SciOPP) is known as a superior catalyst for Kumada– Tamao–Corriu coupling; Hatakeyama, T.; Fujiwara, Y.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1030.

(20) Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M.; Yoon, S. K. *Tetrahedron Lett.* **1992**, 33, 1553.

(21) With FeBr_2·(dppb) and FeBr_2·(SciOPP), 11 was obtained in 20% and 25% yields, respectively.

(22) (a) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, 47, 1777. (b) Onaka, M.; Matsuoka, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, *10*, 531.

(23) 2-Thiopyridine esters are known to be activated in the presence of CuBr₂ and CuCl₂: Kim, S.; Lee, J. I. J. Org. Chem. **1984**, 49, 1712.

(24) In the previous synthesis, the *trans*-vinyl iodide at C39 was introduced via Takai *trans*-iodoolefination; see: Takai, K.; Nitta, K.; Utimoto, K. J. Am. Chem. Soc. **1986**, 108, 7408. (b) Takai, K.; Ichiguchi, T.; Hikasa, S. Synlett **1999**, 1999, 1268.