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A Novel Ketone Synthesis by a Palladium-Catalyzed Reaction of Thiol Esters and Organozinc Reagents[†]

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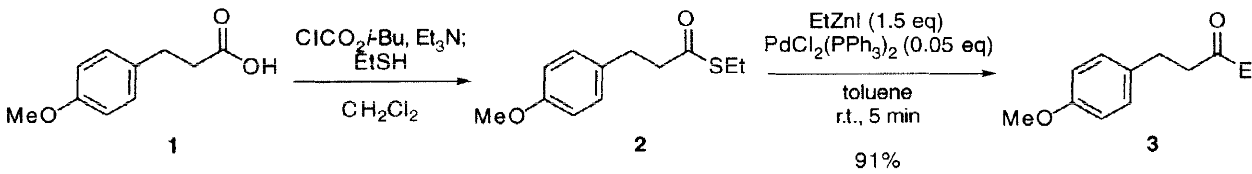
Abstract: A variety of ketones have been prepared by a palladium-catalyzed reaction of ethanethiol esters with organozinc reagents. Various functional groups, including esters, ketones, aromatic halides and aldehydes, tolerate the reaction conditions. The reaction can also be applied to the synthesis of α-amino ketones using the corresponding L-α-amino thiol esters without racemization.

Extensive efforts have been made for the synthesis of ketones by means of nucleophilic addition of organometallic reagents to carboxylic acids and their derivatives.[1] A number of techniques have been developed to suppress the formation of the tertiary alcohols arising from addition of nucleophiles to the desired ketones. For example, addition of Grignard reagents and organolithium to heterosubstituted amides and esters like *N*-methoxy-*N*-methyl amides[2] or *S*-(2-pyridyl) thiolates[3] is known to give the corresponding ketones in high yields.[4] In these cases, the initial adducts are stabilized by chelation to the metal, thereby preventing the premature ketone liberation. Reactions of organocopper reagents with acid chlorides, *S*-(2-pyridyl) thiolates, or thiol esters[5] and transition metal-catalyzed reaction of acid halides with organotin[6] or organozinc[7] reagents are widely used as well.[8] With respect to functional group compatibility, currently available methods, however, are not particularly suited for the synthesis of multifunctional ketones. We have previously reported a facile and mild reduction of thiol esters to aldehydes with triethylsilane and a catalytic amount of palladium on carbon.[9] During the course of this investigation, we then focused on a transition metal-catalyzed synthesis of ketones from thiol esters. We report herein a novel ketone synthesis by palladium-catalyzed reaction of thiol esters and organozinc reagents.



After screening various combinations of transition metal catalysts and organometallic reagents, we have found that treatment of thiol ester **2** with a catalytic amount of PdCl$_2$(PPh$_3$)$_2$ (5 mol%) and EtZnI (1.5 eq) in toluene at room temperature for 5 minutes furnished the corresponding ethyl ketone **3** in 91% isolated yield.[10,11] In the absence of the catalyst, however, only a minute amount of **3** was formed (7%) with recovery of 83% of **2** even after 15 hours of stirring at room temperature. As shown in Table 1, ethylzinc iodide as well as *i*-butyl-, benzyl-, phenyl-, β-phenethyl-, and vinylzinc iodides reacted smoothly to afford the

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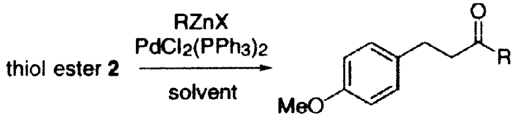
corresponding ketones.[12] Ester- and protected amine-containing zinc reagents could also be used.[13,14] In addition, the geometry of the olefins on the alkyl chains was retained in the reaction.

The generality of our methodology has been tested using thiol esters bearing various functionalities (Table 2). Alkyl, aryl, and α,β-unsaturated thiol esters could be converted into the corresponding ethyl ketones in good to excellent yields. It should be noted that a variety of sensitive functional groups including ketone, α-acetate, sulfide, aromatic bromide, chloride and even aldehyde are compatible with this protocol. This remarkable chemoselectivity indicates that the ketone formation is much faster than oxidative addition of palladium to aromatic bromide or nucleophilic addition of zinc reagents to aldehydes.

Table 1. Palladium-catalyzed ketone synthesis with various organozinc reagents.



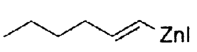
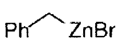
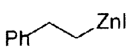
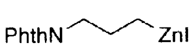
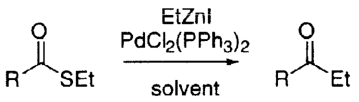
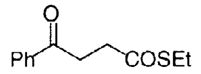
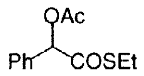
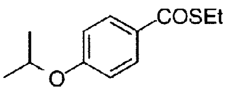
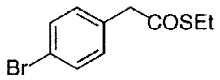
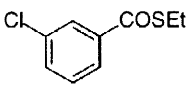
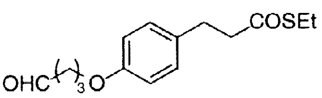
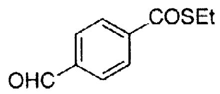
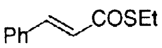
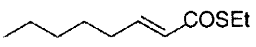
R'Zn	(eq)	$PdCl_2(PPh_3)_2$, (eq) solvent, time (min)	%yield
EtZnI	1.5	0.05 toluene, 5	91
EtZnI	1.5	0.05 THF, 5	74
i-BuZnI	2.0	0.05 THF, 15	90
	1.5	0.1 CH_2Cl_2, 15	92
	1.5	0.1 toluene, 5	87
	2.0	0.1 toluene, 120	79
PhZnI	2.0	0.1 toluene, 60	50
	3.0	0.1 toluene, 60	86
	2.0	0.1 toluene, 30	50
	2.0	0.1 toluene, 40	83

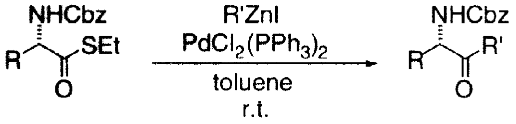
Table 2. Palladium-catalyzed ketone synthesis with various thiol esters.

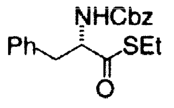
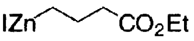
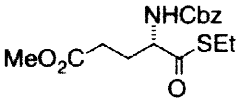
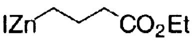
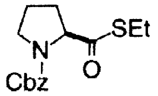
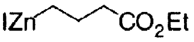


thiol ester	EtZnI (eq)	$PdCl_2(PPh_3)_2$, (eq) solvent, time (min)	%yield
	1.5	0.05 toluene, 10	99
	2.0	0.05 toluene, 50	75
	2.0	0.1 toluene, 30	78
	2.0	0.05 toluene, 7	98
	1.5	0.05 toluene, 5	91
	1.5	0.05 THF, 60	76
	2.0	0.1 toluene, 15	83
	3.0	0.1 toluene, 45	79
	1.5	0.1 THF, 205	69
	1.5	0.05 THF, 30	67

Given the encouraging results stated above, we next examined a conversion of thiol ester derivatives of *N*-protected L-α-amino acids into the corresponding amino ketones. As shown in Table 3, the ketone formation proceeded smoothly to give the desired α-amino ketones in good to high isolated yields from the optically pure *N*-Cbz-L-α-phenylalanine thiol esters without appreciable racemization (entries 1 and 2).[15] Combinations of functionalized organozinc reagents and L-glutamic acid or L-proline derivatives afforded structurally intriguing amino ketones in good yields. Presumably due to the steric reasons, the proline derivative was less reactive.

Table 3. Synthesis of α-amino ketones from L-α-amino thiol esters.



entry	thiol ester[a]	R'ZnI	(eq)	time (min)	% yield
1		EtZnI	2.5	15	88[b]
2			2.0	40	88[c]
3			2.0	15	82[d]
4		PhZnI	3.0	90	58[d]
5			3.0	90	64[d]
6		EtZnI	2.0	90	82[d]
7			2.0	90	82[d]
8		EtZnI	2.0	180	73[e]
9			2.0	110	64[d]

[a]For entries 1-5 and 8-9, ee of the starting thiol esters were determined to be >99%. [b]99% ee. [c]98% ee. [d]The ee of the products were not determined. [e]>99% ee,[16] $[\alpha]^{22}_{D}$ -43.8° (*c* 1.26, $CHCl_3$).

In summary, we have developed an efficient methodology for the synthesis of ketones from thiol esters. Our procedure could be characterized by an unusually high chemoselectivity and may find widespread use in organic synthesis.

Typical procedure: A dry, Ar-purged 50-mL flask containing a magnetic stirring bar is charged with *N*-Cbz-L-phenylalanine ethanethiol ester[17] (1.00 g, 2.91 mmol), $PdCl_2(PPh_3)_2$ (284 mg, 10 mol%), and toluene (10 mL). To the stirred mixture was added EtZnI (0.90 M in THF, 8.09 mL, 3.0 eq)[18] at room temperature and stirring was continued for 15 min. Diethyl ether (20 mL) was added and the suspension was passed through a pad of celite. The filtrate was washed with 1N HCl, sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Filtration and concentration on rotary evaporator afforded a crude product. Purification on silica gel column chromatography (15~25% EtOAc in hexane gradient) gave the desired ketone (800 mg, 88% yield).[19]

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References and Notes

† This paper is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

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5. (a) Review: Posner, G. H. *An Introduction to Synthesis using Organocopper Reagents,* Wiley, New York, 1980. (b) Reaction of organocopper reagents with thiol ester: Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654. (c) Masamune, S. *Pure Appl. Chem.* **1988**, *60*, 1587. (d) Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 2013.
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7. (a) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. -T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181. (b) $NiCl_2$ catalyzed ketone formation from *S*-(2-pyridyl) thioates in the presence of Zn and alkyl iodide: Onaka, M.; Matsuoka, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 531.
8. Fe(III)-catalyzed reaction of Grignard reagents with thiol esters: (a) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 3595. (b) Cardellicchio, C.;Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053.
9. (a) Fukuyama, T.; Lin, S. -C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050. (b) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451.
10. According to our preliminary investigations, Sonogashira coupling reaction (thiol ester **2**, 1-hexyne, $PdCl_2(PPh_3)$, CuI, HMPA, in NEt_3-DMF) gave an acetylenic ketone in 68% yield and Suzuki-coupling reaction (thiol ester **2**, *p*-benzyloxyphenyl boronic acid, $Pd(PPh_3)_4$, Ag_2CO_3, in toluene-water) gave the desired aryl ketone in low yield.
11. When commercially available THF solution of Et_2Zn was added instead of EtZnI, the corresponding aldehyde was isolated. Mechanistic details of this unexpected reduction are not clear. The rate of the reaction was dependent upon the choice of the solvent. While the rate was comparable in CH_2Cl_2 and CH_3CN, the reaction proceeded considerably slowly in THF and benzene. The reaction in DMF did not proceed at all.
12. (a) For a general review of preparation of organozinc reagents, see: Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117, and references cited therein. (b) Bouhlel, E.; Rathke, M. W. *Syn. Commun.* **1991**, *21*, 133. (c) β-Phenethylzinc iodide; Grondin, J.; Hajjad, F.; Vottero, P.; Blancou, H.; Commeyras, A. *C. R. Acad. Sci. Paris, t, 307, Ser II* **1988**, 1699. (d) Benzylzinc iodide; Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5791. (e) Phenylzinc iodide; Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.
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14. Yeh, M. C. P.; Chen, H. G.; Knochel, P. *Org. Synth.* **1991**, *70*, 195.
15. HPLC analyses were performed with a chiral HPLC column using a racemic mixture as references (DAICEL Chiralcel-OJ, 4.6 mm I.D. x 250 mm, 90/10 n-hexane/2-propanol, 1.0 mL/min, 40 °C).
16. HPLC analysis was performed with a chiral HPLC column using a racemic mixture as references (DAICEL Chiralcel-OD, 4.6 mm I.D. x 250 mm, 95/5 n-hexane/2-propanol, 1.0 mL/min, 40 °C).
17. The thiol ester was prepared from *N*-Cbz-L-phenylalanine via mixed anhydride; see ref. 9a.
18. EtZnI was prepared by heating activated zinc powder (3.1 g, activated according to ref. 14) and ethyl iodide (1.93 mL) in refluxing THF (24 mL) for 2 hours. The concentration of the reagent was estimated by titration to be 0.90 M.
19. Mp, 62-63 °C (benzene-hexane); $[\alpha]^{25}_{D}$ +72.5° (*c* 1.01, $CHCl_3$); IR (film, cm^{-1}) 3333, 3063, 3031, 2939, 1714, 1604, 1504, 1455, 1248, 1070, 1027, 744, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.0 Hz, 3 H), 2.20-3.20 (m, 2 H), 3.00 (dd, *J* = 6.1, 13.9 Hz, 1 H), 3.07 (dd, *J* = 6.8, 13.9 Hz,1 H), 4.25 (dd, *J* = 6.8, 13.9 Hz, 1 H), 5.08 (dd, *J* = 12.5, 14.9 Hz, 2 H), 5.39 (br s, 1 H), 7.00-7.50 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.29, 34.08, 37.96, 60.19, 66.85, 127.05, 128.00, 128.12, 128.48, 128.63, 129.14, 135.87, 136.24, 155.65, 209.22; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 72.99; H, 6.79; N, 4.44. Found: C, 73.29; H, 6.80; N, 4.50.