

CHEMISTRY

AN ASIAN JOURNAL

Accepted Article

Title: Highly Chemoselective and Versatile Method for Direct Conversion of Carboxylic Acids to Ketones Utilizing Zinc Ate Complexes

Authors: Ryo Murata; Keiichi Hirano; Masanobu Uchiyama

This manuscript has been accepted after peer review and the authors have elected to post their Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Asian J. 10.1002/asia.201500308

Link to VoR: <http://dx.doi.org/10.1002/asia.201500308>

An **ACES** journal

A sister journal of *Angewandte Chemie*
and *Chemistry – A European Journal*

Supported by



ChemPubSoc
Europe



Federation of
Asian Chemical
Societies

WILEY-VCH

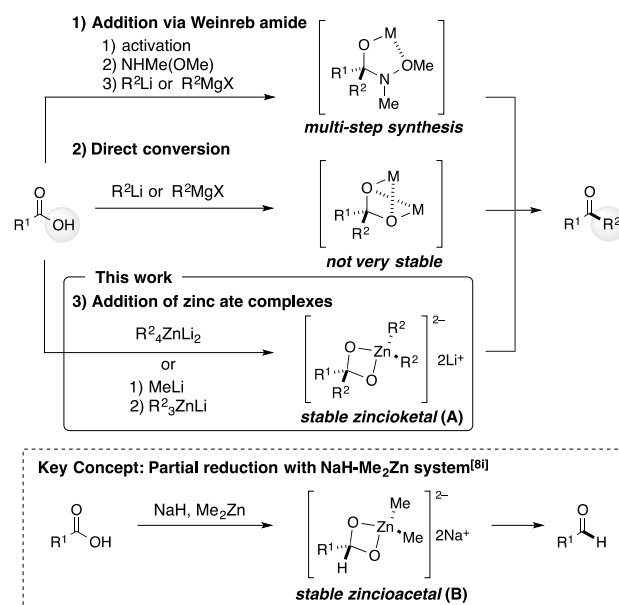
Highly Chemoselective and Versatile Method for Direct Conversion of Carboxylic Acids to Ketones Utilizing Zinc Ate Complexes

Ryo Murata,^[a] Keiichi Hirano,^{*[a,b]} and Masanobu Uchiyama^{*[a,b]}

Abstract: Various carboxylic acids were directly transformed to the corresponding ketones by utilizing organozinc ate complexes, which provide high chemoselectivity without any overreaction to undesired tertiary carbinol, owing to formation of a stable tetrahedral zincoketal intermediate. This method offers good overall atom/step/pot economy and operational simplicity.

Ketone is a fundamental chemical motif in organic chemistry, providing a starting point for various chemical elaborations. Thus, development of a simple, efficient, and highly chemoselective method to provide ketones with high level of atom-^[1] and step economy^[2] is still of great interest in organic synthesis. Currently, addition of organometallic reagents, such as organolithiums or Grignard reagents, to Weinreb amides *via* stable 5-membered chelate complex formation^[3] is the most reliable way to prepare ketones cleanly in high yield without formation of over-addition by-products, though this method requires three steps: 1) activation of carboxylic acid,^[4] 2) amide bond formation, and 3) addition of organometallic (Scheme 1). Direct conversion of carboxylic acid to ketone by addition of organometallic reagents such as organolithiums is another well-known synthetic approach,^[5,6] but it is not a general method and its application to complex organic molecules is limited by 1) possible tertiary alcohol formation, 2) low functional group tolerance, 3) the need for strict control of reaction conditions, and 4) the extremely low temperature typically required for such reactions. In 2011, Posner and Genna reported a novel approach to these problems.^[7] Lipshutz-type cuprates enable ketonization of a broad range of carboxylic acids without formation of tertiary alcohols, albeit a large excess (> 5 eq.) of cuprate is required. Here, we report a highly efficient and chemoselective direct ketonization reaction of carboxylic acids by using tetra-alkyl zincates or tri-alkyl zincates, in which the key step is formation of a stable “zincoketal” intermediate (**A**). We show that the reactions of carboxylic acids with Me₄ZnLi₂ followed by acidic work-up are a powerful tool for chemoselective, direct, and one-pot preparation of methyl ketone derivatives. Alternatively, the

reactions of lithium carboxylate with trialkylzincates provide direct and efficient access to various functionalized ketones, which are potentially valuable as synthetic intermediates.



Scheme 1. Highly Chemoselective Direct Ketonization of Carboxylic Acid with Organozincates.

We have been extensively working on development of novel synthetic methodologies based on organozincates, taking advantage of their high functional group compatibility and tunable reactivity.^[8] During the course of our studies, we have found that ate complexes prepared from Me₂Zn and NaH or LiH efficiently reduce aldehydes and ketones, and very intriguingly, they also react with carboxylic acids to afford the corresponding aldehydes.^[8] Notably, in those cases, no over-reduction to alcohols was observed. We hypothesized that this unique chemoselectivity is attributable to the robust structure of the initial adduct, a “zincioacetal” intermediate (Scheme 1, **B**). We considered that this zincioacetal is very likely stable *in situ* and acts as a protecting group of the generated aldehyde to prevent further attack by hydride.

We commenced by treating 4-anisic acid (**1a**) with various zincates (Table 1). Gratifyingly, 1.5 eq of Me₄ZnLi₂, prepared from Me₂Zn and MeLi (LiBr free), afforded the desired ketone **2a** in 90% isolated yield (entry 1). It is important to note that no trace of over-reacted by-product, tertiary alcohol **3a**, was detected in the crude mixture. On the other hand, a significant amount of **3a** was obtained when Me₄ZnLi₂ prepared from ZnCl₂

[a] R. Murata, Dr. K. Hirano,* and Prof. Dr. M. Uchiyama*
Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
E-mail: k1hirano@mol.f.u-tokyo.ac.jp, uchiyama@mol.f.u-tokyo.ac.jp
[b] Dr. K. Hirano* and Prof. Dr. M. Uchiyama*
Advanced Elements Chemistry Research Team, RIKEN Center for Sustainable Resource Science, and Elements Chemistry Laboratory
RIKEN
2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan

Supporting information for this article is given via a link at the end of the document.

and MeLi was employed (entry 2). These results suggested that the presence of LiCl may destabilize the zincoketal intermediate. External addition of LiCl to the reaction mixture of entry 1 resulted in the formation of **3a** in 10% yield, confirming the deleterious effect of LiCl (entry 3). When *mono*-anionic Me₃ZnLi was used, **1a** was recovered quantitatively (entry 4), whereas pre-lithiation of **1a** gave the desired **2a** in 73% yield (entry 5). Another dianionic zincate prepared from Me₂Zn and MeMgBr, Me₄Zn(MgBr)₂, gave a complex mixture (entry 6). Conventionally used MeLi gave a significant amount of **3a** under these reaction conditions (entry 7).

Table 1. Selection of Organometallic Reagent.^[a]

Entry	Reagent (1.5 eq)	Yield [%] ^[b]		
		2a	3a	Rec. 1a
1	Me ₄ ZnLi ₂	95 (90)	0	0
2	Me ₄ ZnLi ₂ ^[c]	84	5	0
3	Me ₄ ZnLi ₂ ^[d]	82	10	0
4	Me ₃ ZnLi	0	0	quant.
5	Me ₃ ZnLi	73	9	0
6	Me ₄ Zn(MgBr) ₂ ^[f]	complex mixture		
7	MeLi	50	40	0

[a] To a solution of organometallic reagent in THF was added **1a** in THF at -78 °C. The resulting mixture was allowed to warm to rt and stirred for 17 h. [b] Determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard; isolated yield is given in parentheses. [c] Me₄ZnLi₂ was prepared from ZnCl₂ (1.5 eq) and MeLi (3.0 eq). [d] Me₄ZnLi₂ was prepared from Me₂Zn (1.5 eq) and MeLi (3.0 eq), and LiCl (3.0 eq) was added. [e] **1a** was lithiated with MeLi (1 eq) prior to addition of Me₃ZnLi (1 eq). [f] Prepared from Me₂Zn (1.5 eq) and MeMgBr (3.0 eq).

Based on the result of entry 1 in Table 1 (standard conditions), further optimization studies were performed (Table 2). Reducing the amount of Me₄ZnLi₂ to 1.2 eq or 1.0 eq decreased the yield of **2a** to 84% and 63%, respectively (entries 1 and 2). Lowering the reaction temperature to -20 °C significantly slowed the reaction (entry 3) and the reaction was shut down completely at -78 °C (entry 4). On the other hand, the reaction at 50 °C was as effective as that at rt (entry 5). The effect of solvents was also examined. 1,4-Dioxane resulted in formation of a trace amount of tertiary alcohol **3a**, albeit it was quite an effective solvent for this transformation (entry 6). Diethyl ether yielded a significant amount of **3a** (entry 7), while a much less polar solvent, toluene, resulted in poor conversion (entry 8).

Table 2. Optimization of the Reaction Conditions.^[a]

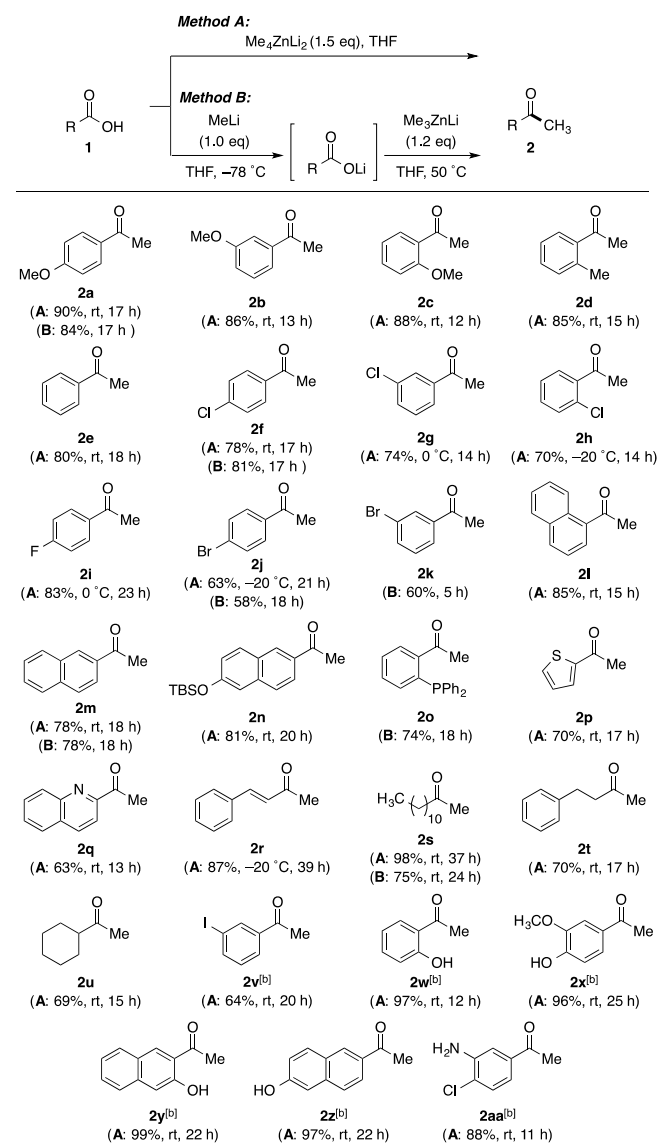
Entry	Difference from standard conditions	Yield [%] ^[b]	
		2a	3a
1	Me ₄ ZnLi ₂ : 1.2 eq instead of 1.5 eq	84	0
2	Me ₄ ZnLi ₂ : 1.0 eq instead of 1.5 eq	63	0
3	-20 °C instead of rt	56	0
4	-78 °C instead of rt	0	0
5	50 °C instead of rt	95	0
6 ^[c]	1,4-dioxane instead of THF	95	trace
7 ^[c]	diethyl ether instead of THF	84	6
8 ^[c]	toluene instead of THF	54	7

[a] To a solution of organometallic reagent in THF was added **1a** in THF at -78 °C. The resulting mixture was allowed to warm to rt and stirred for 17 h. [b] Determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Me₄ZnLi₂ was prepared in THF, and then volatiles were evaporated *in vacuo*. The resulting residue was dissolved or suspended in the indicated solvent.

With optimized conditions in hand, various carboxylic acids were converted directly to methyl ketones utilizing method A with Me₄ZnLi₂ and method B with Me₃ZnLi (Table 3). The substitution pattern of anisic acids had no apparent effect on the reaction progress and the corresponding methyl ketones were obtained in high yields (**2a**, **2b**, and **2c**). A methyl group at the *ortho*-position was not deleterious, and **2d** was obtained in 85% yield. The parent system forming acetophenone (**2e**) was equally efficient. The reactions with halogenated benzoic acids required temperature control, depending on the position and nature of the halogen atoms in order to obtain the corresponding ketones in maximal yields. Although 4-chlorobenzoic acid could be employed without difficulty, the 3- and 2-chloro analogues did not give satisfactory results due to undesired side reactions. However, when the reaction temperature was lowered to 0 °C for 3-chlorobenzoic acid, and to -20 °C for 2-chlorobenzoic acid, the desired products, **2g** and **2h**, were obtained in 74% and 70% yields, respectively. For 4-fluorobenzoic acid, the reaction at 0 °C was optimal to suppress nucleophilic aromatic substitution reaction and deprotonative benzyne formation.^[9] Notably, the reaction with 4-bromobenzoic acid gave **2j** in 63% yield without any bromine-zinc exchange reaction at -20 °C.^[8h,10] The utility of method B was clearly demonstrated with 4-bromobenzoic acid **1j** and 3-bromobenzoic acid **1k**: the carbon-bromine bond was preserved even at 50 °C, affording **2j** and **2k** in 58% and 60% yields, respectively. Naphthalenecarboxylic acids were also good substrates, and importantly, phenolic TBS-ether survived under these reaction conditions to give **2n** in 81% yield without

any trace of desilylated by-products. 2-Diphenylphosphinobenzoic acid was converted to the corresponding ketone **2o** in 74% yield by means of method B.

Table 3. Substrate Scope of Methyl Ketones using Me_4ZnLi_2 and Me_3ZnLi .^[a]

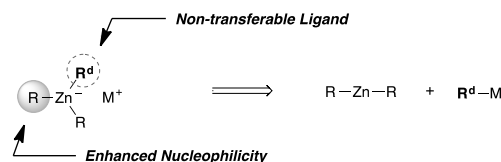


[a] Me_4ZnLi_2 was prepared from Me_2Zn (0.75 mmol) and MeLi (1.5 mmol) at -78 °C. The solution of **1** (0.5 mmol) in THF was transferred to the zincate solution via cannulation at -78 °C and the reaction mixture was warmed to the indicated temperature. Isolated yields are reported. [b] Reaction with 3 eq of Me_4ZnLi_2 for 17 h at rt, followed by addition of 10 eq of I_2 and stirring for 3 h at rt. [c] 3.0 eq of Me_4ZnLi_2 was used in order to quench the phenolic or aniline proton.

Heteroaromatic ketones were synthesized with the same protocol. 2-Acetylthiophene (**2p**) and 2-acetylquinoline (**2q**) were obtained in moderate yields. α,β -Unsaturated ketone **2r** was obtained in 87% yield without formation of any 1,4-addition product.^[13] Aliphatic carboxylic acids were also available, affording the desired ketones (**2r**, **2s**, **2t**, and **2u**). Lauric acid was converted cleanly to the corresponding methyl ketone **2r** in 98% yield, without deprotonation of the α -C–H bond. **2r** was also

obtained in high yield by means of method B. Cyclohexylmethyl ketone **2u** was obtained in 69% yield even with the sterically demanding secondary alkyl group. Conversion of 3-iodobenzoic acid **1v** required a modified procedure. The reaction of **1v** with 1.5 eq of Me_4ZnLi_2 did not afford the desired product, and instead, the major product was acetophenone **2e**. As we have already reported,^[8h,10] iodoarenes undergo an extremely rapid iodine-zinc exchange reaction with Me_4ZnLi_2 , and so the reason for this failure might be that the interconversion is faster than deprotonation and ketonization. To overcome this problem, we employed 3.0 eq of Me_4ZnLi_2 in order to form the doubly metalated **1v** rapidly, and then we *re*-iodinated the product by quenching with I_2 to obtain the desired **2v** in 64% yield.^[11,12] Substrates bearing a phenolic proton, which is not compatible with basic organometallic reagents, were converted to corresponding methyl ketones by means of a similar approach. By using a 2-fold excess of Me_4ZnLi_2 , **2w**, **2x** (apocynin: antioxidant), **2y**, and **2z** were obtained in excellent yields. Even *N*-unprotected aminobenzoic acid afforded the desired product **2aa** in 88% yield with the same procedure. *It should be emphasized that no tertiary alcohol formation was detectable in any of these reactions.*

We next extended this strategy to the introduction of other alkyl and aryl groups (Table 4). One of the attractive features of organozincates is the flexibility of the coordination environment; heteroleptic complexes are easy to form simply by mixing a diorganozinc and a lithium/magnesium reagent.^[16] Addition of a less-transferable ligand, *i.e.*, a dummy ligand (R^d), to diorganozinc (R_2Zn) should increase the nucleophilicity of R and enable selective ligand transfer of R over R^d to carboxylate (Scheme 2).



Scheme 2. Heteroleptic Zincate: Concept for Variety of Ketones.

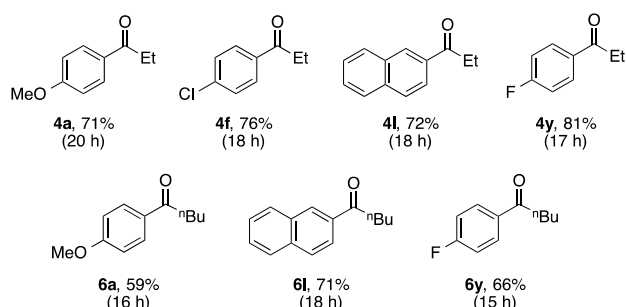
We assessed several lithium bases as dummy ligands for Et_2Zn (Table 4).^[16] The *t*-Bu-group was an excellent choice, and $\text{Et}_2(\text{t-Bu})\text{ZnLi}$ gave the desired ethylketone **4l** in 77% yield without any trace of *tert*-butylketone (entry 1).^[8e] On the other hand, Et_2MeZnLi gave a mixture of ethyl- and methylketone in 45% and 41% yields, respectively (entry 2). $\text{Et}_2^n\text{BuZnLi}$ underwent the desired ethyl addition preferentially, but with formation of 11% *n*-butylketone (entry 3). The zincate prepared from a lithium acetylide and Et_2Zn yielded the ethylketone with complete selectivity, albeit with low conversion (entry 4). This presumably reflects the low electron-donating ability of the acetylide anion. Though LDA could activate Et_2Zn , the yield of **4l** was low and the reaction became messy (entry 5). Et_2Zn was not sufficiently activated by LiO^tBu , resulting in quantitative recovery of **1l** (entry 6). The substrate scope was briefly examined under the conditions of entry 1. Electron-rich (OMe) and poor (Cl, F) benzoic acids gave the desired ethylketones **4a**, **4f**, and **4y** in

high yields. Reactions with ${}^n\text{Bu}_2({}^t\text{Bu})\text{Zn}$ gave the corresponding *n*-butylketones **6a**, **6l**, and **6y** in satisfactory yields.

Table 4. Heteroleptic Zincate for Ethylation and *n*-Butylation.^[a]

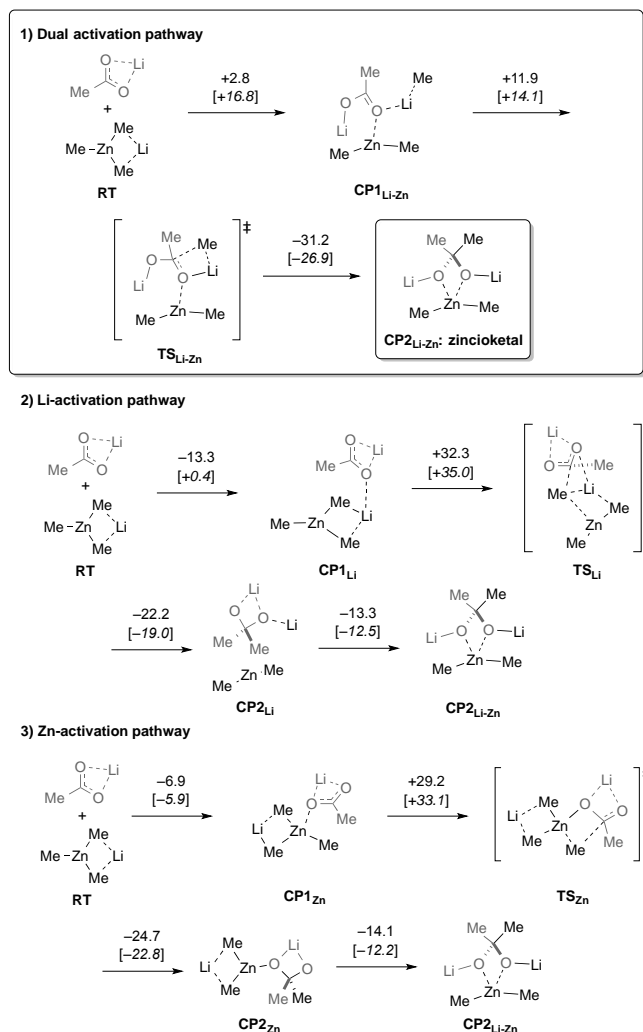
Entry	Reagent ($\text{Et}_2\text{R}^d\text{ZnLi}$)	Yield [%] ^[b]		
		4I	5I	Rec. of 11
1	$\text{Et}_2({}^t\text{Bu})\text{ZnLi}$	77 (72)	–	trace
2	Et_2MeZnLi	45	41	–
3	$\text{Et}_2({}^n\text{Bu})\text{ZnLi}$	71	11	–
4	$\text{Et}_2(\text{C}_4\text{H}_9\text{C}\equiv\text{C})\text{ZnLi}$	38	47	–
5	$\text{Et}_2({}^i\text{Pr}_2\text{N})\text{ZnLi}$	38	–	–
6	$\text{Et}_2({}^t\text{BuO})\text{ZnLi}$	–	–	quant.

Scope of Ethylation and *n*-Butylation:



[a] The experimental procedure is described in detail in Supporting Information. [b] Determined by ${}^1\text{H}$ NMR spectroscopy with mesitylene as an internal standard.

In order to shed light on the mechanism of this transformation, we performed DFT calculation for the model reaction between lithium acetate and Me_3ZnLi at the level of M06/6-31+G* (for C, H, O, and Li) and SVP (for Zn). Since Me_3ZnLi is a heterobimetallic complex, three different modes of activation of lithium carboxylate should be viable: 1) dual activation by Li and Zn, 2) activation by Li, and 3) activation by Zn (Scheme 3). In the dual activation pathway, the initial complexation ($\text{CP1}_{\text{Li-Zn}}$) causes slight destabilization due to deformation of the zincate (+2.8 kcal/mol). However, the activation energy for $\text{TS}_{\text{Li-Zn}}$ is sufficiently low (+11.9 kcal/mol) to allow facile methyl transfer from zinc to carboxylate. Tracking the minimum energy path from $\text{TS}_{\text{Li-Zn}}$ in the forward direction using the intrinsic reaction coordinate method^[17] identified zincioketal intermediate $\text{CP2}_{\text{Li-Zn}}$ as a local minimum with large energy gain (–31.2 kcal/mol). Pathways 2 and 3 have significantly higher activation barriers of methyl transfer than the dual activation pathway, so it is reasonable to conclude that this reaction proceeds *via* dual activation of lithium carboxylate by Li and Zn.



Scheme 3. Mechanistic Investigation by means of DFT calculations at the level of M06/6-31+G* (C, H, O, and Li) and SVP (Zn). SCRf calculations (THF) were carried out with the PCM model. ΔE (kcal/mol) values are shown.

In conclusion, we have developed a new, simple, and highly chemoselective direct ketone-forming reaction from carboxylic acids by utilizing organozincates. Various carboxylic acids were cleanly converted to the corresponding ketones without formation of over-reacted tertiary alcohol by-products, owing to the high functional group tolerance of organozincates. Theoretical studies indicated that the heterobimetallic nature of organozincates enables facile alkylation of carboxylates *via* dual activation by Li and Zn, and also supported the idea that the *in situ*-generated zincioketal intermediate serves as a protecting group to block over-reaction.

Experimental Section

Method A: To a Schlenk tube charged with THF (3.0 ml) were added Me_2Zn (1.02 M hexane solution or 1.0 M heptane solution, 1.5 mmol) and MeLi (1.13 M Et_2O solution, LiBr free, 3.0 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature, then cooled to –78 °C.

Carboxylic acid (1.0 mmol) in THF (3.0 ml) was added *via* a cannula, and the reaction mixture was gradually warmed to the indicated temperature and stirred for the indicated time. The reaction was quenched with aqueous sat. NH_4Cl , and the mixture was extracted with Et_2O (3 \times 15 mL). The combined organic layer was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: hexane/ Et_2O) to afford the desired methylketone. **Method B:** To a Schlenk tube charged with THF (3.0 ml) were added Me_2Zn (1.02 M heptane solution, 1.2 mmol) and MeLi (1.17 M Et_2O solution, LiBr free, 1.2 mmol) at 0 $^\circ\text{C}$. The mixture was stirred for 1 h at the indicated temperature to generate Me_3ZnLi . Lithium carboxylate was prepared by the reaction of carboxylic acid (1.0 mmol) and MeLi (1.17 M Et_2O solution, 1.0 mmol) in THF (3.0 ml) for 1 h at -78 $^\circ\text{C}$ in another Schlenk tube. The solution of Me_3ZnLi was transferred to the solution of lithium carboxylate dropwise *via* a cannula. The resultant mixture was allowed to warm gradually to 50 $^\circ\text{C}$ and stirred for the indicated time. Workup and purification were performed as described for Method A.

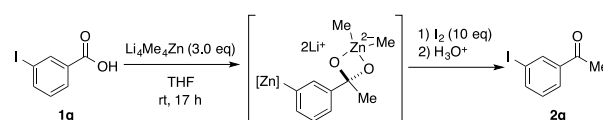
Acknowledgements

This work was supported by JSPS KAKENHI (S) (No. 24229011), Takeda Science Foundation, The Asahi Glass Foundation, Daiichi-Sankyo Foundation of Life Sciences, Mochida Memorial Foundation, Tokyo Biochemical Research Foundation, Foundation NAGASE Science Technology Development, and Sumitomo Foundation (to M. U.), JSPS Grant-in-Aid for Young Scientists (Start-up) (No. 24850005) and JSPS Grant-in-Aid for Young Scientists (B) (No. 26860010) (to K. H.) (No. 24850005). The calculations were performed on the Riken Integrated Cluster of Clusters (RICC). We gratefully acknowledge Advanced Center for Computing and Communication (RIKEN) for providing computational resources.

Keywords: ketone • carboxylic acid • organozincates • chemoselective • DFT calculation

- [1] a) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; b) B. M. Trost, *Science* **1991**, *254*, 1471.
- [2] a) P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505; b) P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197.
- [3] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815.
- [4] Representative non-catalytic addition reactions of organometallics to acid chlorides: **Cu**: a) G. H. Posner, C. E. Whitten, P. E. McFarland, *J. Am. Chem. Soc.* **1972**, *94*, 5106; b) R. M. Wehmeyer, R. D. Rieke, *Tetrahedron Lett.* **1988**, *29*, 4513; c) K. Takai, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1281; d) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390. **Mg**: X. Wang, L. Zhang, X. Sun, Y. Xu, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2005**, *7*, 5593. Also see references cited therein for catalytic and non-catalytic transformations using various metal species. Recent example

- of Friedel-Crafts acylation type reaction, see: M. C. Wilkinson, *Org. Lett.* **2011**, *13*, 2232.
- [5] After the seminal discovery by Gilman in 1933, this approach became one of the most straightforward methods to access ketones. a) W. D. Lubell, H. Rapoport, *J. Am. Chem. Soc.* **1988**, *110*, 7447; b) T. M. Bare, H. O. House, *Org. Synth.* **1973**, *5*, 775; c) M. J. Jorgenson, *Org. React.* **1970**, *18*, 1; d) H., Gilman, P. R. van Ess, *J. Am. Chem. Soc.* **1933**, *55*, 1258; e) F. Alonso, E. Lorenzo, M. Yus, *J. Org. Chem.* **1996**, *61*, 6058; f) R. Levine, M. J. Karten, W. M. Kadunce, *J. Org. Chem.* **1975**, *40*, 1770; g) G. M. Rubottom, C.-W. Kim, *J. Org. Chem.* **1983**, *48*, 1550.
- [6] Grignard reagents are generally not as effective as organolithiums for this transformation. For a recent publication on addition reactions of organomagnesium reagents to carboxylate salts, see: M. Ohki, M. Asaoka, *Chem. Lett.* **2009**, *38*, 856;
- [7] D. T. Genna; G. H. Posner, *Org. Lett.* **2011**, *13*, 5358.
- [8] Selected publications on this topic, see: a) Y. Nagashima, R. Takita, K. Yoshida, K. Hirano, M. Uchiyama, *J. Am. Chem. Soc.* **2013**, *135*, 18730; b) C. Wang, T. Ozaki, R. Takita, M. Uchiyama, *Chem. Eur. J.*, **2012**, *18*, 3482; c) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.*, **2008**, *130*, 472; d) M. Uchiyama, Y. Matsumoto, S. Usui, Y. Hashimoto, K. Morokuma, *Angew. Chem., Int. Ed.* **2007**, *46*, 926; e) M. Uchiyama, T. Furuyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.*, **2006**, *128*, 8404; f) S. Nakamura, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.*, **2005**, *127*, 13116; g) S. Nakamura, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.*, **2004**, *126*, 11146; h) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.*, **1998**, *120*, 4934; i) M. Uchiyama, S. Furumoto, M. Saito, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.*, **1997**, *119*, 11425.
- [9] J. Burdon, H. S. Gill, I. W. Parsons, J. C. Tatlow, *J. Chem. Soc., Chem. Commun.* **1979**, 1147.
- [10] M. Uchiyama, M. Koike, M. Kameda, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.*, **1996**, *118*, 8733.
- [11] Proposed simultaneous or consecutive double zincation.



- [12] For halogen-metal exchange-based double functionalization, see: C. Despotopoulou, R. C. Bauer, A. Krasovskiy, P. Mayer, J. M. Stryker, P. Knochel, *Chem. Eur. J.*, **2008**, *14*, 2499.
- [13] M. Isobe, S. Kondo, N. Nagasawa, T. Goto, *Chem. Lett.* **1977**, 679.
- [14] Y. Kondo, N. Takazawa, C. Yamazaki, T. Sakamoto, *J. Org. Chem.* **1994**, *59*, 4717.
- [15] For details, see Supporting Information.
- [16] A series of heteroleptic triorganozincates was prepared and studied in conjugate addition reactions by Oshima et al., see: W. Tückmantel, K. Oshima, H. Nozaki, *Chem. Ber.* **1986**, *119*, 1581.
- [17] (a) K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363. (b) K. Ishida, K. Morokuma, A. Komornicki, *J. Chem. Phys.* **1977**, *66*, 2153. (c) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154. (d) H. B. Schlegel, C. Gonzalez, *J. Phys. Chem.* **1990**, *94*, 5523.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

Author(s), Corresponding Author(s)*

Page No. – Page No.

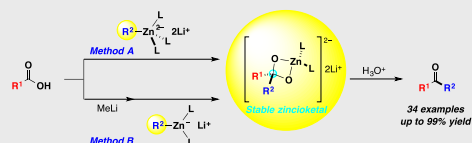
Title

Layout 2:

COMMUNICATION

Ryo Murata, Keiichi Hirano,* and
Masanobu Uchiyama*

Page No. – Page No.

**Highly Chemoselective and Versatile
Method for Direct Conversion of
Carboxylic Acids to Ketones Utilizing
Zinc Ate Complexes**

Various carboxylic acids were directly transformed to the corresponding ketones by utilizing organozinc ate complexes, which provide high chemoselectivity without any overreaction to undesired tertiary carbinol, owing to formation of a stable tetrahedral zincoketal intermediate. This method offers good overall atom/step/pot economy and operational simplicity.