ORGANIC LETTERS

2013
Vol. 15, No. 13
3378–3380

Catalytic Asymmetric Aldol-Type Reaction of Zinc Enolate Equivalent of Amides

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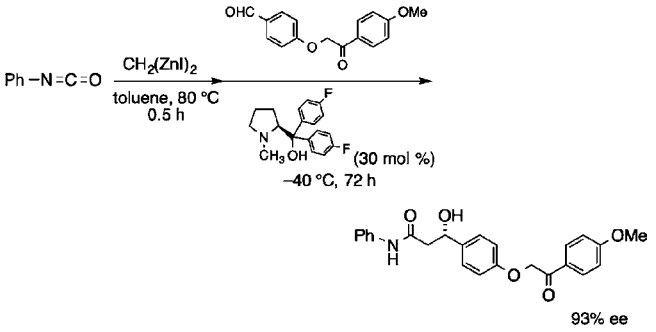
Received May 20, 2013

ABSTRACT

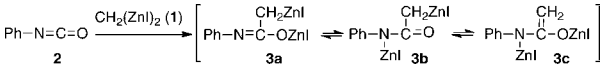


Treatment of phenyl isocyanate with bis(iodozincio)methane gave a zinciomethylenated product, which acts as an amide-enoate equivalent. It did not react with an aldehyde efficiently, but gave the corresponding adduct in good yield in the presence of an aminoalcohol. Use of a catalytic amount of chiral aminoalcohol led the process to the catalytic asymmetric Aldol-type reaction.

Organozinc reagents are considered one of the most important main-metal reagents because of their compatibility with many functional groups.[1] An organic reagent carrying various functional groups has been developed; it can be used, through a C–C bond formation reaction, to directly introduce functional groups to a substrate.[2] During the course of our studies on bis(iodozincio)methane (**1**) prepared by the reduction of diiodomethane with zinc, we have shown several examples of zinciomethylenation, which involve the direct introduction of a C–Zn bond.[3] The reaction of bis(iodozincio)methane with an acylating reagent affords an α-zinciocarbonyl, which is an enolate. We have already reported the palladium-catalyzed cross coupling of **1** with a thioester to afford the corresponding zinc enolate of ketone.[4] Along this line, we focused on the insertion reaction of the C–Zn bond of **1** into a heterocumulene as an alternative for enolate equivalent preparation.

The zinciomethylation of an isocyanate with **1** affords an equivalent of an amide enolate. As shown in Scheme 1, phenylisocyanate (**2**) was treated with an equimolar amount of dizinc **1**. An addition would afford three possible types of adducts **3a**–**c**. To complete the addition reaction in THF or toluene within 0.5 h, it was necessary for the reaction of **1** and **2** to be performed at 80 °C, as shown in Table 1.

Scheme 1. An Addition of Bis(iodozincio)methane with Phenyl Isocyanate



As shown in Scheme 2, the addition of benzaldehyde (**5a**) to **3** afforded the corresponding aldol-type adduct. Surprisingly, to obtain the product of **3** and **5a** in reasonable

(1) (a) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedorn* **1998**, *54*, 8275. (b) Knochel, P.; Scade, M. A.; Bernhardt, S.; Manolikakes, G.; Metzger, A.; Piller, F. M.; Rohbogner, C. J.; Mosrin, M. *Beil. J. Org. Chem.* **2011**, *7*, 1261.

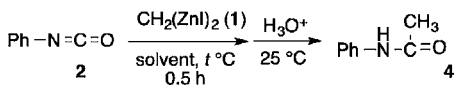
(2) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. Functionalized Organozinc Compounds. In *The Chemistry of Organozinc Compounds Part 1*; Rappoport, Z.; Marek, I., Eds.; John Wiley & Sons: West Sussex, England; 2006; pp 287–393.

(3) (a) Ikeda, Z.; Oshima, K.; Matsubara, S. *Org. Lett.* **2005**, *7*, 4859. (b) Hirayama, T.; Oshima, K.; Matsubara, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3293. (c) Utimoto, K.; Toda, N.; Mizuno, T.; Kobata, M.; Matsubara, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2804.

(4) (a) Ikeda, Z.; Hirayama, T.; Matsubara, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8200. (b) Ooguri, A.; Ikeda, Z.; Matsubara, S. *Chem. Commun.* **2007**, 4761. (c) Matsubara, S.; Kawamoto, K.; Utimoto, K. *Synlett* **1998**, 267.

10.1021/ol401425s
Published on Web 06/11/2013

Table 1. Preparation of Zinc Enolate Equivalent from Phenyl Isocyanate and Bis(iodozincio)methane[a]



entry	solvent	*t*/°C	yield of **4**/%
1	THF	20	48
2		50	73
3		80	99
4	toluene	80	99
5	hexane	80	0[b]

[a] **1** (0.5 M in THF, 1.0 mL) and **2** (0.5 mmol) in the solvent (1.0 mL) were used. [b] The isocyanate was recovered.

yield, a temperature of over 100 °C was necessary. Considering the low reactivity of the enolate equivalent **3** with the aldehyde, it may not have an O-enolate form **3c** but an alkylzinc form **3a,b**.[5] It is well-known that the low reactivity of alkylzinc can be improved by the addition of an aminoalcohol. This activation is crucial for asymmetric induction. Several enantioselective alkylations of aldehydes by organozinc reagents have been performed in the presence of an optically active aminoalcohol.[6] Along this line, the reaction of **3** with aldehydes in the presence of an optically active aminoalcohol was examined to perform an asymmetric induction in the aldol-type reaction. Although a variety of catalytic asymmetric alkylations using an organozinc reagent has been developed, examples of a catalytic asymmetric aldol-type reaction using zinc enolate are limited.[7] A tandem-type reaction, which contains the asymmetric 1,4-addition of organozinc to enone in the presence of a chiral catalyst followed by the 1,2-addition of the formed enone to aldehyde, showed high asymmetric induction in the first 1,4-addition, but the second aldol-type reaction did not always show reasonable diastereoselectivities.[8] Several examples of a Reformatsky reaction using a stoichiometric amount of a chiral source[9] and only a few examples of catalytic asymmetric zinc-enolate aldol reactions[10] had already been reported.

(5) (a) ^{1}H NMR analysis for **3** implied the alkyl zinc structure (SI). (b) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2005**, *24*, 4116.

(6) (a) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467. (b) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. (c) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (d) Smaardijk, A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135. (e) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K. *Tetrahderon: Asymmetry* **1999**, *10*, 133.

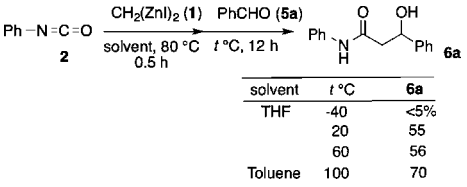
(7) Lombardo, M.; Trombini, C. The Chemistry of Zinc Enolate. In *The Chemistry of Organozinc Compounds Part 2*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: West Sussex, England; 2006; pp 797−861.

(8) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (b) Alexakis, A.; Trevitt, G. P.; Bernardinelli *J. Am. Chem. Soc.* **2001**, *123*, 4358.

(9) (a) Soai, K.; Oshio, A.; Saito, T. *J. Chem. Soc., Chem. Commun.* **1993**, 811. (b) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217. (c) Fujiwara, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6161.

(10) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Fernández-Ibáñez, M. A.; Marciá, B.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1317. (c) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951.

Scheme 2. Addition Reaction of **3** with Benzaldehyde



In Scheme 3, optically active aminoalcohols **7**, which were derived from L-proline and effective for the catalytic asymmetric addition of alkylzinc to aldehydes, were added in a catalytic amount (30 mol %) to activate the enolate equivalent **3** for the addition to *p*-tolyl aldehyde (**5b**). In all cases, asymmetric induction was observed. Among **7**, (*S*)-bis(4-fluorophenyl)(1-methylpyrrolidin-2-yl)methanol (**7g**)[11] induced the highest enantioselectivity (87% ee).

Scheme 3. Asymmetric Induction in the Reaction of **3** with *p*-Tolaldehyde in the Presence of L-Proline Derived Aminoalcohols

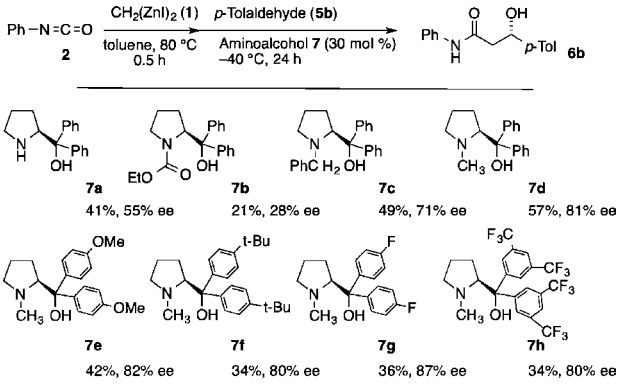
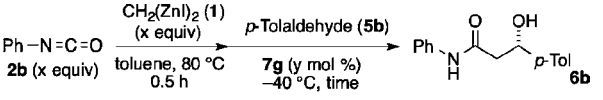


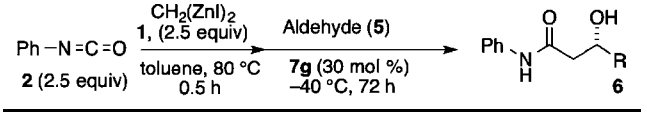
Table 2. Optimization of the Reaction of **3** with *p*-Tolaldehyde (**5b**) in the Presence of a Catalytic Amount of **7g**[a]



entry	*x*/ equiv	*y*/ mol %	time/ h	yield of **6b**	ee/ %
1	2.0	30	48	35	79
2	2.0	30	72	52	77
3	2.5	30	72	99	84
4	2.5	20	72	68	84
5	2.5	10	72	56	84

[a] **5b** (0.5 mmol) was used. In the reaction of entry 1, **1** (0.5 M in THF, 2.0 mL) and **2** (1.0 mmol) in toluene (2.0 mL) were premixed for 0.5 h at 80 °C; **7g** (0.15 mmol) in toluene (0.5 mL) and **5b** (0.5 mmol) in toluene (1.0 mL) were added at −40 °C subsequently.

Table 3. Examples of the Reaction of **3** with Aldehydes (**5**) in the Presence of a Catalytic Amount of **7g**[a]



entry	**R** in **6**		yield/%	ee/%[b]
1	4-MeC_6H_4–	**6b**	99	84
2	2-MeC_6H_4–	**6c**	91	84
3	4-FC_6H_4–	**6d**	77	89
4	4-ClC_6H_4–	**6e**	76	79
5	4-BrC_6H_4–	**6f**	47	77
6	4-MeOC_6H_4–	**6g**	65	94
7	4-t-BuC_6H_4–	**6h**	57	84
8	mesityl	**6i**	63	84
9	2-naphtyl	**6j**	89	88
10	2-thienyl	**6k**	73	94
11	2-furyl	**6l**	92	76
12	Me–	**6m**	45	76
13	*t*-Bu–	**6n**	49	83

[a] **1** (0.5 M in THF, 2.5 mL) and **2** (1.25 mmol) in toluene (2.0 mL) were premixed for 0.5 h at 80 °C; **7g** (0.15 mmol) in toluene (0.5 mL) and **5** (0.5 mmol) in toluene (1.0 mL) were added at −40 °C subsequently. [b] The absolute configuration of the product in entry 11 was determined by the authentic sample (see ref 12). Absolute configurations in other products were estimated by referring to this result.

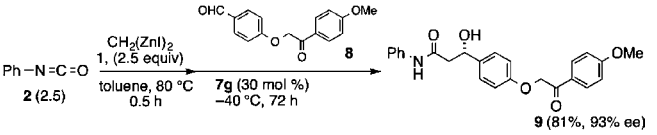
The optimization of the addition of enolate equivalent **3** to *p*-tolyl aldehyde in the presence of **7g** was examined as shown in Table 2. When the reaction was performed by adding 2 equiv of **3** to **5b** in the presence of 30 mol % **7g**, the adduct **6b** was obtained in 99% yield with 84% ee.

As shown in Table 3, various aldehydes were examined under the conditions of entry 3 in Table 2. In all cases, the products were obtained with over 76% ee.[12] Compared to the already reported catalytic asymmetric Reformatsky-type reaction, the present results show competitive optical yields.[10b,c]

(11) (a) Zhao, G.; Li, X.-G.; Wang, X.-R. *Tetrahedron; Asymmetry* **2001**, *12*, 399. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

(12) The value of ee was detemined by HPLC analysis using a chiral column. The absolute configuration of **6l** was determined by the optical rotation ($[\alpha]_D^{20}$ −21.2 (*c* 0.70, CH_2Cl_2)) by comparison with the reported value. Demizu, Y.; Kubo, Y.; Matsumura, Y.; Onomura, O. *Synlett* **2008**, 433.

Scheme 4. Asymmetric Induction in Chemoselective Reformatsky-Type Reaction



The moderate reactivity of the enolate equivalent can realize asymmetric induction in the aldol reaction in the presence of a ketone group. As shown in Scheme 4, the treatment of ketoaldehyde **8** with **3** afforded the corresponding product **9** in 81% yield with 93% ee.

Because the enolate equivalent **3** prepared by the addition of bis(iodozincio)methane (**1**) to phenyl isocyanate possesses only low nucleophilicity, the activation by addition of an aminoalcohol catalyst makes it a highly selective synthetic reagent as an amide enolate equivalent. Preparation of a metal enolate of amide has been performed by treatment of an amide with a strong base or a reduction of α-haloamide with a low valent metal. When these procedures are applied to asymmetric induction methods, the existing conjugate acid or Lewis acidic metal halide, which was formed stoichiometrically in the reaction mixture during the preparation, would cause poor asymmetric induction. The present method, a direct introduction of the C−Zn bond using a *gem*-dizinc reagent, however, does not suffer from these obstacles. Preparations of various enolate equivalents from a *gem*-dizinc reagent and heterocumelene are studied now in our group.

Acknowledgment. This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Supporting Information Available. Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.