ORGANIC
LETTERS

2013
Vol. 15, No. 20
5154–5157

Zinc-Mediated Highly α-Regioselective 1,4-Addition of Chalcones with Prenyl Bromide in THF

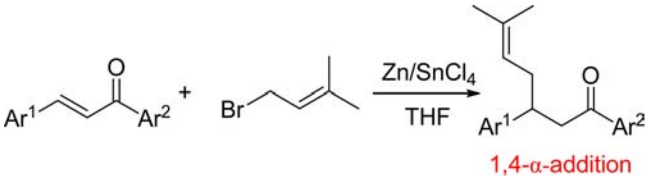
Li-Ming Zhao,* Shu-Qing Zhang, Fei Dou, and Rui Sun

School of Chemistry and Chemical Engineering, and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, Jiangsu, China

lmzhao@jsnu.edu.cn

Received July 16, 2013

ABSTRACT



α-Regioselective addition to chalcones was realized by use of in situ generated prenylzinc reagents from zinc and prenyl bromide in the presence of $SnCl_4$ in a 1,4-addition fashion. The approach uses the reagent combination of prenyl bromide, zinc, and $SnCl_4$ in THF, all of which are inexpensive, readily available, and easily removable after the reaction.

Regioselectivity is an important research area in modern organic synthesis. Development of highly regioselective C–C bond formation reactions has long been a desirable goal for chemists. The conjugate addition of allylmetals to α,β-unsaturated carbonyl compounds (hereafter called enones) represents an important method of C–C formation, since the installed allyl moiety is a versatile handle for further synthetic manipulations.[1] Despite significant advances in the conjugate allylation of enones (such as Hosomi–Sakurai reaction),[2] analogous reactions that involve the α-selective conjugate prenylation of enones still remain scarce due to the challenging issue of regioselectivity as shown in Figure 1. Compared with allylic species, the presence of two methyl groups on the terminal olefin of prenylic species led to a mixture of a primary prenylmetallic type and a tertiary prenylmetallic type in mobile equilibrium.[3] In addition to the inherent regioselective problem of prenyl metal anions, 1,2-addition of the prenyl group to the carbonyl group can compete with the 1,4-conjugate addition reaction.[4] Therefore, the development of an α-selective conjugate prenylation Michael reaction constitutes a big challenge. The introduction of a prenyl

---

(1) For selected recent examples, see: (a) Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187. (b) Amat, M.; Perez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem.—Eur. J.* **2010**, *16*, 9438. (c) Kuang, Y.; Liu, X.; Chang, L.; Wang, M.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 3814. (d) Matsumoto, K.; Koyachi, K.; Shindo, M. *Tetrahedron* **2013**, *69*, 1043. (e) Saha, M.; Carter, R. G. *Org. Lett.* **2013**, *15*, 736.

(2) Initial discovery using allylsilanes: (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. For a review of the Hosomi–Sakurai reaction, see: (b) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. Representative 1,4-allylation examples: (c) Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* **1986**, *51*, 1745. (d) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214. (e) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978. (f) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049. (g) Dumas, A. M.; Fillion, E. *Org. Lett.* **2009**, *11*, 1919. (h) Brozek, L. A.; Sieber, J. D.; Morken, J. P. *Org. Lett.* **2011**, *13*, 995. Representative 1,4-γ-crotylation examples: (i) Davis, C. E.; Duffy, B. C.; Coates, R. M. *J. Org. Chem.* **2003**, *68*, 6935. (j) Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun.* **2003**, 2220. (k) Hanessian, S.; Mainetti, E.; Lecomte, F. *Org. Lett.* **2006**, *8*, 4047.

(3) (a) Whitesides, G. M.; Nordlander, J. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 2010. For reviews on the chemistry of allylic compounds, see: (b) Benkeser, R. A. *Syntheis* **1971**, 347. (c) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

(4) For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. For selected 1,2-addition examples, see: (c) Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710. (d) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955. (e) Loh, T.-P.; Zhou, J.-R.; Zheng, Y. *Org. Lett.* **1999**, *1*, 1855. (f) Sinha, P.; Roy, S. *Chem. Commun.* **2001**, 1798. (g) Matsukawa, S.; Funabashi, Y.; Imamoto, T. *Tetrahedron Lett.* **2003**, *44*, 1007. (h) Ma, C.; Schiltz, S.; Le Goff, X. F. *Chem.—Eur. J.* **2008**, *14*, 7314. (i) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073. (j) Fleury, L. M.; Ashfeld, B. L. *Org. Lett.* **2009**, *11*, 5670. (k) Fleury, L. M.; Kosal, A. D.; Masters, J. T.; Ashfeld, B. L. *J. Org. Chem.* **2013**, *78*, 253.

10.1021/ol402000m

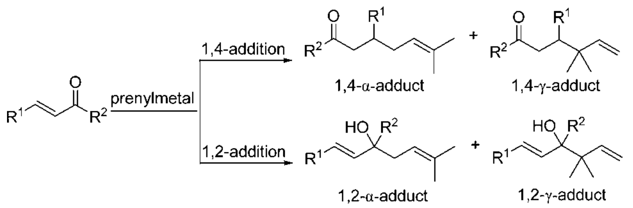
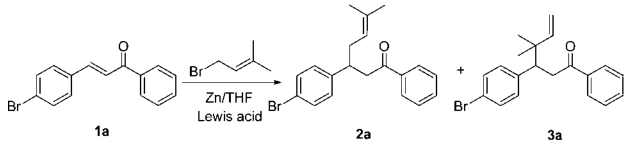


Figure 1. Competing reactions for the addition of a prenylmetal reagent to α,β-unsaturated carbonyl compounds.

group is, however, of great importance from a practical point of view because the prenyl fragment occurs widely in a variety of natural products and biologically important molecules.[5] A literature survey showed that most reported conjugate prenylation reactions were γ-regioselective or often complicated by the formation of mixtures of α- and γ-regioisomers.[6] To the best of our knowledge, only one report has demonstrated the feasibility of the α-selective conjugate prenylation of enones.[7] Although the method can deliver the α-adduct in a 1,4-addition fashion, it is limited to a few aliphatic α,β-unsaturated ketones only. To address the limitation, a far more detailed study on the 1,4-addition of crotyl and prenyl Grignard-derived organocopper reagents was performed by the same group.[8] However, the results are unsatisfactory because the relatively modest α-regioselectivity was observed and the mixtures containing an amount of γ-adduct were formed in all cases. Therefore, the conjugate addition reaction of prenylmetals to enones with high control of the α-regioselectivity is still undeveloped. On the other hand, it is known that organozinc reagents hold a special position among organometallics owing to their highly covalent character of the C−Zn bond.[9] However, the possibility of using an allylzinc reagent in a conjugate addition reaction has not been demonstrated yet despite the fact that various allylmetals such as allylsilane,[2a,c,10] allylbarium,[6a] allylcopper,[7,8] allylmanganese,[11] allyltin,[2j,6d,12] allyllithium,[6b] and allylindium[6c,13] have found applications in conjugate addition reactions. It is noteworthy that there are several advantages associated with the use of organozinc reagents, including their higher functional group compatibility, their stability at high temperature due to the strong metal−carbon bond, and the cheap commercial availability of zinc. In continuing our interest in organozinc reagents and based on our previous endeavors in developing α-regioselective allylation reactions,[14] herein we report a simple and practical method for the α-selective conjugate prenylation using inexpensive and readily available prenyl bromide and zinc with perfect control of regioselectivity.

It is well-known that Lewis acids can affect the selectivity and reactivity of Michael-type reactions.[15] Although various Lewis acids can be used in the Hosomi−Sakurai reaction, $TiCl_4$ and $AlCl_3$ are generally considered as the most effective for the conjugate allylations of α,β-unsaturated carbonyl compounds. As a result, preliminary studies were performed on the same Lewis acids, and the Michael addition of chalcone **1a** with prenyl bromide in tetrahydrofuran (THF) was chosen as a model reaction. The results depicted in Table 1 showed that the reactivity depended on the reaction temperature. We found that the reaction did not proceed below 50 °C and the starting material was almost recovered quantitatively (entry 1), but gave the addition reaction at more elevated temperatures.

Table 1. Optimization of Reaction Conditions of the 1,4-Addition[a]



entry	Lewis acid (equiv)	temp (°C)	t (h)	**2a** (%)[b]	**3a** (%)	recovery of **1a**[b]
1	$TiCl_4$ (1.3)	50	20	ND	ND	>98%
2	$TiCl_4$ (1.3)	reflux	14	58[c]	30[c]	ND
3	$AlCl_3$ (1.3)	reflux	14	70	trace	trace
4	$SnCl_4$ (1.5)	reflux	14	59	ND	10
5	$SnCl_4$ (1.0)	reflux	16	81	ND	trace
6	$ZnBr_2$ (1.0)	reflux	16	58	trace	18

[a] Reactions were performed with **1** (1.0 mmol), prenyl bromide (2.0 mmol), and zinc (2.5 mmol). [b] Isolated yield. [c] GC-MS yield.

---

(5) (a) Thomasar, A. F.; Bessiere, Y. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley: New York, 1988; Vol 7, p 275. (b) Mann, J.; Davidson, R. S.; Hobbs, J. B.; Banthorpe, D. V.; Harborne, J. B. In *Natural Products: Their Chemistry and Biological Significance*; Longman Scientific & Technical: Essex, 1994; p 289. (c) Morales-Rios, M. S.; Suarez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186. (d) Ahmad, N. M.; Rodeschini, V.; Simpkins, N. S.; Ward, S. E.; Blake, A. J. *J. Org. Chem.* **2007**, *72*, 4803. (e) Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 5234. (f) McGrath, N. A.; Binner, J. R.; Markopoulos, G.; Brichacek, M.; Njardarson, J. T. *Chem. Commun.* **2011**, *47*, 209.

(6) (a) Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130. (b) Ooi, T.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **1997**, *36*, 1183. (c) Lee, P. H.; Lee, K.; Kim, S. *Org. Lett.* **2001**, *3*, 3205. (d) Shibata, I.; Kano, T.; Kanazawa, N.; Fukuoka, S.; Baba, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1389. (e) Ito, H.; Nagahara, T.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 994.

(7) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404.

(8) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437.

(9) (a) Antes, I.; Frenking, G. *Organometallics* **1995**, *14*, 4263. For review, see: (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415.

(10) (a) Wu, M. -J.; Yeh, J.-Y. *Tetrahedron* **1994**, *50*, 1073. (b) Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Satheesh, G. *Tetrahedron Lett.* **2002**, *43*, 9695.

(11) Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *Chem. Commun.* **1997**, 2077.

(12) Takuwa, A.; Nishigaichi, Y.; Iwamoto, H. *Chem. Lett.* **1991**, 1013.

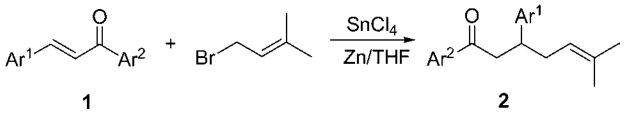
(13) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37.

(14) (a) Zhao, L.-M.; Jin, H.-S.; Wan, L.-J.; Zhang, L.-M. *J. Org. Chem.* **2011**, *76*, 1831. (b) Zhao, L.-M.; Wan, L.-J.; Jin, H.-S.; Zhang, S.-Q. *Eur. J. Org. Chem.* **2012**, 2579. (c) Zhao, L.-M.; Zhang, S.-Q.; Jin, H.-S.; Wan, L.-J.; Dou, F. *Org. Lett.* **2012**, *14*, 886.

(15) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2773.

On the other hand, although $TiCl_4$ and $AlCl_3$ were promising catalysts for this transformation, the process was relatively less regioselective because both Lewis acids gave mixtures of α- and γ-adducts (entries 2 and 3), especially the case of using $TiCl_4$ as a Lewis acid. Separation of the α-adduct **2a** and γ-adduct **3a** is a challenging task due to the similar polarity of two compounds. Therefore, other Lewis acids were examined and we were pleased to find that using $SnCl_4$ as the Lewis acid gave a satisfactory regioselective result and the corresponding α-adduct was obtained with 59% yield in 14 h albeit with the recovery of starting material **1a** (entry 4). The conversion of starting material **1a** can be further improved with an extended reaction time (entry 5). In terms of yield and regioselective outcome, $SnCl_4$ was the best choice for the model reaction because the possible γ-regioisomer **3a** was not observed in the reaction mixtures, which makes the purification of the product much easier. Lowering the amount of $SnCl_4$ to 1.0 equiv had no influence on the reaction (entry 5).

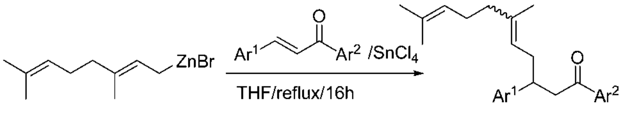
Table 2. 1,4-Addition of Prenyl Bromide to Chalcones **1**[a]



entry[b]	**1**	Ar^1, Ar^2	**2**	yield (%)[c]	α/γ[e]
1	**1b**	Ph, Ph	**2b**	67	100:0
2	**1c**	4-ClC_6H_4, Ph	**2c**	85	100:0
3	**1d**	2,6-$Cl_2C_6H_3$, Ph	**2d**	64	100:0
4	**1e**	4-MeC_6H_4, Ph	**2e**	73	>99:1
5	**1f**	4-$MeOC_6H_4$, Ph	**2f**	66	>99:1
6	**1g**	4-$CF_3C_6H_4$, Ph	**2g**	82	100:0
7	**1h**	4-$COOHC_6H_4$, Ph	**2h**	69	98:2
8	**1i**	Ph, 4-ClC_6H_4	**2i**	85	>99:1
9	**1j**	Ph, 4-BrC_6H_4	**2j**	70	100:0
10	**1k**	Ph, 4-MeC_6H_4	**2k**	62	>99:1
11	**1l**	2-MeC_6H_4, 4-BrC_6H_4	**2l**	62	100:0
12	**1m**	3-MeC_6H_4, 4-BrC_6H_4	**2m**	79	94:6
13	**1n**	3-$MeOC_6H_4$, 4-BrC_6H_4	**2n**	52	>99:1
14	**1o**	4-BrC_6H_4, 4-MeC_6H_4	**2o**	60	100:0
15	**1p**	2-FC_6H_4, 4-MeC_6H_4	**2p**	64	>99:1
16	**1q**	4-ClC_6H_4, 2-BrC_6H_4	**2q**	51	93:7
17	**1r**	3-MeC_6H_4, 4-MeC_6H_4	**2r**	64	100:0
18	**1s**	4-BrC_6H_4, 4-$MeOC_6H_4$	**2s**	82	100:0
19	**1t**	2-BrC_6H_4, 4-$CF_3C_6H_4$,	**2t**	87	100:0
20	**1u**	Ph, 2-naphthyl	**2u**	63	100:0
				86[d]	100:0
21	**1v**	Ph, 2-fural	**2v**	38	100:0
22	**1w**	2-thienyl, Ph	**2w**	40	>99:1

[a] Unless noted elsewhere, reactions were performed with **1** (1.0 mmol), prenyl bromide (2.0 mmol), and zinc (2.5 mmol) in the presence of $SnCl_4$ (1.0 mmol) in refluxing THF for 16 h (excess zinc was removed after the formation of prenylzinc reagent). [b] In all cases excess zinc metal was removed before addition of the enone. [c] Isolated yield. [d] No $SnCl_4$ was used. [e] Determined by GC-MS.

Scheme 1. Conjugate Addition of Geranylzinc with Chalcones



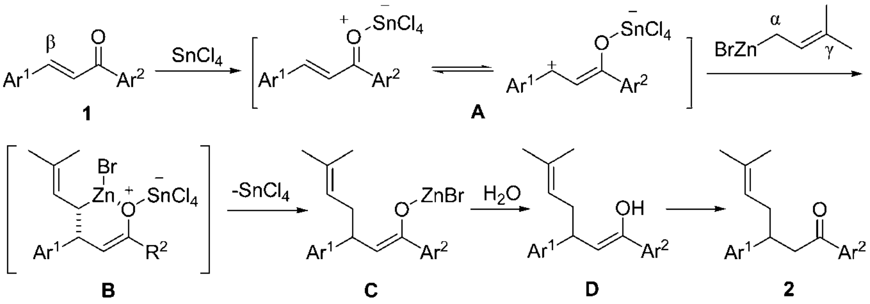
Ar^1= 4-MeC_6H_4 Ar^2= Ph **4a** 79% *E*:*Z* 67:33
Ar^1= 4-$MeOC_6H_4$ Ar^2= Ph **4b** 86% *E*:*Z* 67:33
Ar^1= 4-ClC_6H_4 Ar^2= Ph **4c** 85% *E*:*Z* 61:39

With the optimal reaction conditions established, we investigated the Michael addition of prenylzinc to various aryl-substituted enones to demonstrate the efficiency and reveal the scope and limitation (Table 2). Treatment of prenylzinc bromide with a range of chalcones **1b**–**1w** afforded the corresponding 1,4-α-adducts in moderate to good yields (entries 1–22). It seemed that neither the electronic nature nor the steric hindrance of the substituents on the phenyl ring (Ar^1 or Ar^2) had a strong influence upon the reactivity (entries 1–19). Notably, in some cases, the conjugate addition could be realized easily without the addition of $SnCl_4$ (entry 20). In addition, the reaction did not work with the substrates with aliphatic substituents such as 4-phenylbut-3-en-2-one, 3-(4-methoxyphenyl)-acrylaldehyde, and 2-cyclohexenone (data not shown). These experimental phenomena indicated that the substrate with the bulkier Ar^2 substituent was more efficient in the 1,4-addition reaction. The reaction also worked with the heteroaromatic substrates such as **1v** and **1w** albeit with low yields (entries 21 and 22). The low yields of α-adducts **2v** and **2w** might be due primarily to the low stability of the furan ring and thiophene ring when exposed to Lewis acids at an elevated temperature overtime. When the reaction of methyl cinnamate with prenylzinc in the presence of $SnCl_4$ was attempted, no reaction was observed and most of the starting material was easily recovered (data not shown). Such a result could be attributed to the low intrinsic reactivity of α,β-unsaturated esters compared with enones. Although the reaction does not work well with the substrates with aliphatic substituents, to our great delight, the addition of prenylzinc to chalcones afforded exclusive 1,4-α-adducts with only trace amounts of 1,2-adducts being detected in all cases. The possible interpretation of the high 1,4-selective manner was that the coordination of $SnCl_4$ to a carbonyl oxygen atom will significantly decrease in the LUMO level and the β-carbon thus has a larger coefficient.[16] Furthermore, it would be also a considerable factor for the 1,4-selectivity that the steric hindrance of the substituent at the carbonyl group shifts the reactivity to the β-carbon to avoid the competitive 1,2-addition. Strong evidence to support this rationalization is that the reaction of chalcone equipped with a sterically bulky naphthyl substituent on the carbonyl remained at a high level of 1,4-selectivity in the absence of $SnCl_4$ (entry 20). Meanwhile, α-adducts were formed predominantly in all cases. This is completely different from previous conjugate allylation, which always was accompanied by a 1,2-product or

---

(16) Cabral, J.; Laszlo, P.; Mahe, L.; Montaufier, M. T.; Randriamahefa, S. L. *Tetrahedron Lett.* **1989**, *30*, 3969.

Scheme 2. Proposed Mechanism for the α-Regioselective 1,4-Addition



provided a *γ*-adduct predominantly. To the best of our knowledge, this is the first direct conjugate addition of prenylzinc to α,*β*-unsaturated carbonyl compounds reported so far that provides the α-addition product in a highly regiocontrolled manner.

Besides the prenylic reagent, other substituted allylic reagents could be also used to give the conjugate α-adducts. For instance, treatment of geranylzinc bromide with chalcones such as 4-methylchalcone, 4-methoxychalcone, and 4-chlorochalcone afforded the corresponding 1,4-α-adducts **4a**−**c** in good yields, respectively (Scheme 1). In all cases, only the 1,4-α-adduct was observed during the reaction course. The formation of other regiochemical products such as the 1,4-*γ*-, 1,2-α-, and 1,2-*γ*-adduct was not observed. Geranylzinc bromide reacted with excellent regioselectivity to afford 1,4-α-adducts; however, the *E*/*Z* forms were obtained in all cases.

Although the exact reason that would account for these results is not clear at the present time, we proposed a plausible mechanism to rationalize the observed high 1,4-α-selectivity (Scheme 2). The first step is the coordination of a Lewis acid to the carbonyl oxygen atom of **1**, resulting in a resonance delocalized cation **A**. The following addition of prenylzinc on the α-position proceeds at the highly cationic *β*-carbon of **1** from the direct conjugate addition via a six-membered transition state **B**,[17] which is analogous to the direct addition of the ketone and the crotyl Grignard via a four-membered transition state.[18] Then, the zinc enolate **C** is formed from **B** by liberating the $SnCl_4$. Finally, the resulting enol intermediate **D** tautomerizes to the carbonyl product **2**. The mechanism of direct attack of prenylzinc on the α-position can be supported by the following facts. First, although the prenylzinc reagent is represented by a rapidly equilibrating mixture of primary prenylzinc species and tertiary prenylzinc species, it should be noted that the equilibrium between them should favor the less sterically encumbered primary prenylzinc.[3] Second, the argument of transition state **B** is chemically reasonable due to the minimization of repulsion between Ar^1 and hydrogen atom of the CH_2 group of primary prenylzinc. By contrast, formation of such a TS via tertiary prenylzinc is difficult and the TS once formed is highly unstable due to the significant steric congestion of the methyl group at the α-position of tertiary prenylzinc and the weak complexation of the carbonyl group with prenylzinc which shows moderate reactivity in comparison with organolithium and Grignard reagents, and so the formation of *γ*-adduct is almost completely prevented.

In summary, we have developed an efficient method for the introduction of a prenyl group into the *β*-position of chalcones by zinc-mediated conjugate addition in the presence of $SnCl_4$. The reaction has proven to be highly α-regioselective in a 1,4-manner, and the α-regioselectivity of these additions is higher than the corresponding regioselective additions of allylic barium, allylic lithium, and allylic copper reagents. Very rare 1,4-α-prenylation was thus achieved. Another important contribution of the present study is to show the possibility of using an organozinc reagent in a Michael-type reaction, thereby providing a new strategy to accomplish this type of conjugate addition process.

Acknowledgment. We are thankful for financial support from Major Program of Natural Science Foundation of Jiangsu Higher Education Institutions (12KJA150005), the Natural Science Foundation of Jiangsu Province (BK2012576), and PAPD of Jiangsu Higher Education Institutions.

Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

---

(17) For the discussions on six-centered transition states of metal-mediated conjugate addition, see: (a) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 4635. (b) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524.

(18) With hindered substrates, the α-adducts might be formed directly from the substrate and the crotyl Grignard via a four-membered transition state, see: (a) Benkeser, R. A.; Siklosi, M. P.; Mozdzen, E. C. *J. Am. Chem. Soc.* **1978**, *100*, 2134. (b) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Tetrahedron Lett.* **2001**, *42*, 8705. For the direct attack of other allylmetal reagents at the *β*-carbons of enones, see ref 6a.