DOI: 10.1002/adsc.200800642

Development and Application of a New General Method for the Asymmetric Synthesis of (*E*)-(2-En-3-ynyl)-amines

Chao Yin,[a] Xin-Ping Hui,[a,*] Peng-Fei Xu,[a,*] Liang-Feng Niu,[a] Yong-Fei Chen,[a] and Binghe Wang[b]

[a] State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, People's Republic of China
Fax: (+86)-931-891-5557; e-mail: xupf@lzu.edu.cn
[b] Department of Chemistry, Georgia State University, Campus Box 4098, Atlanta, GA 30302-4098, USA

Received: October 20, 2008; Revised: January 21, 2009; Published online: February 6, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800642.

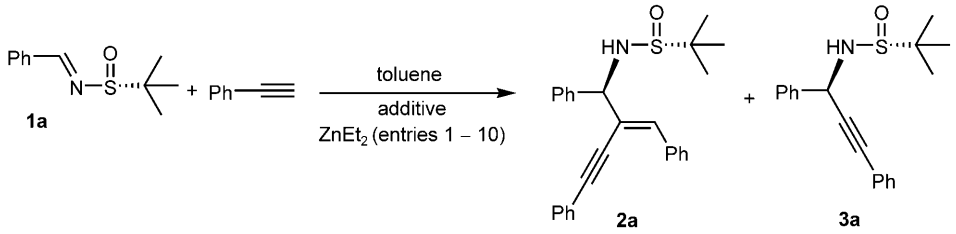
Abstract: The first direct approach for the asymmetric synthesis of (*E*)-2-arylidene-1,4-diphenylbut-3-yn-1-amines by addition of alkynylzinc to chiral *N*-*tert*-butylsulfinylimines is reported with excellent diastereoselectivity and good yield. This asymmetric addition reaction provides a practical, economical and concise synthesis of multifunctional molecules with the 1,3-enyne side chain and an amino group. In addition, this methodology can be applied to the synthesis of substituted vinyl iodide compounds, and substituted chiral dihydropyrroles.

Keywords: alkynes; asymmetric synthesis; cyclization; diethylzinc; *N*-*tert*-butanesulfinylimines

Multifunctional molecules with double and triple bonds and an amino group, such as 1,3-enynamines, are important key building blocks for diversity-oriented organic synthesis; therefore, their efficient syntheses have attracted the interest of synthetic organic chemists.[1] 1,3-Enynamines were normally synthesized by separate multistep processes.[1b,2] In particular, it is difficult to synthesize chiral 1,3-enynamines with stereocontrol. To the best of our knowledge, there was only one report on the stereoselective synthesis of chiral 1,3-enyne-containing α-amino acid esters, which were prepared by hydrogen-mediated reductive coupling of 1,3-diynes and ethyl *N*-(*tert*-butylsulfinyl)iminoacetate using $Rh(COD)_2OTf$ and BIPHEP as catalysts.[3] Recently, Kazmaier, et al.[4] reported the convenient synthesis of peptides containing a 1,3-enyne side chain by the Sonogashira reaction using the transition metal catalysts $Rh(COD)_2OTf$ or $Pd(PPh_3)_4$. Herein, we report for the first time the efficient asymmetric synthesis of (*E*)-2-arylidene-1,4-diphenylbut-3-yn-1-amines in high diastereoselectivity *via* the addition of alkynylzinc species to *N*-*tert*-butansulfinylimines, which are stable, easy to prepared, and widely used for various applications.[5–9]

In our work, we used Ellman's enantiomerically pure, *R*-configured *N*-*tert*-butanesulfinylimines, which can be used as chiral nitrogen-containing intermediates for the preparation of a wide range of chiral amines. The asymmetric addition of an alkynylzinc to (*R*)-*tert*-butylsulfinylbenzaldimine (**1a**) led to the formation of two major compounds, **2a** and **3a**. As shown in Table 1, the amounts of $ZnEt_2$ and alkyne have a significant effect on the yield and the ratio of **2a** to **3a**, which increased significantly when the amounts of phenylacetylene and diethylzinc increased from 1 to 3 equivalents (Table 1, entries 1–3). Then, we varied the ratio of phenylacetylene over diethylzinc (Table 1, entries 4, 5) and found that a ratio of 1:2.5:5 for the sulfinylimine, diethylzinc, and phenylacetylene gave the best results. Therefore, subsequent studies were conducted with 2.5 equivalents diethylzinc and 5 equivalents phenylacetylene. Temperature was also a crucial factor in this reaction. The reaction did not occur at ambient temperature or 60 °C; and it gave a low 40% yield at 80 °C (Table 1, entries 6–8). It was found that when the reactions were performed under reflux they gave high yield and diastereoselectivity (Table 1, entries 3–5). Three solvents were examined and toluene was found to be the best choice (Table 1, entries 5, 9, 10). Other additives, such as $InCl_3$, Et_2AlCl were studied; however, none of them worked as well as diethylzinc (Table 1, entries 11, 12). The reaction with dimethylzinc as additive gave lower ratios of **2a/3a** and low yields (Table 1, entry 13). Therefore, the optimal conditions were those of entry 5 in Table 1, which led to the formation of **2a** in

Table 1. Reaction optimization.



Entry	Additive (equiv.)	Ph–C≡CH (equiv.)	Temperature	**2a**/**3a**	Yield [%]	*dr*[a]
1	1	1	reflux	10:1	19	>99:1
2	2	2	reflux	28:1	65	>99:1
3	3	3	reflux	34:1	90	>99:1
4	2	4	reflux	50:1	87	>99:1
5	2.5	5	reflux	50:1	93	>99:1
6	2.5	5	r.t.	N.R.	–	–
7	2.5	5	60 °C	N.R.	–	–
8	2.5	5	80 °C	10:1	40	>99:1
9[b]	2.5	5	reflux	N.R.	–	–
10[c]	2.5	5	reflux	N.R.	–	–
11[d]	2.5	5	reflux	N.R.	–	–
12[e]	2.5	5	reflux	N.R.	–	–
13[f]	2.5	5	reflux	25:1	87	>99:1

[a] Only one isomer was obtained and determined by ^{1}H NMR (400 MHz) of the crude products.
[b] Reaction was carried out in *n*-hexane.
[c] Reaction was carried out in THF.
[d] $InCl_3$ as additive.
[e] Et_2AlCl as additive.
[f] $ZnMe_2$ as additive

high yield (93%) and excellent diastereoselectivity ($dr > 99:1$).

With the optimized reaction conditions in hand, a survey of different *N-tert*-butanesulfinylimines was carried out and the results are summarized in Table 2. For the less sterically hindered 4-substituted *N-tert*-butanesulfinylaldimines, excellent diastereoselectivities ($dr > 99:1$) were achieved; however, the 2-substituted *N-tert*-butanesulfinylaldimines resulted in lower diastereoselectivities except for 2-fluoro-*N-tert*-butanesulfinylaldimine. The diastereoselectivities were excellent when aromatic and alphatic alkynes were used (Table 2, entries 14 and 17). The addition reaction to *N-tert*-butanesulfinylketoimine was also examined and compound **2p** was not obtained; instead, *N-tert*-butanesulfinylpropargylamine (**3p**) was obtained in low yield and low diastereoselectivity ($dr = 87:13$, Table 2, entry 16).

The stereochemistry of the compound **2a** was determined by X-ray crystallography on the basis of compound **5**.[10] (See Supporting Information) which was derived from compound **2a** in a two-step reaction sequence (Figure 1). A key feature of this methodology is the use of the products **2** in subsequent transformations. For example, deprotection and acetylization can

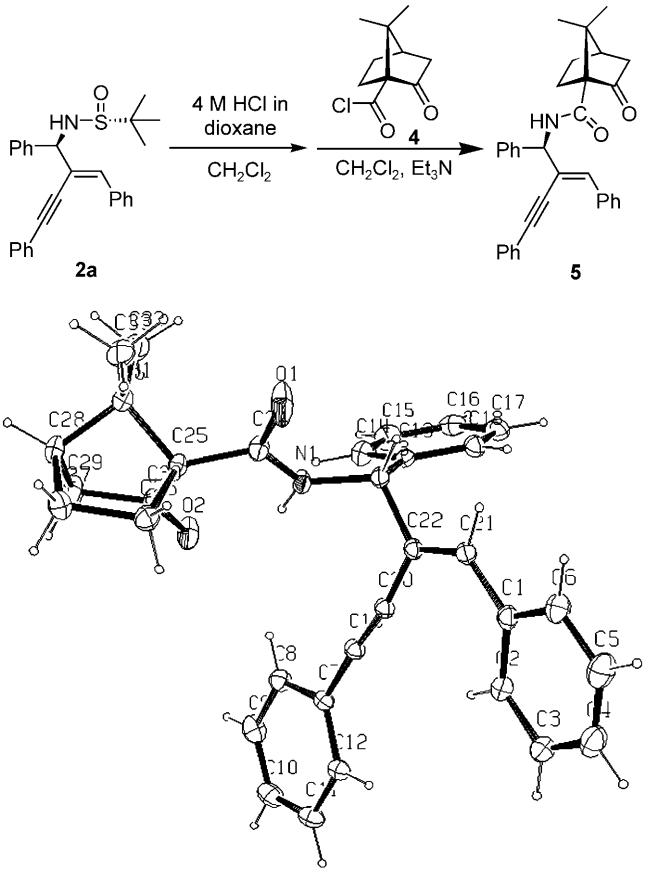
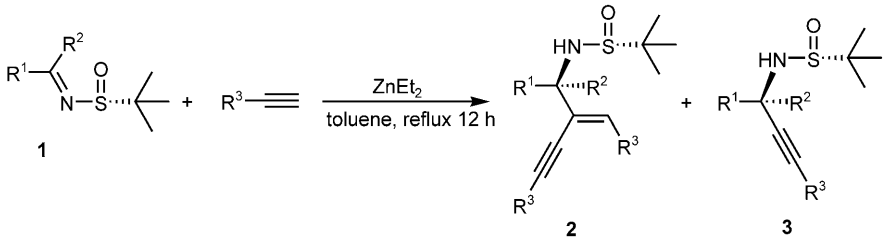


Figure 1. Synthesis and X-ray crystallography structure of compound **5.**

Table 2. Asymmetric addition of phenylacetylene to chiral *N-tert*-butanesulfinylimines.[a]

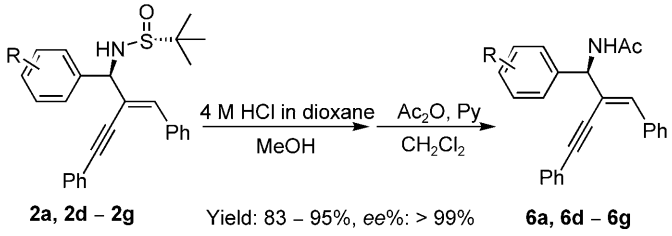


Entry	R^1	R^3	2/3	Yield [%][b]	*dr*[c]
1	C_6H_5	C_6H_5	50:1	93 (**2a**)	>99:1
2	*p*-CH_3-C_6H_4	C_6H_5	28:1	92 (**2b**)	>99:1
3	*o*-CH_3O-C_6H_4	C_6H_5	28:1	86 (**2c**)	95:5
4	*p*-CH_3O-C_6H_4	C_6H_5	34:1	91 (**2d**)	>99:1
5	*o*-Cl-C_6H_4	C_6H_5	28:1	88 (**2e**)	95:5
6	*m*-Cl-C_6H_4	C_6H_5	42:1	91 (**2f**)	97:3
7	*p*-Cl-C_6H_4	C_6H_5	24:1	88 (**2g**)	>99:1
8	*o*-F-C_6H_4	C_6H_5	40:1	90 (**2h**)	>99:1
9	*m*-F-C_6H_4	C_6H_5	40:1	86 (**2i**)	>99:1
10	*o*-Br-C_6H_4	C_6H_5	20:1	78 (**2j**)	90:10
11	naphthyl	C_6H_5	20:1	85 (**2k**)	>99:1
12	*n*-butyl	C_6H_5	40:1	83 (**2l**)	>99:1
13	*p*-Et_2N-C_6H_4	C_6H_5	16:1	60 (**2m**)	>99:1
14	C_6H_5	*p*-Cl-C_6H_4	99:1	95 (**2n**)	>99:1
15[d]	C_6H_5	C_6H_5	50:1	94 (**2o**)	>99:1
16[e]	C_6H_5	C_6H_5	<1:99	51 (**3p**)	87:13
17	C_6H_5	*n*-C_5H_{11}	25:1	81 (**2q**)	>99:1

[a] See Supporting Information for reaction details, $R^2 = H$ (entries 1–15); $R^2 = CH_3$ (entry 16).
[b] Isolated yields of compound **2**.
[c] The *dr* values were determined by ^1H NMR (400 MHz) of the crude materials.
[d] (*S*)-*tert*-Butanesulfinylimine was used.
[e] The *dr* value was determined on the basis of compound **3p**.

be accomplished in high yields without loss of enantioselectivity (Scheme 1).

To study the reaction mechanism, a series of experiments was performed. There was no reaction when 1,4-diphenylbutanediyne and imine **1a** were used as starting materials, which indicated the 1,4-diphenylbutanediyne was not a intermediate. When we used compound **3a** instead of imine **1a** as starting material, no reaction was found which suggested the product **2a** was not derived from **3a** under this conditions. Then, we carried out deuterium labeling studies. When the reaction of **1a** with phenylacetylene was quenched by



Scheme 1. Conversion of the addition products.

D_2O, the ratio of H to D of the double bond was 55 to 45.[11] When the reaction was performed with deuterated phenylacetylene and then quenched by D_2O and H_2O, the ratios of H to D of the double bond were 6 to 94 and 46 to 54, respectively.

Our current hypothesis is that alkynylzinc is formed *in situ* in analogy to the known chemistry of terminal alkynes and dialkylzinc (Figure 2). First, the 1,2-addition of alkynylzinc to **1a** affords intermediate $\mathbf{T_1}$, which undergoes attack by another alkynylzinc to form a cyclic intermediate $\mathbf{T_2}$.[1d,12] The carbon-zinc and nitrogen-zinc bonds can be split by excess phenylacetylene to give intermediates **T3** and **T3′**. Then, the reaction is quenched by H_2O to give product **2a**. In support of this postulate, we examined the reactivity of the proposed intermediate **T3′**, excess benzaldehyde was added to the reaction system after the addition reaction of alkynylzinc to *N-tert*-butanesulfinylimine was completed, the expected addition product, compound **7** was obtained. Such results are consistent with the formation of intermediate **T3′**; the *N*-attack product (from **T3**) is an aza-hemiacetal, which is unstable under work-up conditions and product **2** was

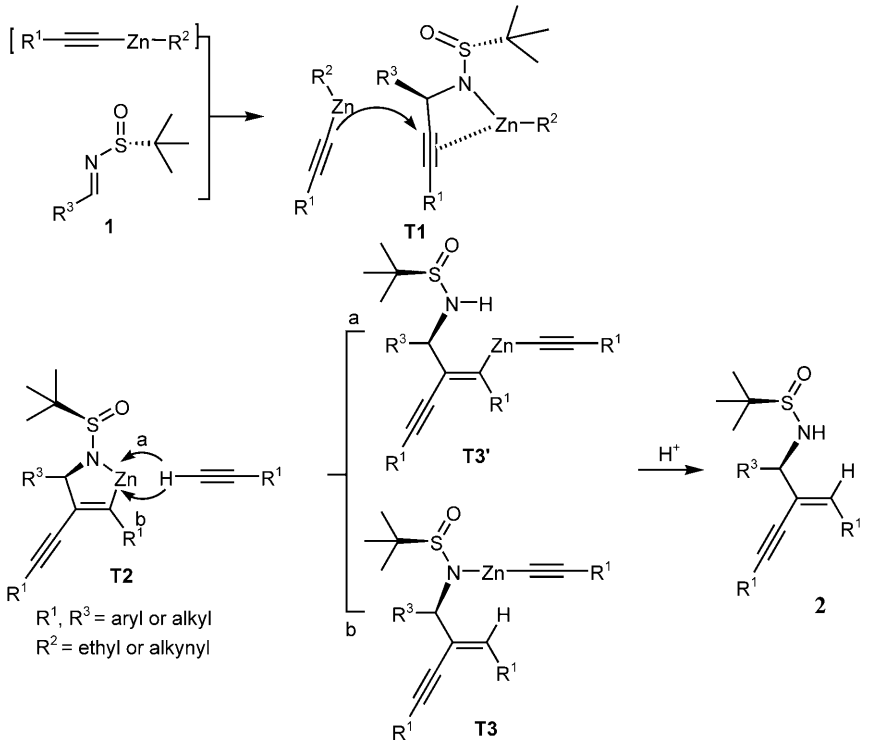
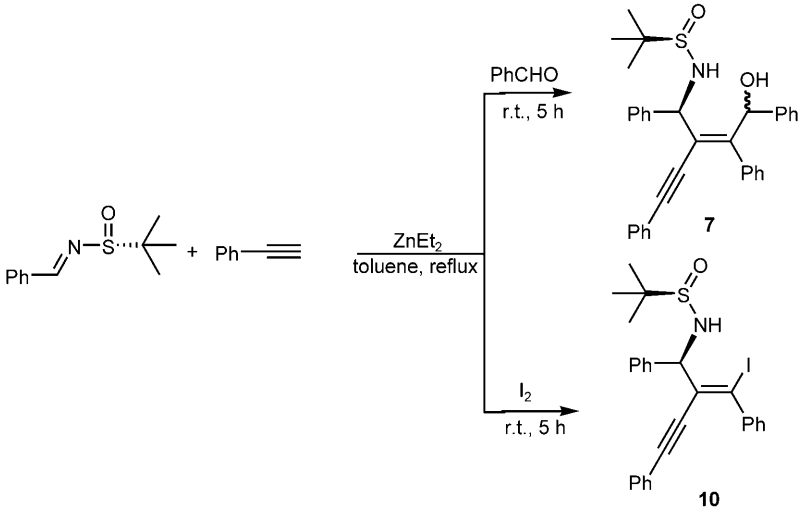


Figure 2. Proposed mechanism.

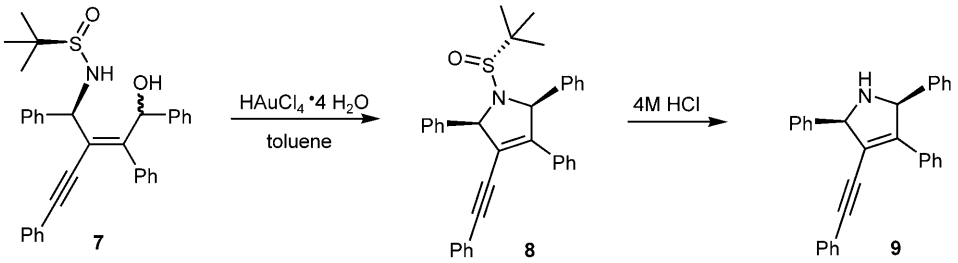
obtained. The proposed mechanism also allows an explanation for the predominant formation of **3p** (Table 2, entry 16). In this case, the methyl group may cause a steric hindrance problem and thus make it unfavorable for the formation of $\mathbf{T_2}$, which is essential for the formation of **2p**.

We further exploited the utility of this methodology. When $ZnEt_2$ (5 equiv.) and phenylacetylene (4 equiv.) were used and the reaction mixture was quenched with benzaldehyde (5 equiv.) or I_2 (5 equiv.), compounds **7** and **10** were obtained in yields of 70% and 65%, respectively (Scheme 2). Compound **7** could be cyclized to compound **8** in the presence of $HAuCl_4 \cdot 4H_2O$; removal of the *N-tert*-butanesulfinyl group in 4 M HCl afforded the chiral multi-substituted dihydropyrrole **9** (Scheme 3).

In summary, we have successfully developed a novel and direct approach for the asymmetric synthesis of (*E*)-2-arylidene-1,4-diphenylbut-3-yn-1-amines by addition of alkynylzinc to chiral *N-tert*-butanesul-



Scheme 2. Synthesis of compounds **7** and **10**.



Scheme 3. Gold-catalyzed cyclization of **7** to pyrrole **8**.

finylimines. This asymmetric addition reaction provides a practical, efficient and concise synthesis of multifunctional molecules, which offer attractive and versatile reaction sites for further transformations. The synthetic applications and the further mechanism study for this reaction are in progress.

Experimental Section

General Procedure for Addition of Phenylacetylene to *N-tert*-Butanesulfinylimines

Under a nitrogen atmosphere, toluene (3.0 mL), phenylacetylene (2.5 mmol, 275 μL) and diethylzinc (1.25 mmol, 1.25 mL) were combined in a Schlenk tube equipped with a condenser, the reaction mixture was heated to reflux for 5 h during which time a white precipitate was generated. Then *N-tert*-butanesulfinyl imine (0.5 mmol, dissolved in 0.5 mL toluene) was added, the solution was refluxed for another 12 h. After being cooled to ambient temperature, the reaction was quenched by H_2O, and extracted with diethyl ether (3×15 mL), washed with brine (3×15 mL), dried with anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel) to give the products.

Acknowledgements

We are grateful for the financial support of the National Natural Science Foundation of China (NSFC 20772051, 20702022), the Program "111" and NCET-05–0880 from the Ministry of Education of P. R. China.

References

[1] a) T. Ishikawa, T. Aikawa, S. Watanabe, S. Saito, *Org. Lett.* **2006**, *8*, 3881–3884; b) B. Gabriele, G. Salerno, A. Fazio, *J. Org. Chem.* **2003**, *68*, 7853–7861; c) S. H. Wang, Y. Q. Tu, P. Chen, X.-D. Hu, F.-M. Zhang, A.-X. Wang, *J. Org. Chem.* **2006**, *71*, 4343–4345; d) L. Zani, C. Bolm. *Chem. Commun.* **2006**, 4263–4275.

[2] a) M. Mukhopadhyay, M. M. Reddy, G. C. Maikap, J. Iqbal, *J. Org. Chem.* **1995**, *60*, 2670–2676; b) N. K. Nayyar, M. M. Reddy, J. Iqbal, *Tetrahedron Lett.* **1991**, *32*, 6965–6968; c) L. S. Hegedus, J. M. McKearin, *J. Am. Chem. Soc.* **1982**, *104*, 2444–2451; d) O. Mitsunobu, *Synthesis* **1981**, 1–28.

[3] J.-R. Kong, C.-W. Cho, M. J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276.

[4] J. Deska, U. Kazmaier, *Angew. Chem.* **2007**, *119*, 4654–4657; *Angew. Chem. Int. Ed.* **2007**, *46*, 4570–4573.

[5] For reviews, see: a) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984–995; b) J. A. Ellman, *Pure Appl. Chem.* **2003**, *75*, 39–46; c) D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869–8965; d) G. Q. Lin, M.-H. Xu, Y.-W. Zhong, X.-W. Sun, *Acc. Chem. Res.* **2008**, *41*, 831–840.

[6] a) G. Kolodney, G. Sklute, S. Perrone, P. Knochel, I. Marek, *Angew. Chem.* **2007**, *119*, 9451–9454; *Angew. Chem. Int. Ed.* **2007**, *46*, 9291–9294; b) Y. Li, J. Hu, *Angew. Chem.* **2007**, *119*, 2541–2544; *Angew. Chem. Int. Ed.* **2007**, *46*, 2489–2492; c) H. Huang, X. Guo, W. Hu, *Angew. Chem.* **2007**, *119*, 1359–1361; *Angew. Chem. Int. Ed.* **2007**, *46*, 1337–1339; d) L. Nielsen, K. B. Lindsay, J. Faber, N. C. Nielsen, T. Skrydstrup, *J. Org. Chem.* **2007**, *72*, 10035–10044; e) M. A. Beenen, D. J. Weix, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 6304–6305; f) K. M. Brinner, J. A. Ellman, *Org. Biomol. Chem.* **2005**, *3*, 2109–2113; g) D. J. Weix, Y. Shi, J. A. Ellman, *J. Am. Chem. Soc.* **2005**, *127*, 1092–1093; h) T. Kochi, J. A. Ellman, *J. Am. Chem. Soc.* **2004**, *126*, 15652–15653; i) L. B. Schenkel, J. A. Ellman, *Org. Lett.* **2004**, *6*, 3621–3624; j) T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2003**, *125*, 11276–11282; k) T. Kochi, ; T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2002**, *124*, 6518–6519.

[7] a) T. P. Tang, S. K. Volkman, J. A. Ellman, *J. Org. Chem.* **2001**, *66*, 8772–8778; b) J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick, P. G. Nantermet, *Tetrahedron Lett.* **2001**, *42*, 2051–2054.

[8] C.-H. Ding, D.-D. Chen, Z.-B. Luo, L.-X. Dai, X.-L. Hou, *Synlett* **2006**, 1272–1274.

[9] R. B. Lettan II, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 3227–3230.

[10] The molecular structure of the corresponding product **5** was determined by X-ray crystallography. For details, see Supporting Information. CCDC 675850 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)-1223–336–033.

[11] The ratio was determined by ^{1}H NMR (400 MHz) of the crude product.
[12] For reviews on carbometallation, see, for example: a) I. Marek, N. Chinkov, D. Banon-Tene, in. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn., (Eds. A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, p 395; b) D. Banon-Tenne, I. Marek, *Carbometalation Reactions of Zinc Enolate Derivatives*, in: *Transition Metals for Organic Synthesis*, (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, p 563; c) I. Marek, *J. Chem. Soc. Perkin Trans. 1* **1999**, 535.

