A Straightforward Approach towards Substituted Morita–Baylis–Hillman Products via Hydrostannation of Acetylenic Ketones

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Received 21 October 2009

Dedicated to Prof. M. Veith on the occasion of his 65th birthday

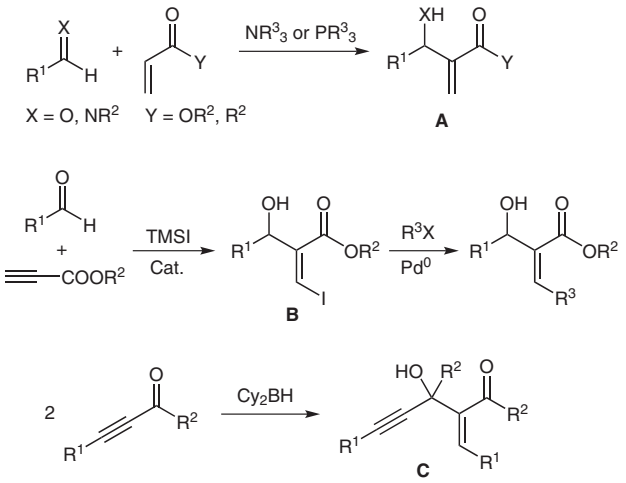
Abstract: Regioselective molybdenum-catalyzed hydrostannations of acetylenic ketones give rise to allenoxystannanes, which can be subjected to subsequent aldol reactions. Because aldehydes are not affected under the reaction conditions used, the hydrostannation–aldol addition can be performed as a one-pot reaction, providing easy access to substituted Morita–Baylis–Hillman-type products in a highly stereoselective fashion.

Key words: aldol addition, alkynes, enolates, hydrostannation, molybdenum, Morita–Baylis–Hillman

During the last decades the Morita–Baylis–Hillman (MBH) reaction has developed into a powerful tool in organic synthesis, giving rise to highly functionalized building blocks.[1] The reaction can be described as the coupling between the α-position of an activated double bond with an electrophile, in general an aldehyde or an imine.[2] A rich chemistry has been developed to convert the MBH adducts into other valuable products, for example, via allylic alkylations[3] and other cross-coupling reactions.[4] The reaction is initiated by the addition of a nucleophilic catalyst, in general a phosphine or an amine, towards the electron-poor double bond. Therefore, best results are obtained with acylates or vinylketones giving rise to α-methylene aldol products **A** (Scheme 1). Related structures with a β-substituted double bond, which might be even more interesting building blocks, are not so easily accessible by this protocol. Therefore, several other approaches have been developed during the last years.[5]

Very recently, Ryu et al. reported on an enantioselective Lewis acid catalyzed addition of alkynoates towards aldehydes giving rise to β-iodinated MBH esters **B**, which could be subjected to further cross-coupling reactions.[6] An alternative approach could be the hydrometalation of alkynyl ketones or esters,[7] if the α-metalated vinylic carbonyls are formed preferentially and if these undergo aldol additions. Kabalka et al. reported such an approach using hydroborations.[8] α,β-Acetylenic ketones could be coupled via in situ formed allenoxyborinates to stereodefined substituted MBH-type products **C**. By using *t*-Bu-ketones (R^2 = *t*-Bu), these borinates could be trapped also with several aldehydes.

Hydrostannations of α,β-acetylenic ketones and esters are also found to be highly regioselective, especially in transition-metal-catalyzed reactions.[9] While the α-stannylated α,β-unsaturated esters are relatively stable compounds, which can be separated, for example, by flash chromatography,[10] the corresponding ketones are much more troublesome. Here, often mixtures of regio- and stereoisomers are obtained, and complete protodestannation during workup is a severe problem.[11] These difficulties can be circumvented by using trineophyltin hydride, instead of the usually applied tributyl or trimethyl analogues. As illustrated by Mitchell et al. good selectivities are obtained under Pd-catalyzed conditions, and these α-stannylated vinylketones can be purified by flash chromatography and subjected to cross-coupling reactions or metal–iodine exchange without problems.[12]



Scheme 1 Synthesis of MBH-type products

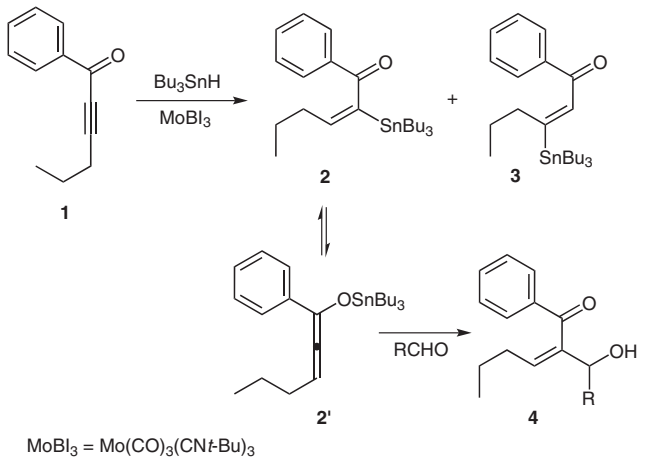
Our group is also involved in hydrostannation chemistry for some time,[13] and we developed a series of catalysts based on molybdenum and tungsten.[14] The most reliable and generally applicable catalyst is $Mo(CO)_3(CN\textit{t}\text{-}Bu)_3$ ($MoBl_3$),[15] which shows high α-selectivities in reactions of functionalized electron-poor alkynes.[16] Best results are obtained under a CO atmosphere, while the CO can interact as a ligand in the catalytic cycle.[17] In analogy to the Pd-catalyzed reactions, we received α-stannylated α,β-unsaturated esters in a highly regio- and stereoselective fashion, while the corresponding ketones could not be isolated, although the conversion of the starting material

SYNLETT 2010, No. 3, pp 0407–0410
Advanced online publication: 14.01.2010
DOI: 10.1055/s-0029-1219196; Art ID: G35209ST

was fast and complete. Trapping of the hydrostannation products with iodine gave the expected α-iodoketones with high regioselectivity.[15a,b] This clearly indicates that the expected hydrostannation product was formed, but probably not as the α-stannated product (as observed for the corresponding esters), but as the allenoxystannane, comparable to the allenoxyborinates described by Kabalka.[8]

In this case one should be able to trap the tin enolates with electrophiles, such as aldehydes, to get directly β-substituted MBH products.

Therefore, we investigated the hydrostannation of ketone **1** in detail (Scheme 2). In principle, two isomeric hydrostannation products can be formed: the α-stannane **2** and the β-metalated ketone **3**. But only **2** can form the tin enolate **2′**, and therefore trapping the reaction mixture with aldehyde should provide **4** and unconverted **3**, which can easily be separated by flash chromatography.

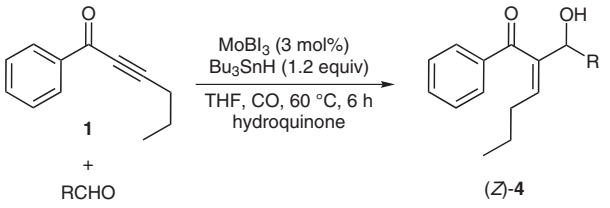


Scheme 2 MBH products **4** via one-pot hydrostannation–aldol reaction

In principle, the hydrostannation occurs already at room temperature, but the reaction is rather slow. Only 10–20% conversion was observed after six hours, while at 60 °C the ketone **1** was completely consumed. Therefore, we used these conditions for the development of a one-pot protocol. Hydroquinone was added to suppress possible radical side reactions, and the reactions were investigated under an atmosphere of CO to get good α-selectivities.[17b] To prove if the aldehyde can be added directly at the beginning of the reaction or if it has to be added after enolate formation, we subjected it to the same reaction conditions. Luckily, no reduction was observed. Therefore, we used this combination to evaluate the one-pot protocol (Table 1, entry 1).[18] With benzaldehyde, the coupling product **4a** was obtained in 40% yield as a 8:92 *E*/*Z*-mixture. The product ratio could easily be determined by NMR using the very characteristic signal for the vinylic β-H.[19] For the preferentially formed *Z*-isomers this signal appear typically around δ = 6 ppm, while in the *E*-isomer the signal shows a downfield shift of 1 ppm, (δ = ca. 7 ppm).[20]

A similar result was obtained with 2-naphthaldehyde (entry 2), while the introduction of electron-donating groups (entries 3 and 4) resulted in a significant drop of yield, whereas the *Z*/*E*-selectivity was nearly unchanged in the range of 20:1. On the other hand, introduction of electron-withdrawing groups increased the yields to 70–75% (entries 5–8). This differentiated reactivity allowed the selective monoaddition towards terephthalaldehyde (entry 7). Not unexpected the best result was obtained with the very electron-poor dinitrobenzaldehyde (entry 9). Heterocyclic aldehydes can be used with similar success. Electron-demanding aldehydes, such as pyridine carbaldehyde (entry 10), gave good yields, while no reaction was observed with the five-membered heterocyclic aldehydes, such as furan carbaldehyde. Unfortunately, aliphatic aldehydes gave low yields of impure products.

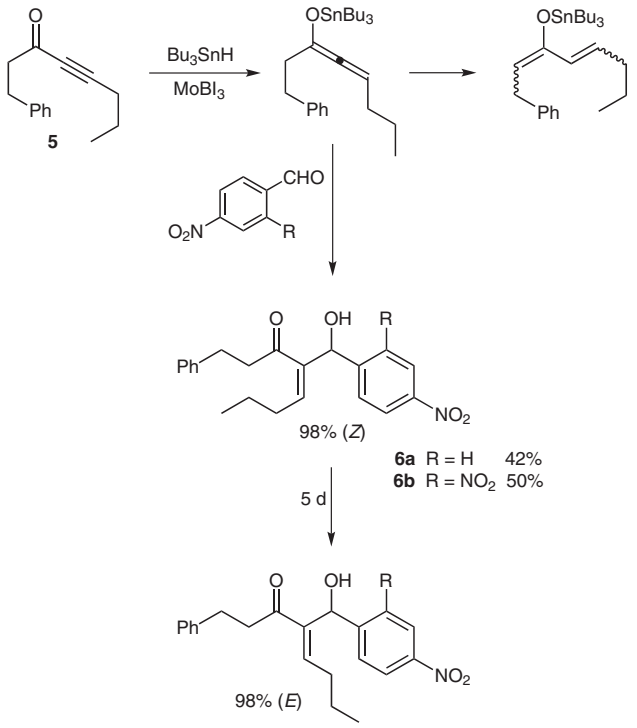
Table 1 MBH Products **4** via One-Pot Hydrostannation–Aldol Reaction



Entry	R	Product	Yield (%)	Ratio *Z*/*E*
1	Ph	**4a**	40	92:8
2	2-Naph	**4b**	45	96:4
3	4-MeC_6H_4	**4c**	15	95:5
4	4-$MeOC_6H_4$	**4d**	10	96:4
5	3,4-$Cl_2C_6H_3$	**4e**	69	97:3
6	4-$F_3CC_6H_4$	**4f**	73	95:5
7	4-$OHCC_6H_4$	**4g**	75	94:6
8	4-$O_2NC_6H_4$	**4h**	75	97:3
9	2,4-$(O_2N)_2C_6H_3$	**4i**	95	98:2
10	2-Py	**4k**	72	94:6

To prove if this one-pot protocol can also be applied to aliphatic ketones such as **5**, or if isomerization of the tin enolate provides regioisomeric products, we reacted **5** with the nitro-substituted aldehydes (Scheme 3). Although no enolate isomerization was observed, with these ketones the reactions were not as clean as with the aromatic ketones, and always 20–30% of the ketone was recovered, even when the tin hydride was used in threefold excess.

In this case, the addition of the aldehyde after the hydrostannation was found to be more effective and the yields could be increased to a preparative useful range. Here, an interesting observation was made. In both cases the *Z*-isomers were formed with excellent stereoselectivi-



Scheme 3 MBH products from aliphatic ketones and isomerization

ty (98%), as determined by NMR. But remeasuring the NMR samples after a few days showed a complete isomerization to the corresponding *E*-products (98%).[20] Similar isomerizations were also reported previously, but not completely as in our case.

In conclusion we could show that the hydrostannation of acetylenic ketones can be used for the synthesis of MBH-type adducts by trapping the in situ formed enolates with aromatic aldehydes. Further attempts to improve the substrate range and investigations concerning the isomerization mechanisms are currently under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.

References and Notes

(1) For recent reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; *Angew. Chem.* **2007**, *119*, 4698. (d) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905; and references cited therein.

(2) For a very recent review on aza-Morita–Baylis–Hillman reactions, see: Declerck, V.; Martinez, M.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1.

(3) (a) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2007**, *9*, 3961. (b) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927. (c) Cui, H. L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5737; *Angew. Chem.* **2009**, *121*, 5847.

(4) (a) Navarre, L.; Darses, S.; Genet, J. P. *Chem. Commun.* **2004**, 1108. (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803. (c) Gowrisankar, S.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2009**, *30*, 726. (d) Alcaide, B.; Almendros, P.; del Campo, T. M.; Quiros, M. T. *Chem. Eur. J.* **2009**, *15*, 3344.

(5) Selected recent examples: (a) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 2358; *Angew. Chem.* **2000**, *112*, 2448. (b) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230. (c) Ramachandran, P.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310. (d) Xue, S.; He, L.; Han, K.-Z.; Liu, Y.-K.; Guo, Q.-X. *Synlett* **2005**, 1247. (e) Xue, S.; He, L.; Han, K.-Z.; Liu, Y.-K.; Guo, Q.-X. *Synthesis* **2006**, 666. (f) Yoshizawa, K.; Shioiri, T. *Tetrahedron Lett.* **2006**, *47*, 757. (g) Reynolds, T. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15382. (h) Reynolds, T. E.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7806; *Angew. Chem.* **2007**, *119*, 7952. (i) Yoshizawa, K.; Shioiri, T. *Tetrahedron* **2007**, *63*, 6259. (j) Tarsis, E.; Gromova, A.; Lim, D.; Zhou, G.; Guoqiang, C.; Coltart, D. M. *Org. Lett.* **2008**, *10*, 4819. (k) Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2008**, *10*, 1649. (l) Wadhwa, K.; Chintareddy, V. R.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 6681.

(6) Senapati, B. K.; Hwang, G.-S.; Lee, S.; Ryu, D. H. *Angew. Chem.* **2009**, *121*, 4462.

(7) Reviews on hydrometallations: (a) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257. (b) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853.

(8) (a) Kabalka, G. W.; Yu, S.; Li, N.-S.; Lipprandt, U. *Tetrahedron Lett.* **1999**, *40*, 37. (b) Yu, S.; Li, N.-S.; Kabalka, G. W. *J. Org. Chem.* **1999**, *64*, 5822.

(9) (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Trost, B. M.; Li, C. J. *Synthesis* **1994**, 1267.

(10) (a) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron Lett.* **1992**, *33*, 4495. (b) Rossi, R.; Carpita, A.; Cossi, P. *Synth. Commun.* **1993**, *23*, 143. (c) Sai, H.; Ogiku, T.; Nishitani, T.; Hiramatsu, H.; Horikawa, H.; Iwasaki, T. *Synthesis* **1995**, 582.

(11) (a) Cochran, J. C.; Bronk, B. S.; Terrence, K. M.; Phillips, H. K. *Tetrahedron Lett.* **1990**, *31*, 6621. (b) Bellina, F.; Carpita, A.; Ciucci, D.; de Santis, M.; Rossi, R. *Tetrahedron* **1993**, *49*, 4677.

(12) (a) Dodero, V. I.; Koll, L. C.; Mandolesi, S. D.; Podesta, J. C. *J. Organomet. Chem.* **2002**, *650*, 173. (b) Dodero, V. I.; Koll, L. C.; Faraoni, M. B.; Mitchell, T. N.; Podesta, J. C. *J. Org. Chem.* **2003**, *68*, 10087.

(13) (a) Kazmaier, U.; Klein, M. *Chem. Commun.* **2005**, 501. (b) Deska, J.; Kazmaier, U. *Angew. Chem. Int. Ed.* **2007**, *46*, 4570; *Angew. Chem.* **2007**, *119*, 4654. (c) Kazmaier, U.; Dörrenbächer, S.; Wesquet, A.; Lucas, S.; Kummeter, M. *Synthesis* **2007**, 320. (d) Wesquet, A. O.; Kazmaier, U. *Angew. Chem. Int. Ed.* **2008**, *47*, 3050; *Angew. Chem.* **2008**, *120*, 3093.

(14) Kazmaier, U.; Braune, S. *J. Organomet. Chem.* **2002**, *641*, 26.

(15) (a) Kazmaier, U.; Schauß, D.; Pohlman, M. *Org. Lett.* **1999**, *1*, 1017. (b) Kazmaier, U.; Pohlman, M.; Schauß, D. *Eur. J. Org. Chem.* **2000**, 2761. (c) Braune, S.; Pohlman, M.;

Kazmaier, U. *J. Org. Chem.* **2004**, *69*, 468. (d) Wesquet, A. O.; Dörrenbächer, S.; Kazmaier, U. *Synlett* **2006**, 1105.

(16) (a) Kazmaier, U.; Schauß, D.; Pohlman, M.; Raddatz, S. *Synthesis* **2000**, 914. (b) Kazmaier, U.; Schauß, D.; Raddatz, S.; Pohlman, M. *Chem. Eur. J.* **2001**, *7*, 456. (c) Kazmaier, U.; Wesquet, A. O. *Synlett* **2005**, *8*, 1271. (d) Jena, N.; Kazmaier, U. *Eur. J. Org. Chem.* **2008**, 3852.

(17) (a) Lin, H.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, 1221. (b) Wesquet, A. O.; Kazmaier, U. *Adv. Synth. Catal.* **2009**, 1395.

(18) **General Procedure for One-Pot Hydrostannation–Aldol Additions**

The acetylenic ketone (1.0 mmol), hydroquinone (10 mol%), and $Mo(CO)_3(CN\textit{t}\text{-}Bu)_3$ ($MoBI_3$) (3 mol%) were dissolved in THF (3 mL) in a Schlenk tube under N_2. Then Bu_3SnH (1.2 mmol) and the corresponding aldehyde (1.2 mmol) were added, the flask was evacuated and flushed with CO. The mixture was warmed to 60 °C for 6 h. After cooling to r.t., the solvent was removed in vacuo, and the reaction mixture was subjected to column chromatography (silica, EtOAc–hexanes).

(19) Leonard, W. R.; Livinghouse, T. *J. Org. Chem.* **1985**, *50*, 730.

(20) **Analytical Data of Selected Products**

Aldol Product 4a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.50 (tt, *J* = 7.6, 1.6 Hz, 1 H), 7.40–7.34 (m, 4 H), 7.32–7.26 (m, 2 H), 7.23–7.19 (m, 1 H), 5.91 (td, *J* = 7.6, 1.2 Hz, 1 H), 5.55 (s, 1 H), 3.24 (br s, 1 H, OH), 1.79 (q, *J* = 7.6 Hz, 2 H), 1.31 (sext, *J* = 7.6 Hz, 2 H), 0.75 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 141.5, 141.4, 137.7, 134.7, 133.3, 129.2, 128.4, 128.3, 127.6, 126.3, 76.5, 31.7, 22.2, 13.5 ppm. HRMS (CI): *m/z* calcd for $C_{19}H_{20}O_2$ $[M]^+$: 280.1463; found: 280.1461.

Aldol Product (*Z*)-6a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.25–7.03 (m, 3 H), 7.06 (dd, *J* = 8.4, 1.6 Hz, 2 H), 5.92 (t, *J* = 7.6 Hz, 1 H), 5.42 (s, 1 H), 3.27 (br s, 1 H, OH), 2.90–2.70 (m, 4 H), 2.18 (q, *J* = 7.6 Hz, 2 H), 1.45 (sext, *J* = 7.6 Hz, 2 H), 0.91 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 150.6, 147.0, 146.9, 140.6, 140.5, 128.5, 128.3, 126.2, 126.0, 123.5, 69.8, 39.5, 30.8, 30.1, 22.0, 14.0 ppm.

Aldol Product (*E*)-6a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 7.29–7.18 (m, 3 H), 7.11 (dd, *J* = 8.4, 1.6 Hz, 2 H), 6.87 (t, *J* = 7.6 Hz, 1 H), 5.69 (s, 1 H), 3.08–2.91 (m, 2 H), 2.85 (t, *J* = 7.6 Hz, 2 H), 2.43 (sext, *J* = 7.6 Hz, 1 H), 2.34 (sext, *J* = 7.6 Hz, 1 H), 1.56 (sext d, *J* = 7.6, 2.0 Hz, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 150.6, 147.0, 146.9, 140.6, 140.5, 128.5, 128.3, 126.3, 126.0, 123.5, 69.9, 39.5, 30.8, 30.1, 22.0, 14.0 ppm. HRMS (CI): *m/z* calcd for $C_{21}H_{23}NO_4$ $[M]^+$: 353.1627; found: 353.1647.