J|A|C|S
COMMUNICATIONS

Published on Web 07/02/2005

Organomediated Morita−Baylis−Hillman Cyclization Reactions

Marie E. Krafft* and Thomas F. N. Haxell

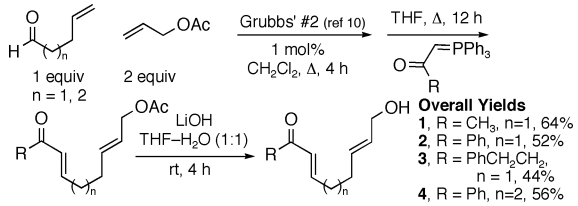
Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306

Received April 4, 2005; E-mail: mek@chem.fsu.edu

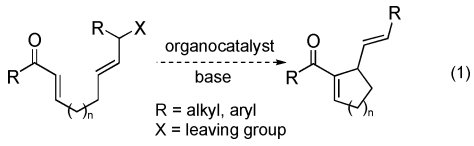
Continuing development in synthetic organic chemistry relies on discovering new, high yielding, selective reactions. The Morita−Baylis−Hillman reaction, originating from both German[1] and Japanese[2] patents, is an organocatalytic reaction involving coupling of the α-position of activated alkenes with carbonyl electrophiles under the catalytic influence of a nucleophilic species, providing a simple and convenient method for the synthesis of interesting densely functionalized molecules.[3] Over the last two decades, the intermolecular Morita−Baylis−Hillman (MBH) reaction has seen tremendous development of all three components and now encompasses a wide range of activated alkenes, electrophiles, and nucleophilic catalysts. However, there has been significantly less research into the intramolecular Morita−Baylis−Hillman reaction.[4,5] While a variety of electrophiles, aldehydes, α-keto esters, 1,2-diketones, and aldimine derivatives have been studied extensively in this valuable carbon−carbon bond-forming reaction, the direct organomediated application of allylic electrophiles in the Morita−Baylis−Hillman reaction has not been thoroughly investigated. Basavaiah has demonstrated the use of ethyl 2-bromomethyl acrylate in an intermolecular allylation to generate 1,4-pentadienes.[6] Using primary allylic carbonates, Krische has cleverly blended organomediated and transition metal-catalyzed reactions in an enone cycloallylation reaction generating monosubstituted alkenes.[7]

Herein, we now report a new intramolecular variant of the Morita−Baylis−Hillman reaction which, for the first time, encompasses allylic leaving groups as the electrophilic partner in a completely organomediated process (eq 1). Both mono- and disubstituted alkenes are readily generated in this reaction. Initial studies evaluated the effectiveness of different leaving groups and organocatalysts. Primary allylic alcohols **1**−**4** were selected as initial test substrates and were readily prepared in good overall yield beginning from 4-pentenal or 5-hexenal (Scheme 1). Due to

Scheme 1. Synthesis of Allylic Alcohols **1**−**4**

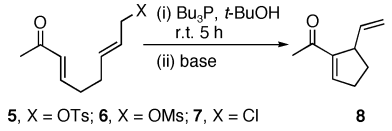


problems with low conversions, it was necessary to use the allylic acetate rather than the allylic alcohol for better results in the alkene cross-metathesis reaction.



(1)

Our early efforts then focused on the reactions of allylic mesylates and tosylates.[8] Use of amine nucleophiles, such as DABCO, quinuclidine, DBU, and DMAP, which are commonly employed in the traditional Morita−Baylis−Hillman coupling, were found to be ineffective at promoting cyclization of either tosylate **5** or mesylate **6** in solvents, such as THF, 1,4-dioxane, acetone, EtOAc, $CHCl_3$, CH_3CN, MeOH, EtOH, *t*-BuOH, and amyl-OH at temperatures from ambient to 63 °C. Accordingly, various tertiary phosphines, such as Bu_3P, Cy_3P, Ph_3P, and Me_3P, also traditional nucleophilic catalysts for the Morita−Baylis−Hillman reaction,[9] were investigated. We found that Bu_3P provided the cyclization adduct **8** in moderate yield from either tosylate **5** or mesylate **6** (eq 2). Optimal yields were obtained using mesylate **6** at ambient temperature, providing cyclic enone **8** in 40% yield within 5 h. Noting that a base might facilitate the process, a variety of bases were screened, including Et_3N, $EtNiPr_2$, DBU, NaH, KH, NaOMe, *t*-BuOK, NaOH and KOH in THF, *t*-BuOH, or MeOH, but despite these additional attempts at optimization, we were unable to improve on this initial result.

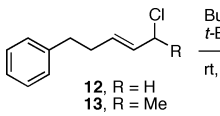


X	Yield (%)
OTs	36
OMs	40
Cl	80

(2)

At this point, we turned our attention to changing the leaving group to chloride. It was discovered that, upon treatment with 1 equiv of Bu_3P in *t*-BuOH (0.5 M) and similar screening of bases, chloride **7** gave an impressive 80% isolated yield of the desired cyclization adduct **8** when KOH was used as the base under phase transfer conditions with $BnEt_3NCl$ (entry 1, Table 1).[11]

To gain insight into the mechanism of this interesting reaction, two reactions were performed using primary and secondary allylic chlorides **12** and **13**, respectively. These were each treated with 1 equiv of Bu_3P in *t*-BuOH under the same conditions as the cyclization reactions. After 5 h, a 90% recovery of each allylic chloride was obtained, discounting the possibility of initial direct S_N2 attack of the phosphine at the allylic chloride moiety to give a phosphonium salt which could also serve as a leaving group (eq 3).

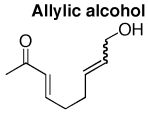
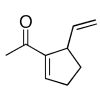
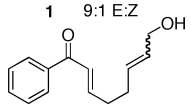
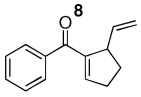
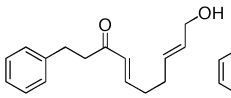
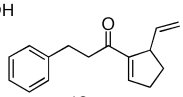
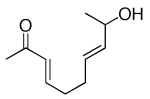
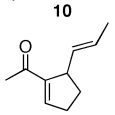
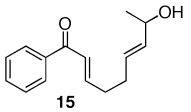
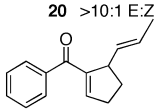
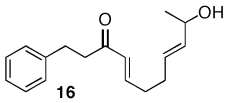
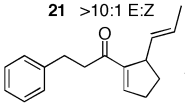
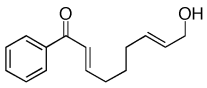
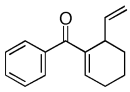
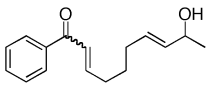
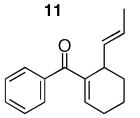


(3)

To further probe the scope of this transformation, we tested the tolerance of the organomediated cyclization to structural alterations at both the enone and allyl moieties. Both aryl enones and sterically more encumbered alkyl enones readily underwent the Morita−Baylis−Hillman cyclization (entries 2 and 3, Table 1). Given these results, we set out to evaluate the tolerance of the cyclization toward substitution at the allylic leaving group. Consequently, a series of secondary alcohols (**14**−**17**) was synthesized.

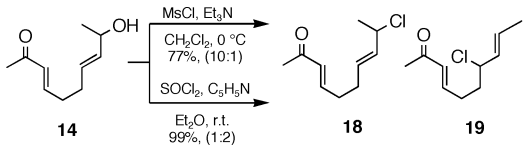
10.1021/ja052146+ CCC: $30.25

Table 1. Organomediated Cyclizations[a]

Entry	Allylic alcohol	Product	Yield (%)[b]
1	 **1** 9:1 E:Z	 **8**	80
2	 **2** 9:1 E:Z	 **9**	82
3	 **3**	 **10**	84
4	 **14**	 **20** >10:1 E:Z	78
5	 **15**	 **21** >10:1 E:Z	94
6	 **16**	 **22**	74
7	 **4**	 **11**	75[c]
8	 **17** 4:1 E:Z	 **23** >10:1 E:Z	80[c]

[a] Regioisomeric mixtures of allylic chlorides. [b] Isolated yields after purification by silica gel chromatography. [c] Me_3P was used.

Conversion of alcohol **14** to the desired allylic chloride **18** using methanesulfonyl chloride resulted in a regioisomeric mixture (10:1) in favor of chloride isomer **18** (eq 4). Changing the chlorinating agent to $SOCl_2$, unfortunately, gave a 1:2 ratio in favor of regioisomer **19**. Remarkably, however, subjecting either regioisomeric mixture of allylic chlorides to the optimized cyclization conditions gave the desired cyclization product **20** (entry 4, Table 1) in 78% yield under equivalent reaction conditions. From a practical standpoint, preparation of the chloride using $SOCl_2$ became the method of choice. These secondary alcohols also tolerated other alkyl groups alpha to the enone without reduction in yield (entries 5 and 6). At this point, we cannot speculate whether the allylic isomers are interconverting under the reaction conditions or if S_N2' and S_N2 mechanisms are operative. Given the result described in eq 3, allylic isomerization is not likely since no isomerization was observed in the control experiment. Thus, direct displacement of the secondary halide under the mild reaction conditions remains a viable option. However, the presence of S_N1 character in the bond-forming step cannot be ruled out and is still under investigation.



(4)

We then turned our attention to the generation of six-membered rings in the cyclization event. Thus, subjecting alcohols **4** and **17** (entries 7 and 8, Table 1) to the optimized cyclization conditions (Bu_3P, *t*-BuOH, CH_2Cl_2, KOH, $BnEt_3NCl$) gave enones **11** and **23** also in excellent yield.

In summary, we have successfully developed a novel, entirely organomediated one-pot convenient method for the synthesis of densely functionalized cyclic enones via the use of an alternative electrophile in the Morita−Baylis−Hillman reaction. This reaction tolerates modification of the enone and the use of primary and secondary allylic chlorides and generates both five- and six-membered rings in excellent yields. Both mono- and disubstituted alkenes are formed with excellent selectivity in the absence of a transition metal catalyst. Further studies will focus on related transformations, changes in the electrophilic partner, and substitutions on the tether.

Acknowledgment. This work was supported by the NSF and the MDS Research Foundation.

Supporting Information Available: Experimental and analytical data for allylic alcohols and enones (^1H NMR, ^{13}C NMR, IR, HRMS, CHN) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Baylis, A. B.; Hillman, M. E. D.; German Patent 2155113, 1972; *Chem. Abstr*. **1972**, *77*, 34174q.

(2) (a) Morita, K. Japan Patent 6803364, 1968; *Chem. Abstr.* **1968**, *69*, 58828s. (b) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(3) For reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (d) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.

(4) (a) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807. (b) Roth, F.; Gygax, P.; Fráter, G. *Tetrahedron Lett.* **1992**, *33*, 1045. (c) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielson, M.; Williams, H. L.; Walshe, N. D. A. *Tetrahedron Lett.* **1997**, *38*, 8561. (d) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Mailik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279. (e) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771. (f) Jung, E. Y.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun*. **2004**, 236.

(5) (a) Wang, L.-C.; Luis, A.-L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2002**, *124*, 2402. (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.

(6) (a) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85. (b) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem*, **2002**, *67*, 7135.

(7) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758.

(8) Lee, H. Y.; Kim, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10156.

(9) (a) Rauhut, M. M.; Currier, H. U.S. Patent 3074999, 1963; *Chem. Abstr.* **1963**, *58*, 11224a. (b) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165. (c) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (d) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689. (e) Koech, P. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350. (f) Cho, C. W.; Kong, J. -R. Krische, M. J. *Org. Lett.* **2004**, *6*, 1337.

(10) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(11) Typical procedure: To $SOCl_2$ (2 equiv) in Et_2O (0.1 M) at ambient temperature was added dropwise over 5 min a 0.1 M Et_2O solution of the alcohol with pyridine (2 equiv). After stirring for 20 min, the Et_2O layer was washed with saturated $NaHCO_3$(aq), dried over Na_2SO_4, and concentrated in vacuo to provide the crude allylic chloride, which was used without further purification. PBu_3 (100 mol %) was then added to a 0.5 M solution of the allylic chloride in *tert*-butyl alcohol, and the mixture was allowed to stir at room temperature until complete consumption of starting material (TLC), at which point $CH_2Cl_2-H_2O$ (1:1) was added to the mixture followed by addition of KOH (200 mol %) and $BnEt_3NCl$ (10 mol %) and stirred until complete (2 h).

JA052146+