JOC Article

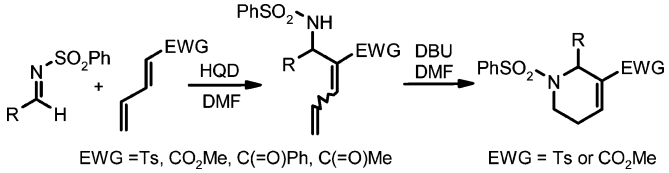
Aza-Morita−Baylis−Hillman Reactions and Cyclizations of Conjugated Dienes Activated by Sulfone, Ester, and Keto Groups

Jovina M. Sorbetti, Kristen N. Clary, Danica A. Rankic, Jeremy E. Wulff, Masood Parvez, and Thomas G. Back*

Department of Chemistry, University of Calgary, Calgary, Alberta T2N 1N4, Canada

tgback@ucalgary.ca

Received December 26, 2006

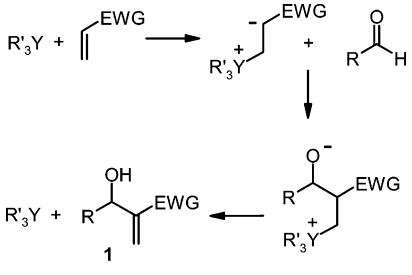


The aza-Morita−Baylis−Hillman reactions of aldimines **2** with several activated conjugated dienes were found to proceed smoothly in DMF in the presence of 3-hydroxyquinuclidine (HQD). Imines **2** reacted with 1-(*p*-toluenesulfonyl)-1,3-butadiene (**3**), methyl 2,4-pentadienoate (**6**), hexa-3,5-dien-2-one (**7**), and 1-phenylpenta-2,4-dien-1-one (**8**) to afford adducts **4**, **13**, **14**, and **15**, respectively. While products **4**, **13**, and **15** were formed as *E*,*Z* mixtures, adducts **14** were obtained as essentially pure *E*-isomers. Cyclization of the *E*-isomers of the products derived from the dienyl sulfone **3** and the dienoate ester **6** occurred via intramolecular conjugate addition under base-catalyzed conditions to afford functionalized piperidines **5** and **16**, respectively. The aza-Morita−Baylis−Hillman reaction and subsequent cyclization of the imine **2a** with **3** were also carried out as a one-pot reaction, while the reaction mixture was simultaneously irradiated at 300 nm to effect the photoisomerization of the unreactive *Z*-adduct of the corresponding **4** to the more reactive *E*-isomer.

Introduction

The Morita-Baylis-Hillman reaction[1,2] is a useful synthetic method that results in carbon−carbon bond-formation between the α-position of a suitably activated alkene and the carbonyl group of an aldehyde or related compound to afford the corresponding allylic alcohol. In its simplest form, a nucleophilic catalyst such as a tertiary phosphine[1a,1b] or amine[1c] first adds to an alkene that is activated by a suitable electron-withdrawing group (EWG) to produce the corresponding zwitterion. Addition of the latter to the aldehyde, followed by proton transfer and elimination of the catalyst, affords the coupled product **1** (Scheme 1).

SCHEME 1



Since the reaction was first discovered, considerable variation has been reported with respect to the nucleophilic catalyst, the activating group on the alkene, and the carbonyl compound.[2] Several recent studies have provided additional insight into the mechanism of the Morita−Baylis−Hillman reaction.[3] The cooperative effects of added water, alcohols or phenols, or other hydrogen-bonding solvents or additives, have been investigated,[3e,4] as well as temperature effects.[5] Byproducts or atypical products that are formed under certain conditions include dioxanes, ethers,

* To whom correspondence should be addressed. Phone: (403) 220-6256. Fax: (403) 289-9488.

(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Morita, K. Japan Patent 43003364, 1968; *Chem Abstr*. **1968**, *69*, 58828s. (c) Baylis, A. B.; Hillman, M. E. D. Ger. Offen. 2,155,113, 1972; *Chem. Abstr*. **1972**, *77*, 34174q.

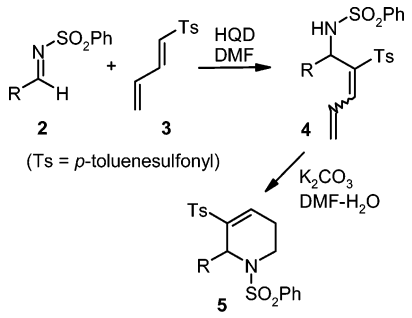
(2) For recent reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049−3052. (e) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670.

10.1021/jo062655+ CCC: $37.00 © 2007 American Chemical Society
Published on Web 03/24/2007

dimers, and other species.[6] Catalysis with Lewis acids,[4a,7] irradiation with microwaves[8] or ultrasound,[5c,9] the use of ionic liquids[10] or supercritical carbon dioxide[6g] as solvents, and high pressure[3f,11] have proved advantageous in some cases. Asymmetric[2d,12] and intramolecular[3k,13] variations have also been reported.

The use of imines in place of carbonyl compounds (generally referred to as the aza-Morita−Baylis−Hillman reaction) was first reported by Perlmutter amd Teo[14] and extends the process to the preparation of allylic amines.[15] Although activated allenes and acetylenes have been investigated in place of alkenes in aza-Morita−Baylis−Hillman reactions,[16] the similar use of conjugated dienes was neglected until very recently, when we reported[17] that aldimines **2** react with dienyl sulfone **3** to produce

SCHEME 2



the corresponding adducts **4**. This was followed by intramolecular conjugate addition, thus affording functionalized piperidines **5** (Scheme 2). Subsequently, as part of their study of the aza-Morita−Baylis−Hillman reactions of crotonates, Shi and Shi[18] also included several examples where phenyl 2,4-pentadienoate was employed. The corresponding adducts were obtained in variable yield, but their further cyclization was not observed. We now describe the expanded results of our preliminary investigation[17] of the aza-Morita−Baylis−Hillman reaction of variously substituted *N*-(phenylsulfonyl)aldimines **2** with dienyl sulfone **3** in the presence of the catalyst 3-hydroxyquinuclidine[3e,3h,4i,4j] (HQD), as well as its extension

(3) For lead references, see: (a) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980−3987. (b) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147−150. (c) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706−1708. (d) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330−4333. (e) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692−700. (f) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, *3*, 285−288. (g) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007−5010. (h) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611−5614. (i) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371−6384. (j) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795−796. (k) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807−2815.

(4) (a) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510−514. (b) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723−4725. (c) Grainger, R. S.; Leadbeater, N. E.; Pàmies, A. M. *Catal. Commun.* **2002**, *3*, 449−452. (d) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413−5418. (e) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165−2169. (f) Basavaiah, D.; Krishnamacharyulu, M.; Rao, A. J. *Synth. Commun.* **2000**, *30*, 2061−2069. (g) Basavaiah, D.; Rao, A. J.; Krishnamacharyulu, M. *ARKIVOC (Gainesville, FL, U.S.)* **2002**, 136−145. (h) Augé, J.; Lubin, N.; Lubineau, A. *Tetrahedron Lett.* **1994**, *35*, 7947−7948. (i) Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495−500. (j) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1565−1572.

(5) (a) de Souza, R. O. M. A.; Vasconcellos, M. L. A. A. *Catal. Commun.* **2004**, *5*, 21−24. (b) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521−1522. (c) Roos, G. H. P.; Rampersadh, P. *Synth. Commun.* **1993**, *23*, 1261−1266.

(6) (a) Patra, A.; Roy, A. K.; Joshi, B. S.; Roy, R.; Batra, S.; Bhaduri, A. P. *Tetrahedron* **2003**, *59*, 663−670. (b) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Helv. Chim. Acta* **2002**, *85*, 1051−1057. (c) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696−701. (d) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666−3679. (e) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* **2001**, 833−834. (f) Shi, M.; Xu, Y.-M. *Chem. Commun.* **2001**, 1876−1877. (g) Rose, P. M.; Clifford, A. A.; Rayner, C. M. *Chem. Commun.* **2002**, 968−969. (h) Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* **2001**, 1612−1613. (i) Perlmutter, P.; Puniani, E.; Westman, G. *Tetrahedron Lett.* **1996**, *37*, 1715−1718. (j) Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. S. *Tetrahedron Lett.* **1993**, *34*, 1205−1208. (k) Drewes, S. E.; Emslie, N. D.; Karodia, N.; Khan, A. A. *Chem. Ber.* **1990**, *123*, 1447−1448.

(7) (a) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183−7189. (b) Aggarwal, V. K.; Tarver, G. J.; McCague, R. *Chem. Commun.* **1996**, 2713−2714. (c) Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45−58.

(8) Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.

(9) (a) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. S.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437−7447. (b) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609−8612.

(10) (a) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015−1060. (b) Rosa, J. N.; Afonso, C. A. M.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4189−4193.

(11) (a) Jenner, G.; Salem, R. B. *High Pressure Res.* **2005**, *25*, 1−9. (b) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M. *Tetrahedron Lett.* **2002**, *43*, 8683−8686. (c) Hill, J. S.; Isaacs, N. S. *J. Chem. Res. Synop* **1988**, 330−331. (d) van Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 6931−6936.

(12) For examples, see: (a) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761−765. (b) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680−3681. (c) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790−3800. (d) Shi, M.; Li, C.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385−1391. (e) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310−1311. (f) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507−4510. (g) Mocquet, C. M.; Warriner, S. L. *Synlett* **2004**, 356−358. (h) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103−3105. (i) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521−2524. (j) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219−10220. (k) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533−2534. (l) Markö, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015−1024. (m) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317−4318. (n) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241−1244. (o) Kündig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413−414. (p) Drewes, S. E.; Emslie, N. D.; Khan, A. A. *Synth. Commun.* **1993**, *23*, 1215−1218. (q) Drewes, S. E.; Khan, A. A.; Rowland, K. *Synth. Commun.* **1993**, *23*, 183−188. (r) Drewes, S. E.; Manickum, T.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1065−1070. (s) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S.; Rao, P. D. *Tetrahedron Lett.* **1990**, *31*, 1621−1624.

(13) For lead references, see: (a) Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4174−4175. (b) Krafft, M. E.; Seibert, K. A.; Haxell, T. F. N.; Hirosawa, C. *Chem. Commun.* **2005**, 5772−5774. (c) Krafft, M. E.; Haxell, T. F. N. *J. Am. Chem. Soc.* **2005**, *127*, 10168−10169.

(14) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951−5952.

(15) For selected examples of aza-Morita−Baylis−Hillman reactions, see: (a) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762−16763. (b) Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417−425. (c) Shi, M.; Xu, Y.-M. *J. Org. Chem.* **2003**, *68*, 4784−4790. (d) Shi, M.; Zhao, G.-L. *Tetrahedron Lett.* **2002**, *43*, 4499−4502. (e) Shi, M.; Zhao, G.-L. *Tetrahedron Lett.* **2002**, *43*, 9171−9174. (f) Sun, S.; Zhang, Q.; Liu, Q.; Kang, J.; Yin, Y.; Li, D.; Dong, D. *Tetrahedron Lett.* **2005**, *46*, 6271−6274. (g) Azizi, N.; Saidi, M. R. *Tetrahedron Lett.* **2002**, *43*, 4305−4308. (h) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729−2730. (i) Génisson, Y.; Massardier, C.; Gautier-Luneau, I.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2869−2872. (j) Campi, E. M.; Holmes, A.; Perlmutter, P.; Teo, C. C. *Aust. J. Chem.* **1995**, *48*, 1535−1540. (k) Cyrener, J.; Burger, K. *Monatsh. Chem.* **1995**, *126*, 319−331. (l) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731−2732.

(16) (a) Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975−9984. (b) Zhao, G.-L.; Shi, M. *Org. Biomol. Chem.* **2005**, *3*, 3686−3694.

(17) Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett.* **2005**, *7*, 2377−2379.

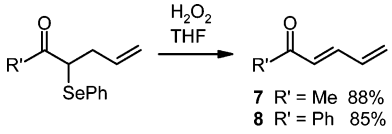
(18) Shi, Y.-L.; Shi, M. *Tetrahedron* **2006**, *62*, 461−475.

TABLE 1. Aza-Morita−Baylis−Hillman Reaction of Aldimines 2 with Dienyl Sulfone 3[a]

imine	R	yield of **4** (%)	*E*:*Z* ratio of **4**
2a	Ph	86	70:30
2b	*p*-Cl-C_6H_4	73	70:30
2c	*m*-Cl-C_6H_4[b]	63	70:30
2d	*o*-Cl-C_6H_4	46	50:50
2e	*p*-CH_3O-C_6H_4	46	60:40
2f	*p*-NO_2-C_6H_4[c]	31	70:30
2g	*p*-CH_3O_2C-C_6H_4	70	70:30
2h	*p*-NC-C_6H_4[c]	75	70:30
2i	α-naphthyl	61	65:35
2j	3-pyridyl	—[d]	—[d]
2k	mesityl	—	—
2l	cyclohexyl	—	—

[a] All reactions were carried out in DMF containing 0.25 equiv of HQD at room temperature for 4−6 h unless otherwise noted. [b] 0.5 equiv of HQD was employed. [c] Reaction was carried out in THF for 16−20 h. [d] The crude product was used directly in a one-pot preparation of **5j** (see Table 2).

SCHEME 3



to similar reactions and cyclizations of methyl 2,4-pentadienoate (**6**). We also report the first examples of aza-Morita−Baylis−Hillman reactions of conjugated dienones, in which **7** and **8** were successfully transformed into the corresponding adducts.

Results and Discussion

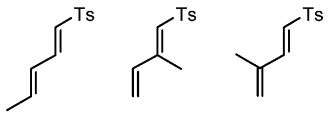
The required imines **2** were prepared from their corresponding aldehydes by a standard procedure.[19] The dienyl ester **6** is commercially available (Fluka), while dienyl sulfone **3** was obtained by a literature method,[20] and dienones **7**[21] and **8**[22] were prepared from the corresponding known[23] α-(phenylseleno)-ketones by selenoxide elimination, as shown in Scheme 3.

Using *N*-(benzylidene)benzenesulfonamide (**2a**) and 1-(*p*-toluenesulfonyl)-1,3-butadiene (**3**) as representative starting materials for the aza-Morita−Baylis−Hillman reaction, a series of different catalysts was screened, including triethylamine, triphenylphosphine, DABCO, DMAP, DBU, and HQD. Catalyst loadings of 0.1, 0.25, 0.5, 1.0, and 3.0 mol equiv were employed in a variety of different solvents, including acetonitrile, methanol, THF, dichloromethane, dioxane, and DMF. Optimal results were generally obtained at room temperature with 25 mol % of HQD in dry DMF. Reactions also proceeded well in THF, but at a slower rate. The optimized conditions, with a few exceptions, were then applied to a series of aldimines, and the results are listed in Table 1.

In some cases, imine **2** was employed in excess over sulfone **3** to compensate for its partial hydrolysis during the reaction. However, equimolar amounts of **2** and **3** afforded comparable yields of **4** if rigorously anhydrous conditions were maintained.

Although dienyl sulfone **3** was prepared and used as the *E*-isomer, adducts **4** were obtained as *E*,*Z* mixtures, presumably because of free rotation in the zwitterionic intermediates prior to elimination of HQD in the product-forming step. The *E*-isomer was predominant in all cases, apart from **2d**, which gave a 1:1 ratio of geometric isomers. Separation by flash chromatography provided pure samples of the less polar *E*-isomers; however the minor *Z*-isomers could generally not be isolated completely free of the remaining *E*-isomers. Differentiation of the two geometric isomers was initially based upon NOE experiments with **4a**. The doublet at δ 5.91 ppm of the major isomer collapsed to a singlet upon D_2O exchange, establishing it as the signal from the benzylic proton α to the sulfonamide moiety. Irradiation of this signal led to an enhancement of 16% for the γ-proton (δ 6.64 ppm) of the dienyl sulfone moiety, while the reverse experiment gave an enhancement of 14%, indicating the *E*-geometry. Subsequently, a crystal structure was obtained for the major isomer of **4a**, clearly demonstrating its *E*-geometry (see Supporting Information). The *E*,*Z* assignments for the other products in Table 1 were based on the similarity of their NMR spectra to the respective geometric isomers of **4a**. The *E*/*Z* ratios in Table 1 are based on integration of the signals of the respective isomers in the unseparated mixtures.

Table 1 reveals that the method is compatible with both electron-withdrawing and -donating substituents on the aryl moiety of the imine. However, the nitro- and cyano-substituted derivatives **2f** and **2h** reacted very rapidly in DMF to afford complex mixtures of products, while the use of THF resulted in slower reactions and improved yields of the corresponding adducts. Adduct **4j**, produced from the reaction of the 3-pyridyl derivative **2j** and dienyl sulfone **3**, could not be isolated in a pure state. The crude product was therefore converted directly into the cyclized product **5j** without isolation (vide infra). The more hindered mesityl derivative **2k** and the aliphatic imine **2l** failed to undergo the aza-Morita−Baylis−Hillman reaction under all of the conditions attempted. Similarly, the methyl-substituted analogs **9**,[20] **10**,[20] and **11**[24] of dienyl sulfone **3** failed to react with imine **2a**, even at elevated temperatures, presumably because of increased steric effects. No significant amounts



9 **10** **11**

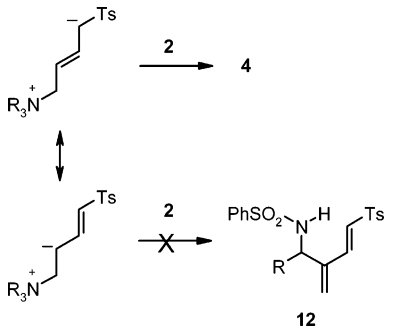
of the regioisomeric products **12** were formed via γ-attack of the sulfone-stabilized zwitterions upon the imines (Scheme 4).

Cyclizations of the *E*-isomers of **4** by intramolecular conjugate addition of their respective anions to the terminal positions of the diene substituents were effected at room temperature in DMF−water (10:1) containing K_2CO_3 to afford the corresponding functionalized piperidines **5** (Scheme 2, Table 2). As expected, the *Z*-isomers failed to cyclize under these conditions because of their inability to adopt a conformation compatible with the 6-centered transition state required for the cyclization. The nitro derivative (*E*)-**4f** gave complex mixtures of products under these conditions.

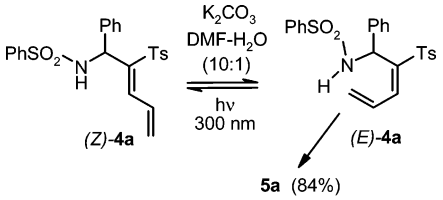
The lack of reactivity of the *Z*-isomers of **4** prompted us to investigate the in situ equilibration of the geometrical isomers

(19) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203−210.
(20) Barluenga, J.; Martinez-Gallo, J. M.; Nájera, C.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2605−2609.
(21) Bloch, R.; Abecassis, J.; Hassan, D. *Can. J. Chem.* **1984**, *62*, 2019−2024.
(22) Yu, Y.; Lin, R.; Zhang, Y. *Tetrahedron Lett.* **1993**, *34*, 4547−4550.
(23) Ponthieux, S.; Outurquin, F.; Paulmier, C. *Tetrahedron* **1997**, *53*, 6365−6376.
(24) Bordwell, F. G.; Mecca, T. G. *J. Am. Chem. Soc.* **1972**, *94*, 5829−5837.

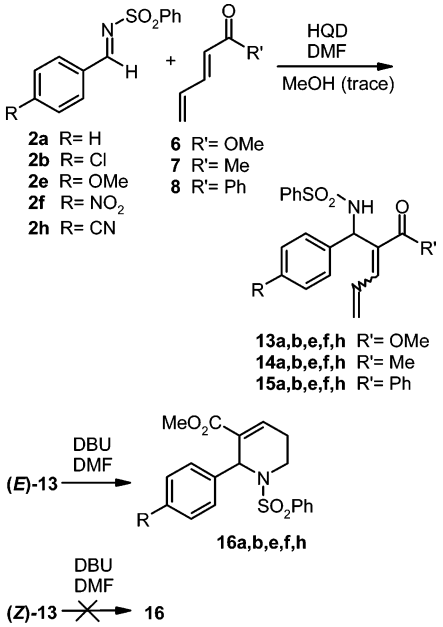
SCHEME 4



SCHEME 5



SCHEME 6



during the cyclization process in order to facilitate the consumption of both isomers from the corrresponding unseparated *E*,*Z* mixtures. We observed in separate control experiments that both pure (*E*)-**4a** and a 40:60 mixture of (*E*)- and (*Z*)-**4a** afforded identical 70:30 mixtures of the two isomers after irradiation with UV light at 300 nm (Scheme 5). Thus, photoisomerization is possible, and the 70:30 ratio represents the system at equilibrium. The feasibility of a one-pot isomerization−cyclization process was demonstrated by subjecting an unseparated 65:35 mixture of (*E*)- and (*Z*)-**4a** to the usual cyclization conditions (K_2CO_3−DMF−H_2O), while simultaneously irradiating the mixture with UV light at 300 nm. Piperidine **5a** was thus produced in 84% yield (Scheme 5), only slightly lower than the 91% yield obtained by cyclization of the pure *E*-isomer and ca. 20% higher than the yield expected from the cyclization of the *E*-isomer present in a 70:30 unseparated *E*/*Z* mixture, without subjecting it to simultaneous isomerization. Attempts to promote the *E*/*Z* equilibration by addition−elimination through prolonged

TABLE 2. Cyclizations of the *E* Isomers of Aza-Morita−Baylis−Hillman Adducts 4[a]

adduct	R	yield of **5** (%)
4a	Ph	91
4b	*p*-Cl-C_6H_4	95
4c	*m*-Cl-C_6H_4	89
4d	*o*-Cl-C_6H_4	82
4e	*p*-CH_3O-C_6H_4	79
4f	*p*-NO_2-C_6H_4	−
4g	*p*-CH_3O_2C-C_6H_4	65
4h	*p*-NC-C_6H_4	80
4i	α-naphthyl	86
4j	3-pyridyl	30[b]

[a] Cyclizations were performed in DMF−water (10:1) containing an equimolar amount of K_2CO_3 for 24 h at room temperature. [b] The yield is for both steps of a one-pot preparation directly from imine **2j** and dienyl sulfone **3**.

TABLE 3. Aza-Morita−Baylis−Hillman Reactions and Cyclizations of Imines 2 with Ester 6[a]

imine	R	yield of **13** (%)	*E*/*Z* ratio of **13**	yield of **16**[b] (%)
2a	H	85	80:20	77
2b	Cl	85	80:20	91
2e	MeO	66	75:25	89
2f	NO_2	61	80:20	49
2h	CN	91	75:25	70

[a] Aza-Morita−Baylis−Hillman reactions were performed in dry DMF in the presence of a trace of MeOH and 25 mol % of HQD for 1−3 days at room temperature. Cyclizations were carried out in DMF containing 1.0 mol equiv of DBU for 1−3 days at room temperature. [b] Yields of **16** are based on the use of the pure *E*-isomers of **13**.

TABLE 4. Aza-Morita−Baylis−Hillman Reactions of Imines 2 with Dienones 7 and 8[a]

product	R	R'	yield (%)	*E*:*Z* ratio
14a	H	Me	80	>95:5
15a	H	Ph	70	65:35
14b	Cl	Me	47	>95:5
15b	Cl	Ph	67	65:35
14e	MeO	Me	−	−
15e	MeO	Ph	30	60:40
14f	NO_2	Me	55	>95:5
15f	NO_2	Ph	68	65:35
14h	CN	Me	61	>95:5
15h	CN	Ph	88	70:30

[a] Aza-Morita−Baylis−Hillman reactions were performed in dry DMF in the presence of a trace of MeOH and 25 mol % of HQD for 6−12 h at room temperature.

reaction in the presence of HQD, or by catalyzing the photoisomerization with diphenyl diselenide,[25] proved less effective than the above protocol. Similarly, the 3-pyridyl derivative **5j** was prepared via the one-pot procedure because the intermediate adduct **2j** could not be isolated in a pure state.

A similar investigation of dienoate ester **6** and of dienones **7** and **8** revealed their facile reactions with representative imines **2a**, **2b**, **2e**, **2f**, and **2h** in anhydrous DMF containing a trace of methanol at room temperature for 1−3 days in the presence of 25 mol % of HQD. The results are shown in Scheme 6 and Tables 3 and 4. Again, compatibility with both electron-withdrawing and electron-donating groups on the aryl moiety of the imine was observed. Products **13** (Table 3) were obtained as *E*/*Z* mixtures, from which the dominant *E*-isomers were separated by flash chromatography. The assignment of *E*/*Z* configuration was confirmed unequivocally for the major isomer

(25) Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1988**, *53*, 2533−2536.

of **13a** by an NOE experiment, in which irradiation of the benzylic hydrogen signal at δ 5.76 (d, J = 10.3 Hz, collapsed to s with D_2O) resulted in an enhancement of 18% to the multiplet assigned to the vinylic hydrogen atom γ to the ester at δ 6.82−6.69 ppm, and vice versa. The *E*/*Z* assignments of **13b**, **13e, 13f**, and **13h** were made by analogy because of the similarity of their NMR spectra to the respective geometrical isomers of **13a**. The *E*,*Z*-configurations of products **14a** and **15a**, derived from dienones **7** and **8**, respectively, were similarly established by NOE experiments. Furthermore, the *E*-configurations of the major isomers of **14f** and **15a** were confirmed by X-ray crystallography (see Supporting Information).

In contrast to the results with phenyl 2,4-pentadienoate reported earlier by Shi and Shi,[18] we observed the smooth cyclization of the *E*-isomers of **13a**, **13b**, **13e**, **13f**, and **13h** in anhydrous DMF in the presence of DBU to the corresponding piperidines **16** (Scheme 6 and Table 3). Once again, the corresponding *Z*-isomers failed to cyclize.

The aza-Morita−Baylis−Hillman reaction of imines **2a**, **2b**, **2e**, **2f**, and **2h** with dienones **7** and **8** proceeded under similarly mild conditions to afford corresponding products **14** and **15**, respectively (Scheme 6, Table 4). Imine **2e**, containing the electron-donating *p*-methoxy derivative, gave the poorest results of the examples studies, affording only 30% of adduct **15e** from the phenyl ketone **8** and no isolable product with the methyl ketone **7**. Interestingly, while **8** afforded *E*/*Z* mixtures of **15a**, **15b**, **15e**, **15f**, and **15h** in the ratio of ca. 2:1, ketone **7** produced the *E*-isomers of **14a**, **14b**, **14f**, and **14h** almost exclusively. Attempts to effect the cyclization of products **14** and **15** in Table 4 under the same conditions that had been used successfully for the preparation of **5** (Table 2) and **16** (Table 3) failed. A variety of other conditions, including the use of potassium carbonate, DABCO, DMAP, and diisopropylethylamine in a variety of solvents, also proved unsuccessful, generally resulting in the gradual polymerization of starting materials **14** and **15**.

In conclusion, these results demonstrate that the aza-Morita−Baylis−Hillman reaction can be carried out between variously substituted *N*-(phenylsulfonyl)aldimines and conjugated dienes activated by sulfone, ester, or ketone moieties to afford highly functionalized allylic amine derivatives. The *E*-isomers of the products from the dienyl sulfone and the dienoate underwent facile intramolecular conjugate additions to produce the corresponding functionalized piperidine derivatives, whereas adducts obtained from the dienones failed to cyclize under similar conditions.

Experimental Section

Imines **2a**−**l** were prepared according to the general procedure of Davis et al.[19] The following imines are known compounds: **2a**,[19] **2b**,[26] **2c**,[26] **2e,**[26] **2f,**[27] **2i,**[28] **2j**,[29] and **2l**.[30] Imines **2d**, **2g**, **2h**, and **2k** were described in the Supporting Information of our preliminary communication.[17] Dienyl sulfones **3**,[20] **9**,[20] **10**,[20] and **11**[24] were obtained by literature methods. The preparations of adducts **4a**−**i** and cyclized piperidines **5a**, **5b**, and **5h** were also reported in the Supporting Information of our preliminary communication.[17] Adduct **4j** and piperidine derivatives **5c**, **5d**, **5e**, **5g, 5i**, and **5j** are described in the accompanying Supporting Information. Methyl 2,4-pentadienoate was purchased from a commercial source.

Typical Procedure for the Morita−Baylis−Hillman Reaction of Aldimines 2 with Methyl 2,4-Pentadienoate (6). Preparation of 13a. A solution of ester **6** (0.200 mL, 1.72 mmol), imine **2a** (426 mg, 1.74 mmol), methanol (60 μL, 1.5 mmol), and HQD (56.5 mg, 0.444 mmol) in 7 mL of anhydrous DMF was stirred for 24 h at room temperature. The reaction mixture was diluted with ether and washed with water and brine. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (toluene−ethyl acetate, 16:1) to afford 526 mg (85%) of **13a** as a mixture of geometrical isomers (*E*:*Z* = 80:20). Further chromatography of the latter product afforded the less polar pure *E*-isomer, followed by a mixture of both geometrical isomers. Ester **(*E*)-13a**: viscous colorless oil; IR (film) 3292, 1716, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 2 H), 7.53−7.48 (m, 1 H), 7.42−7.37 (m, 2 H), 7.26−7.20 (m, 5 H), 7.14 (d, J = 11.8 Hz, 1 H), 6.82−6.69 (dt, J = 16.4, 10.8 Hz, 1 H), 6.39 (d, J = 10.8 Hz, 1 H, exchanged with D_2O), 5.76 (d, J = 10.3 Hz, 1 H), 5.70−5.62 (m, 2 H), 3.57 (s, 3 H); irradiation of the proton at δ 6.82−6.69 showed an NOE of 18% for the signal at δ 5.76 and vice versa; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 141.6, 141.1, 138.8, 132.6, 130.6, 128.9, 128.7, 128.6, 127.6, 127.1, 126.0, 53.9, 52.1; mass spectrum (*m*/*z*, %) 341 (M^+ − O, 11), 216 (10), 200 (26), 185 (17), 141 (18), 104 (13), 77 (100). HRMS calcd for $C_{19}H_{19}NO_3S$ (M^+ − O): 341.1086. Found: 341.1102.

Products **13b**, **13e**, **13f**, and **13h** were prepared similarly in the yields and *E*/*Z* ratios given in Table 3. Their properties are given in the Supporting Information.

Typical Procedure for the Morita−Baylis−Hillman Reaction of Aldimines 2 with Dienones 7 and 8. Preparation of Methyl Ketone 14a. A solution of imine **2a** (54.6 mg, 0.223 mmol), HQD (9.1 mg, 0.072 mmol), methanol (5 μL, 0.1 mmol), and **7** (18.7 mg, 0.195 mmol) in dry DMF was stirred at room temperature for 6 h. The solution was poured into water, extracted with ether, and washed with water and brine. The organic fractions were combined, dried, and concentrated. The crude product was chromatographed (toluene:ethyl acetate, 16:1), followed by recrystallization (ethyl acetate−toluene) to afford 53.6 mg (80%) of the product **(*E*)-14a** as a single geometrical isomer: off-white solid; mp 95−99 °C (from ethyl acetate−toluene); IR (film) 3278, 1657, 1332, 1163, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 7.2 Hz, 2 H), 7.53−7.47 (m, 1 H), 7.43−7.36 (m, 2 H), 7.28−7.18 (m, 5 H), 6.92−6.77 (m, 2 H), 6.50 (d, J = 10.3 Hz, 1 H, exchanged with D_2O), 5.77−5.67 (m, 3 H), 2.03 (s, 3 H); the sample was shaken with D_2O, and irradiation of the signal at δ 5.64 ppm resulted in an NOE of 19% for the signal at δ 6.8, while irradiation of the signal at δ 6.8 gave an NOE of 18% for the signal at δ 5.64 ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 142.9, 141.2, 139.0, 137.1, 132.5, 131.1, 129.3, 128.9, 128.5, 127.5, 127.2, 125.9, 54.4, 26.2; mass spectrum (*m*/*z*, %) 341 (M^+, 0.6), 246 (8), 200 (97), 141 (25), 77 (100). HRMS calcd for $C_{13}H_{11}NO_2S$ (M^+ − C_6H_8O): 245.0511. Found: 245.0518. Calcd for $C_{13}H_{14}NO$ (M^+ − $C_6H_5SO_2$): 200.1075. Found: 200.1063.

Products **14b**, **14f, 14h, 15a**, **15b**, **15e**, **15f**, and **15h** were prepared similarly in the yields and *E*/*Z* ratios given in Table 4. Their properties are given in the Supporting Information. All reactions were performed at room temperature for durations between 6 and 12 h. Products **14** were produced as essentially pure *E*-isomers, while **15** were obtained as *E*/*Z*-mixtures. In all cases where *E*/*Z*-mixtures were produced, except for **15c**, the *E*-isomers could be isolated in a relatively pure state and are described below, while the *Z*-isomers were contaminated with the *E*-isomers. The opposite was true for **15c,** and the reported properties are those of the pure minor *Z*-isomer.

Typical Procedure for Cyclization Reactions of Esters 13. Preparation of Piperidine 16a. A mixture of the *E*-isomer of

(26) Jin, T.-S.; Feng, G.-L.; Yang, M.-N.; Li, T.-S. *J. Chem. Res. Synop.* **2003**, 591−593.
(27) Davis, F. A.; Lal, S. G.; Durst, H. D. *J. Org. Chem.* **1988**, *53*, 5004−5007.
(28) Stojanovic, M. N.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9921−9922.
(29) Batal, D. J.; Madison, S. A. U.S. Patent 5041232, 1991; *Chem. Abstr.* **1991**, *115*, 258737.
(30) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75−77.

adduct **13a** (61.1 mg, 0.171 mmol) and DBU (26 μL, 0.17 mmol) was stirred in 4 mL of dry DMF at room temperature for 3 days. The reaction mixture was diluted with ether and washed once with water and once with brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography (toluene−ethyl acetate, 16:1) to afford 47.0 mg (77%) of product **16a**: off-white solid; mp 114−116 °C (from ethyl acetate−toluene); IR (film) 1714, 1344, 1161, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.2 Hz, 2 H), 7.57−7.51 (m, 1 H), 7.46−7.41 (m, 2 H), 7.30−7.28 (m, 5 H), 7.04 (t, J = 3.6 Hz, 1 H), 6.01 (s, 1 H), 3.82−3.70 (m, 1 H), 3.65 (s, 3 H), 3.05−2.95 (m, 1 H), 2.21−2.14 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 140.8, 139.0, 138.6, 132.6, 129.7, 128.9, 128.4, 128.2, 128.0, 127.0, 55.0, 51.9, 36.7, 24.1; mass spectrum (*m/z*, %) 357 (M^+, 2), 280 (55), 216 (100), 77 (79). HRMS calcd for $C_{19}H_{19}NO_4S$ (M^+): 357.1035. Found: 357.1042.

Products **16b**, **16e**, **16f**, and **16h** were prepared similarly, using reaction times of 1−3 days in the yields given in Table 3. Their properties are given in the Supporting Information.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. J.M.S. acknowledges receipt of Postgraduate Scholarships from NSERC and Alberta Ingenuity. D.A.R. thanks NSERC for an Undergraduate Summer Research Assistantship. J.E.W. thanks NSERC, the Alberta Heritage Foundation for Medical Research, and the Killam Foundation for Postgraduate Scholarships.

Supporting Information Available: Characterization data, ^1H and ^{13}C NMR spectra of new compounds, and X-ray crystallographic data for **4a**, **14f**, and **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062655+