

# Sml<sub>2</sub>-Promoted Reformatsky-Type Coupling Reactions in Exceptionally Hindered Contexts

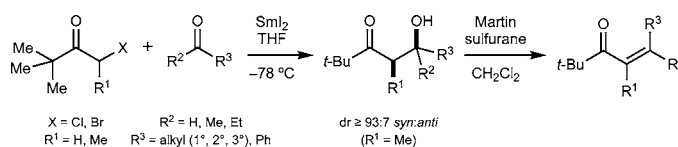
Brian A. Sparling, Ryan M. Moslin, and Timothy F. Jamison\*

Department of Chemistry, Massachusetts Institute of Technology,  
Cambridge, Massachusetts 02139

tffj@mit.edu

Received January 22, 2008

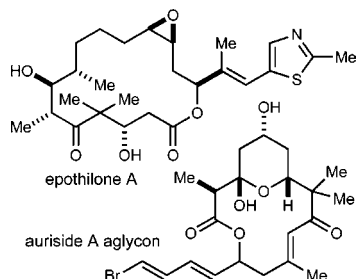
## ABSTRACT



Highly substituted, very hindered enones were synthesized using a two-step procedure that utilizes a diiodosamarium-promoted Reformatsky-type coupling and dehydration using Martin sulfurane. Both  $\alpha$ -chloro- and  $\alpha$ -bromoketones were coupled with a variety of carbonyl nucleophiles to form the intermediate  $\beta$ -hydroxyketones, occurring with excellent diastereoselectivity, favoring the *syn* isomer ( $\text{R}^1 = \text{Me}$ ). This technique complements other methods and enables the preparation of enones outside of the scope of current olefination methodology.

The  $\beta$ -hydroxyketone and  $\alpha,\beta$ -unsaturated ketone are frequently used as sites of fragment couplings in target-oriented synthesis.<sup>1,2</sup> In numerous natural products, a quaternary alkyl-substituted carbon exists adjacent to this functional group (Figure 1).<sup>3</sup> However, despite this prevalence, these highly

techniques commonly used to form similar, less sterically hindered systems.<sup>6,7</sup>



**Figure 1.** Natural products containing all-carbon,  $\alpha$ -quaternary ketones.

hindered enones are rarely exploited as a site of fragment assembly.<sup>4,5</sup> The significant steric demand posed by these  $\alpha$ -quaternary carbon centers prevents the use of most

(1) Reviews of the aldol reaction: (a) Heathcock, C. H. *Science* **1981**, *214*, 395. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(2) Reviews of the Horner-Wadsworth-Emmons olefination and related methods: (a) Prunet, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Martin, S. F. *Synthesis* **1979**, 633.

(3) (a) Acutiphycin: Barchi, J. J., Jr.; Moore, R. E.; Patterson, F. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 8193. (b) Aurisides A–B: Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 8956. (c) Chaetoglobosins A–E, G, J–M, Q–R, and T: Jiao, W.; Feng, Y.; Blunt, J. W.; Cole, A. L. J.; Munro, M. H. G. *J. Nat. Prod.* **2004**, *67*, 1722. (d) Chalcocaryanones C–D: Dumontet, V.; Gaspard, C.; Hung, N. V.; Fahy, J.; Tchertanov, L.; Sévenet, T.; Guéritte, F. *Tetrahedron* **2001**, *57*, 6189. (e) Epothilones A–I: Hardt, I. H.; Steinmetz, H.; Gerth, K.; Sasse, F.; Reichenbach, H.; Höfle, G. *J. Nat. Prod.* **2001**, *64*, 847. (f) Euphoscopins A–C and E–L: Yamamura, S.; Shizuri, Y.; Kosemura, S.; Ohtsuka, J.; Tayama, T.; Ohba, S.; Ito, M.; Saito, Y.; Terada, Y. *Phytochem.* **1989**, *28*, 3421.

(4) For example, the syntheses of aurisides A and B do not employ this approach, and the authors note unforeseen difficulties with an alternative Mukaiyama aldol coupling strategy: Paterson, I.; Florence, G. J.; Heimann, A. C.; Mackay, A. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1130.

(5) Syntheses of the epothilones frequently employ this strategy via lithium enolates formed using LDA. The ketones used in these reactions are largely unfunctionalized and are therefore compatible with the strong base. Recent review of epothilone syntheses: Watkins, E. B.; Chittiboyina, A. G.; Avery, M. A. *Eur. J. Org. Chem.* **2006**, 4071.

The Reformatsky reaction is an excellent synthetic tool for site-selective formation and subsequent elaboration of an enolate.<sup>8</sup> Many metals such as magnesium, chromium, and zinc can be used to promote this transformation. Nevertheless, only a few examples of such reactions involving quaternary substitution adjacent to the  $\alpha$ -bromoketone have been described. Dubois has reported the use of chromium(II) chloride to promote the Reformatsky-type coupling of pinacolone-type  $\alpha$ -bromoketones with aldehydes;<sup>9</sup> however, to date, this coupling has found limited utility. Other metallic species, namely magnesium<sup>10</sup> and diethylzinc,<sup>11</sup> have been used to promote the pinacolone-type Reformatsky-type coupling, but the low degree of functional group compatibility of these reagents places significant restrictions on these methods.<sup>12</sup>

Since the advent of diiodosamarium as a reagent in organic synthesis, it has been extensively employed in intramolecular Reformatsky-type reactions.<sup>13</sup> In contrast, this reagent has found little use in intermolecular Reformatsky-type coupling reactions, presumably due to the numerous side reactions that can occur.<sup>14</sup> Our recent total synthesis of (+)-acutiphycin demonstrated the first use of diiodosamarium to promote a chemoselective Reformatsky-type fragment coupling of a pinacolone-like  $\alpha$ -bromoketone.<sup>15</sup> On the basis of this work, we hypothesized that an  $\alpha'$ -quaternary group on the  $\alpha$ -bromoketone would reduce the likelihood of side reactions of the ketone. Herein, the generality of this method is described.

The coupling of 1-bromopinacolone proved general across a range of aldehyde electrophiles (Table 1). Aldehydes

**Table 1.**  $\alpha$ -Bromoketone–Aldehyde Couplings Promoted by SmI<sub>2</sub><sup>a</sup>

entry	R <sup>1</sup>	R <sup>2</sup>	yield (%)	<i>syn:anti</i>
1	H	<i>n</i> -Bu	60 <sup>b</sup>	na
2	H	Cy	94 <sup>b</sup>	na
3	H	<i>t</i> -Bu	85	na
4	H	Ph	72	na
5	Me	<i>n</i> -Bu	85	95:5
6	Me	Cy	80	93:7
7	Me	<i>t</i> -Bu	84	>98:2
8	Me	Ph	70	94:6

<sup>a</sup> Standard procedure: A THF solution of the  $\alpha$ -bromoketone (1 equiv) and the aldehyde (1 equiv) was prepared and added dropwise over 25 min to a THF solution of SmI<sub>2</sub> (5 equiv) at  $-78$  °C, and the reaction was stirred 1 h. Air was bubbled through the solution for 5 min before a sodium thiosulfate workup. Compounds were isolated using standard column chromatography. See Supporting Information for details. <sup>b</sup> A minor product was also isolated and is tentatively assigned as an Evans–Tischenko-type<sup>18</sup> monoprotected diol, formed from the addition a second equivalent of the aldehyde to the Reformatsky-type coupling product.

containing secondary (entry 1), tertiary (entry 2), quaternary (entry 3), and aromatic (entry 4)  $\alpha$ -substitution performed well in the coupling reaction. More sterically demanding

1-bromopinacolone derivatives were also effective; coupling reactions of 3-bromo-2,2-dimethyl-3-butanone with the same series of aldehydes proceeded in good yields and excellent diastereoselectivities, favoring, as determined by <sup>1</sup>H NMR, the *syn* diastereomer (entries 5–8).<sup>16</sup>

The remarkably high reactivity observed in the aldehyde couplings led us to also consider ketones as electrophiles (Table 2). The intermolecular Reformatsky-type coupling of

**Table 2.**  $\alpha$ -Bromoketone–Ketone Couplings Promoted by SmI<sub>2</sub><sup>a</sup>

entry	R <sup>1</sup>	R <sup>2</sup>	yield (%)
1	Me	Me	77
2	Et	Me	63
3	Et	Et	75
4	<i>t</i> -Bu	Me	98
5	<i>t</i> -Bu	Et	51

<sup>a</sup> Standard procedure: See Table 1, footnote *a*.

$\alpha$ -haloketones with ketones traditionally requires harsh Lewis acids or elevated temperatures to obtain a serviceable yield of the desired product.<sup>17,18</sup> Using the diiodosamarium method, however, simple ketones coupled efficiently (entries 1–3), and remarkably, even pinacolone (entry 4) served as an effective electrophile. Despite the less electrophilic nature of ketones, the reaction proceeded efficiently at  $-78$  °C, without significant alterations to the procedure.

(6) Examples involving the synthesis of  $\alpha,\beta$ -unsaturated ketones derived from 1-bromopinacolone: Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.

(7) Examples involving the synthesis of  $\alpha$ -aryl ketones derived from pinacolone under S<sub>RN</sub>1 conditions: (a) Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1983**, *48*, 1180. (b) Layman, W. J., Jr.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. M. *J. Org. Chem.* **2005**, *70*, 9147.

(8) Reviews of the Reformatsky reaction: (a) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325. (b) Fürstner, A. *Synthesis* **1989**, 571.

(9) Dubois, J.-E.; Axiotis, G.; Bertounesque, E. *Tetrahedron Lett.* **1985**, *26*, 4371.

(10) Fellmann, P.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 1349.

(11) Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069.

(12) The use of magnesium requires refluxing the  $\alpha$ -bromoketone with magnesium in benzene prior to introduction of the aldehyde, whereas the diethylzinc reaction must be concentrated in vacuo prior to introduction of the aldehyde substrate.

(13) Reviews: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (c) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.

(14)  $\alpha$ -Bromoesters often “self-couple” to form products of reductive dimerization, among others. Moreover, SmI<sub>2</sub> promotes numerous reactions of aldehydes themselves. For further examples see ref 13 and Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745.

(15) (a) Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106. (b) Moslin, R. M.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 9736.

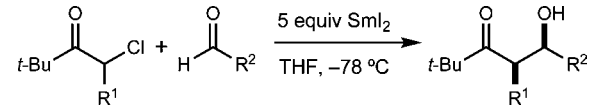
(16) (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (b) Ando, A.; Shioiri, T. *Tetrahedron* **1989**, *45*, 4969.

(17) Aoyagi, Y.; Yoshimura, M.; Tsuda, M.; Tsuchibuchi, T.; Kawamata, S.; Tateno, H.; Asano, K.; Nakamura, H.; Obokata, M.; Ohta, A.; Kodama, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 689.

(18) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

Reformatsky-type coupling was also achieved with the  $\alpha$ -chloroketones, that is, 1-chloropinacolone and 3-chloro-2,2-dimethyl-3-butanone. Using the same aldehyde electrophiles and reactions conditions as above,  $\beta$ -hydroxyketones were formed in yields comparable to or higher than the analogous  $\alpha$ -bromoketone coupling reactions (Table 3). A

**Table 3.**  $\alpha$ -Chloroketone–Aldehyde Couplings Promoted by  $\text{SmI}_2^a$



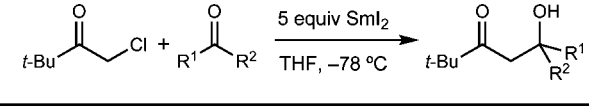
entry	R <sup>1</sup>	R <sup>2</sup>	yield (%)	syn:anti
1	H	<i>n</i> -Bu	77 <sup>b</sup>	na
2	H	Cy	>99	na
3	H	<i>t</i> -Bu	>99	na
4	H	Ph	72	na
5	Me	<i>n</i> -Bu	90	95:5
6	Me	Cy	94	93:7
7	Me	<i>t</i> -Bu	90	>98:2
8	Me	Ph	71	94:6

<sup>a</sup> Standard procedure: See Table 1, footnote a. <sup>b</sup> See Table 1, footnote b.

quantitative yield was observed in cases where the aldehyde contained tertiary and quaternary (entries 2–3) substitution at the  $\alpha$ -position. Excellent diastereoselectivity was also observed in the reactions of 3-chloro-2,2-dimethyl-3-butanone (entries 5–8).

The coupling of 1-chloropinacolone with hindered ketones also proceeded in good yield (Table 4). The increased yields

**Table 4.**  $\alpha$ -Chloroketone–Ketone Couplings Promoted by  $\text{SmI}_2^a$



entry	R <sup>1</sup>	R <sup>2</sup>	yield (%)
1	Me	Me	81
2	Et	Me	84
3	Et	Et	77
4	<i>t</i> -Bu	Me	93
5	<i>t</i> -Bu	Et	65

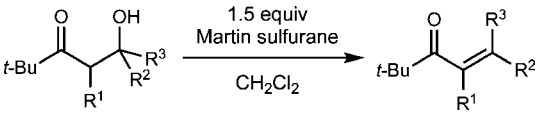
<sup>a</sup> Standard procedure: See Table 1, footnote a.

observed in these cases may be a result of the higher reduction potential of the C–Cl bond compared to that of the C–Br bond in  $\alpha$ -haloketones; a smaller concentration of the samarium enolate in the case of  $\alpha$ -chloroketones precludes the formation of possible side products, such as the Evans–Tischenko-type monoprotected diol. These conditions are the first reported to effect the Reformatsky-type

coupling of  $\alpha$ -chloroketones with ketones and nonaromatic aldehydes.<sup>19</sup>

Dehydration to form the *E*-disubstituted enones proceeded smoothly using a half-molar excess of the Martin sulfurane reagent at room temperature (Table 5).<sup>20</sup> This method was

**Table 5.** Dehydration of  $\beta$ -Hydroxyketones with Martin Sulfurane<sup>a</sup>

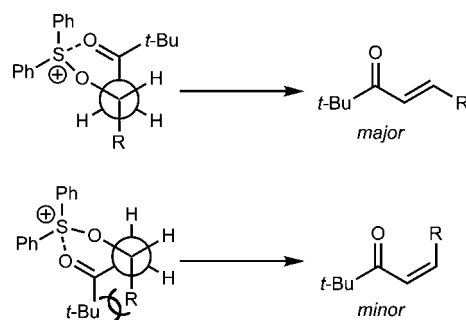


entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%)	<i>E</i> : <i>Z</i> ratio
1	H	<i>n</i> -Bu	H	89	>98:2
2	H	Cy	H	>99	>98:2
3	H	<i>t</i> -Bu	H	68	>98:2
4	H	Ph	H	89	>98:2
5	H	Et	Me	92	72:28
6	H	<i>t</i> -Bu	Me	37	77:23
7	Me	<i>n</i> -Bu	H	94	>98:2

<sup>a</sup> Standard procedure: A solution of Martin sulfurane (1.5 equiv,  $\text{CH}_2\text{Cl}_2$ ) was added to the  $\beta$ -hydroxyketone in  $\text{CH}_2\text{Cl}_2$ , and the reaction was stirred for 30 min. The reaction was quenched with sat. aq  $\text{NaHCO}_3$ , extracted with  $\text{Et}_2\text{O}$ , and washed ( $4 \times 1 \text{ M NaOH}$ ) prior to purification via column chromatography.

highly successful for secondary (entry 1), tertiary (entry 2), and quaternary (entry 3) aliphatic substitution adjacent to the alcohol. The product of entry 3 cannot be accessed using a Wittig olefination approach.<sup>6</sup> Benzylic alcohols were also dehydrated efficiently (entry 4).

The observed *E*/*Z* selectivity can be explained using Newman projection models (Figure 2). The lower selectivity



**Figure 2.** Stereoselectivity model for Martin sulfurane dehydration.

with tertiary alcohols (entries 5 and 6) may be due to increasing  $E_1$ -type elimination character, which is com-

(19) Prior examples of  $\alpha$ -chloroketones in couplings that afford  $\beta$ -hydroxyketones: (a) Ishihara, T.; Yamanaka, T.; Ando, T. *Chem. Lett.* **1984**, 1165. (b) Kagayama, A.; Igarashi, K.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, 73, 2579. (c) Yanagisawa, A.; Takahashi, H.; Arai, T. *Chem. Commun.* **2004**, 580. (d) Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, 4, 301.

monly observed for Martin sulfurane dehydrations of tertiary alcohols.<sup>20</sup> *E*-Trisubstituted enones can also be formed from the  $\alpha$ -methyl- $\beta$ -hydroxy coupling products (entry 7).

Overall, this method represents a mild and efficient two-step synthesis of a class of challenging  $\alpha,\beta$ -unsaturated enones and is complementary to the standard olefination procedures. Diiodosamarium-promoted Reformatsky-type couplings of  $\alpha$ -haloketones with various aldehyde and ketone electrophiles yielded  $\beta$ -hydroxyketones in good to excellent yield and diastereoselectivity. These hindered  $\beta$ -hydroxyketones were dehydrated using Martin sulfurane to yield  $\alpha,\beta$ -unsaturated enones with excellent yields and diastereoselectivity, in most cases. Currently, extensions of this methodology are being explored, including Reformatsky-type couplings catalytic in diiodosamarium.

---

(20) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

**Acknowledgment.** This work was supported by the NIGMS (GM-063755). B.A.S. thanks the MIT Undergraduate Research Opportunities Program (UROP) for funding, including the Thomas A. Spencer Endowed UROP Fund and the Paul E. Gray Endowed Fund for UROP. We are grateful to Ms. Li Li for obtaining mass spectrometric data for all new compounds (MIT Department of Chemistry Instrumentation Facility, which is supported in part by the NSF (CHE-9809061 and DBI-9729592) and the NIH (1S10RR13886-01)).

**Supporting Information Available:** General experimental procedures and spectral and analytical data for all new compounds, including <sup>1</sup>H and <sup>13</sup>C NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL800099A