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Sml₂-Promoted Reformatsky-Type Coupling Reactions in Exceptionally Hindered Contexts

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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 α -chloro- and α -bromoketones were coupled with a variety of carbonyl nucleophiles to form the intermediate β -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 β -hydroxyketone and α,β -unsaturated ketone are frequently used as sites of fragment couplings in target-oriented synthesis.^{1,2} In numerous natural products, a quaternary alkyl-substituted carbon exists adjacent to this functional group (Figure 1).³ However despite this prevalence, these highly hindered enones are rarely exploited as a site of fragment assembly.^{4,5} The significant steric demand posed by these α -quaternary carbon centers prevents the use of most techniques commonly used to form similar, less sterically hindered systems.^{6,7}

The Reformatsky reaction is an excellent synthetic tool for site-selective formation and subsequent elaboration of an enolate.⁸ 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 α -bromoketone have been described. Dubois has reported the use of chromium(II) chloride to promote the Reformatsky-type coupling of pinacolone-type α -bromoketones with aldehydes;⁹ however, to date this coupling has found limited utility. Other metallic species, namely magnesium¹⁰ and diethylzinc,¹¹ 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.¹²

Since the advent of diiodosamarium as a reagent in organic synthesis, it has been extensively employed in intramolecular Reformatsky-type reactions.¹³ In contrast, this reagent has found little use in intermolecular Reformatsky-type coupling reactions, presumably due to the numerous side reactions that can occur.¹⁴ Our recent total synthesis of (+)-acutiphycin

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

demonstrated the first use of diiodosamarium to promote a chemoselective Reformatsky-type fragment coupling of a pinacolone-like α -bromoketone.¹⁵ Based on this work, we hypothesized that an α' -quaternary group on the α -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 containing secondary (entry 1), tertiary (entry 2), quaternary (entry 3), and aromatic (entry 4) α -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 ¹H NMR, the *syn* diastereomer (entries 5–8).¹⁶

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 α -haloketones with ketones traditionally requires harsh Lewis acids or elevated temperatures to obtain a serviceable yield of the desired product.¹⁷ 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.

Reformatsky-type coupling was also achieved with the α -chloroketones, i.e., 1-chloropinacolone and 3-chloro-2,2-dimethyl-3-butanone. Using the same aldehyde electrophiles and reactions conditions as above, β -hydroxyketones were formed in yields comparable to or higher than the analogous α -bromoketone coupling reactions (Table 3). A quantitative yield was observed in cases where the aldehyde contained tertiary and quaternary (entries 2–3) substitution at the α -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 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 α -haloketones; a smaller concentration of the samarium enolate in the case of α -chloroketones precludes the formation of possible side products, such as the Evans–Tischenko-type mono-protected diol. These conditions are the first reported to effect the Reformatsky-type coupling of α -chloroketones with ketones and nonaromatic aldehydes.¹⁹

Dehydration to form the *E*-disubstituted enones proceeded smoothly using a half-molar excess of the Martin sulfurane reagent at room temperature (Table 5).²⁰ This method was highly successful for secondary (entry 1), tertiary (entry 2), and quaternary (entry 3) aliphatic substitution adjacent to the alcohol. It is worth noting that the product of entry 3 cannot be accessed using a Wittig olefination approach.⁶ 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 with tertiary alcohols (entries 5 and 6) may be due to increasing E₁-type elimination character, which is commonly observed for Martin sulfurane dehydrations of tertiary alcohols.²⁰ *E*-Trisubstituted enones can also be formed from the α -methyl- β -hydroxy coupling products (entry 7).

Overall this method represents a mild and efficient two-step synthesis of a class of challenging α,β -unsaturated enones and is complementary to the standard olefination procedures. Diiodosamarium-promoted Reformatsky-type couplings of α -haloketones with various aldehyde and ketone electrophiles yielded β -hydroxyketones in good to excellent

yield and diastereoselectivity. These hindered β -hydroxyketones were dehydrated using Martin sulfurane to yield α,β -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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Natural products containing all-carbon, α -quaternary ketones.

Figure 2.
Stereoselectivity model for Martin sulfurane dehydration.

Table 1 α -Bromoketone-aldehyde couplings promoted by SmI₂^a

entry	R ¹	R ²	yield (%)	syn:anti
1	H	<i>n</i> -Bu	60 ^b	na
2	H	Cy	94 ^b	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

^aStandard procedure: A THF solution of the α -bromoketone (1 equiv) and the aldehyde (1 equiv) was prepared and added dropwise over 25 min to a THF solution of SmI₂ (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.

^bA minor product was also isolated and is tentatively assigned as an Evans–Tischenko-type¹⁸ mono-protected diol, formed from the addition a second equivalent of the aldehyde to the Reformatsky-type coupling product.

Table 2 α -Bromoketone-ketone couplings promoted by SmI₂^a

entry	R ¹	R ²	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

^aStandard procedure: See Table 1, ref. *a*.

Table 3 α -Chloroketone-aldehyde couplings promoted by SmI₂ ^a

entry	R ¹	R ²	yield (%)	syn:anti
1	H	<i>n</i> -Bu	77 ^b	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

^a Standard procedure: See Table 1, ref. *a*.^b See Table 1, ref. *b*.

Table 4 α -Chloroketone-ketone couplings promoted by SmI₂^a

entry	R ¹	R ²	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

^aStandard procedure: See Table 1, ref. *a*.

Table 5

Dehydration of β -hydroxyketones with Martin sulfurane^a

entry	R ¹	R ²	R ³	yield (%)	E:Z 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

^aStandard procedure: A solution of Martin sulfurane (1.5 equiv, CH₂Cl₂) was added to the β -hydroxyketone in CH₂Cl₂, and the reaction was stirred for 30 min. The reaction was quenched with sat. aq. NaHCO₃ extracted with Et₂O, and washed (4 $\times$ 1M NaOH) prior to purification via column chromatography.