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Tin-Free Enantioselective Radical Reactions Using Silanes

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Abstract

Readily available hexyl silane is an excellent choice as a H-atom donor and a chain carrier in Lewis acid mediated enantioselective radical reactions. Conjugate radical additions to α,β -unsaturated imides at room temperature proceed in good yields and excellent enantioselectivities.

Organotin reagents play a significant role in radical reactions.¹ Due to the nature of the weak Sn-H bond, tin hydride reagents have been and continue to be reagents of choice to carry out chain radical reactions. Although very popular and highly useful for the successful execution of radical reactions, tin reagents have significant drawbacks.² Organotin reagents are toxic and the tin byproducts from radical reactions often prove to be very difficult to remove. To overcome these significant liabilities, several alternatives to tin reagents³ have been put forward in the literature. Of these, silicon,⁴ phosphorus,⁵ sulfur,⁶ indium,⁷ Lewis acid-activated water,⁸ and cyclohexadiene⁹ based reagents have shown the most promise (Figure 1).

The P-H, O-H, and C-H bonds are comparatively much stronger than the Sn-H bond. Thus it is much more difficult to carry out chain reactions with these reagents at low temperatures, a condition required for optimal organization of the complex that provides face selectivity in chiral Lewis acid mediated reactions. At the present time there are only a handful of examples in the literature that do not utilize tin reagents for execution of enantioselective radical reactions.¹⁰ Recently, radical reactions mediated by organocatalysts have been reported.¹¹ Over the past several years, we have been very interested in the development of tin-free enantioselective radical reactions using silanes or phosphorous acids. The lower reactivity of the silicon and phosphorous based reagents necessitates the need to generally carry out reactions at room temperature or higher. Thus it is necessary to have a substrate-chiral catalyst complex that can provide reactivity enhancements to allow for reactions with the less efficient

Si-H and P-H reagents and at the same time provide high selectivity. In this work we demonstrate that readily available silanes are effective as hydrogen atom donors and chain carriers in chiral Lewis acid mediated enantioselective radical conjugate additions.¹²

We began our work with the goal of identifying an optimal silane for conjugate radical addition and these results are presented in Table 1. For our initial work, we chose the imide **1** as a substrate due to its relatively high reactivity, and we used the chiral Lewis acid derived from magnesium triflimide and bisoxazoline **2**.¹³ The reactions were carried out at room temperature using triethylborane/oxygen as an initiator. Tris(trimethylsilyl)silane (TTMSS), the most well known alternative to tinhydride, was evaluated first. The reaction gave the isopropyl addition product **3** in high yield and excellent enantioselectivity (entry 1). A minor amount of the ethyl radical addition product was also formed. Other commercially available silanes were also evaluated (entries 2–6). Of these, diphenyl silane (entry 2), phenyl silane (entry 5) and hexyl silane (entry 6) gave the product in good yield and nearly identical selectivity. In contrast to other silanes (entries 2–5), hexyl silane gave minor amounts of ethyl addition product (entry 6). A control experiment in the absence of hexyl silane gave the radical adduct in low yield (entry 7).¹⁴ These experiments demonstrate that eco-friendly silanes are excellent alternatives to tributyltin hydride in enantioselective radical reactions. Of the two most effective silanes examined in this study, tris(trimethylsilyl)silane is less atom economical (1H atom for a molecular weight of 252). However, it is more effective than hexyl silane (vide infra).

Having established that silanes are effective mediators in enantioselective radical reactions, we next examined conjugate additions to crotonates attached to two different well established achiral templates. Isopropyl radical addition to oxazolidinone crotonate **4** was carried out using two different chiral Lewis acids and the two most promising silanes (Table 2). Reaction using TTMSS and Mg(NTf₂)₂/ligand **2** gave **5** in high yield and low ee (entry 1). An identical reaction except using hexyl silane also gave the product in modest yield and low ee (entry 2). Reactions using a chiral Lewis acid derived from Zn(NTf₂)₂/ligand **2** were not highly effective with either of the silanes (entries 3 and 4).

We have previously shown that pyrazolidinones are very effective as achiral templates and provide enantioselectivity enhancements in a variety of reactions including conjugate radical additions.¹⁵ Isopropyl radical addition to **6** using TTMSS (entry 1, Table 3) or hexyl silane (entry 2) were not very effective with respect to both chemical efficiency or selectivity. As a comparison experiment, reaction using tributyltin hydride as the H-atom donor gave **7** in high yield and selectivity (entry 5).^{15b} Thus of the three different achiral templates investigated, only the most reactive imides were effective using silanes as H-atom donors.

In an effort to improve reactivity and/or selectivity we examined the effect of the imide substituent on conjugate radical addition and these results are shown in Table 4. As discussed earlier, reactions with **1** with a phenyl imide substituent proceeds in good yield and selectivity (entries 1 and 2). Reaction with substrate **8** containing a 4-Cl-phenyl substituent using TTMSS gave **10** in high yield (entry 3). However, there was an increase in the amount of ethyl addition product (compare entry 3 with 1). The same trend was observed with hexyl silane along with a lowering of the yield (compare entry 4 with 2). A tert-butyl imide substituent, **9**, was very effective in reaction using TTMSS (entry 5). Lowering the amount of radical precursor from 10 equivalents (entry 1) to 5 equivalents (entry 6) to 3 equivalents (entry 7) did not have a significant impact on yield or selectivity. However, a significant increase in ethyl addition was observed while using lower amounts of the radical precursor. Isopropyl radical addition to **9** using hexyl silane was slightly less efficient than that with TTMSS (compare entry 8 with 5). Reactions with hexyl silane using lower amounts of the radical precursor (entries 9 and 10) displayed a trend similar to that observed with TTMSS. Lowering reaction temperature had a positive impact on enantioselectivity (entries 11 and 12) reaching a high of 90% but chemical

yields suffered. Additionally, reaction at -30°C showed a better discrimination between isopropyl and ethyl radical addition: the less nucleophilic ethyl radical adds less efficiently at lower temperatures (entry 12).

We have evaluated the scope of the radical precursor as well as the β -substituent in conjugate radical additions using hexyl silane and a chiral Lewis acid derived from $\text{Mg}(\text{NTf}_2)_2/\text{ligand } \mathbf{2}$ and these results are shown in Table 5. Addition of ethyl radical to **1** was feasible but the enantioselectivity was only modest (entry 1). As noted earlier, isopropyl radical adds efficiently to provide **3** in good yield and selectivity (entry 2). The bulky and more nucleophilic tert-butyl radical gave the conjugate addition product in high yield and selectivity with minimal contamination from ethyl radical addition (entry 3). Interestingly, cyclohexyl radical addition to **1** proceed with only modest efficiency (entry 4). The functionalized tertiary radical gave the product in excellent yield and selectivity (entry 5). The addition of tert-butyl radical to different substrates was investigated. Conjugate addition to cinnamate **12** proceeded well and gave the product in good yield and excellent selectivity (entry 6). Even higher yield and selectivity was obtained using **13** as a substrate (entry 7). The formation of **20** with 94 % ee for a reaction at room temperature is highly noteworthy.

In conclusion, we have developed an efficient ‘tin free’ methodology for enantioselective conjugate radical additions using readily available silanes. Conjugate additions using an imide template provides products in good yields and selectivity for reactions at room temperature. Experiments are underway to further extend the methodology to other enantioselective radical reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Silanes

Phosphorous
acids

Thiols

Indium
Hydrides

Water-Lewis Acid

Cyclohexadienes

Figure 1.
Alternate Reagents for Radical Reactions

Table 1
Identification of Optimal Silane for Conjugate Radical Additions

entry	silane	yield, % ^b	prod: ethyl ^c	ee, % ^d
1	(TMS) ₃ SiH	91	30:1	81
2	Ph ₂ SiH ₂	86	15:1	78
3	Et ₃ SiH	31	12:1	80
4	Et ₂ SiH ₂	53	12:1	80
5	PhSiH ₃	75	12:1	79
6	HexylSiH ₃	76	30:1	80
7	-	29	30:1	-

^a For experimental details see Supporting Information.

^b Isolated yields.

^c Determined by ¹H NMR.

^d Determined by chiral HPLC.

Table 2

Investigation of Oxazolidinone Derived Crotonate.^a

<div> </div>					
entry	silane	Lewis acid	yield ^b	prod: ethyl ^c	ee, % ^d
1	(TMS) ₃ SiH	Mg(NTf ₂) ₂	87	12:1	20
2	HexylSiH ₃	Mg(NTf ₂) ₂	54	15:1	11
3	(TMS) ₃ SiH	Zn(OTf) ₂	55	20:1	8
4	HexylSiH ₃	Zn(OTf) ₂	20 ^e	10:1	7

^aFor experimental details see Supporting Information.

^bIsolated yields.

^cDetermined by ¹H NMR.

^dDetermined by chiral HPLC.

^e62% of the starting material was recovered.

Table 3Investigation of Pyrazolidinone Derived Crotonate.^a

entry	H-donor	Lewis acid	yield, % (SM) ^b	ee, % ^c
1	(TMS) ₃ SiH	Mg(NTf ₂) ₂	56	51
2	HexylSiH ₃	Mg(NTf ₂) ₂	33	54
3 ^d	Bu ₃ SnH	Cu(OTf) ₂	80	95

^aFor experimental details see Supporting Information.^bIsolated yields.^cDetermined by chiral HPLC.^dReaction at -78 °C (data from reference 15b).

Table 4

Optimization of the Imide Substituent

<div> <div> </div> </div>				
entry	R	silane	yield, % ^b	prod: ethyl ^c
1	C ₆ H ₅	(TMS) ₃ SiH	91	30:1
2	C ₆ H ₅	Hexyl SiH ₃	76	30:1
3	p-ClC ₆ H ₄	(TMS) ₃ SiH	93	10:1
4	p-ClC ₆ H ₄	Hexyl SiH ₃	62	6:1
5	t-Bu	(TMS) ₃ SiH	83	>50:1
6 ^e	t-Bu	(TMS) ₃ SiH	70	5:1
7 ^f	t-Bu	(TMS) ₃ SiH	70	4:1
8	t-Bu	Hexyl SiH ₃	76	10:1
9 ^e	t-Bu	Hexyl SiH ₃	70	5:1
10 ^f	t-Bu	Hexyl SiH ₃	70	3:1
11 ^g	t-Bu	Hexyl SiH ₃	72	15:1
12 ^h	t-Bu	Hexyl SiH ₃	56	20:1

^a For experimental details see Supporting Information.

^b Isolated yields.

^c Determined by ¹H NMR.

^d Determined by chiral HPLC.

^e Reaction with 5 eq of i-PrI.

^f Reaction with 3 eq of i-PrI.

^g Reaction at 0 °C.

^h Reaction at -30 °C.

Table 5

Breadth and Scope Studies^a

ent			R ¹	R ²	yield (%) ^b	prod ethyl ^c	ee (%) ^d
	9, 12-14	11, 15-21					
1		CH ₃ (9)	CH ₃ (9)	Et (15)	64	-	43
2		CH ₃ (9)	CH ₃ (9)	i-Pr (11)	73	10:1	83
3		CH ₃ (9)	CH ₃ (9)	t-Bu (16)	81	>50:1	86
4		CH ₃ (9)	CH ₃ (9)	Cyclohexyl (17)	60	2:1	70
5		CH ₃ (9)	CH ₃ (9)		95	>50:1	82
6		C ₆ H ₅ (12)	C ₆ H ₅ (12)	t-Bu (19)	71	>50:1	91
7		4-Cl-C ₆ H ₄ (13)	4-Cl-C ₆ H ₄ (13)	t-Bu (20)	89	>50:1	94
8		4-MeOC ₆ H ₄ (14)	4-MeOC ₆ H ₄ (14)	t-Bu (21)	88	>50:1	90

^aFor experimental details see Supporting Information.

^bIsolated yields.

^cDetermined by ¹H NMR.

^dDetermined by chiral HPLC.