ORGANIC LETTERS

2008
Vol. 10, No. 23
5349−5352

Tin-Free Enantioselective Radical Reactions Using Silanes

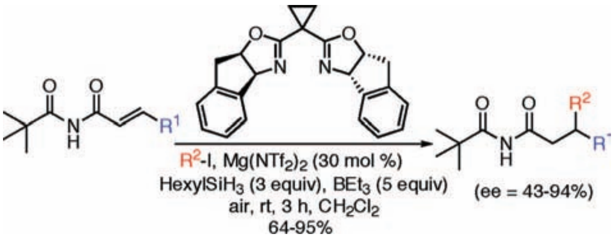
Mukund P. Sibi,* Yong-Hua Yang, and Sunggi Lee

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

mukund.sibi@ndsu.edu

Received September 15, 2008

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 reagents[3] have been put forward in the literature. Of these, silicon,[4] phosphorus,[5] sulfur,[6] indium,[7] Lewis acid activated water,[8] and cyclohexadiene[9] based reagents have shown the most promise (Figure 1).

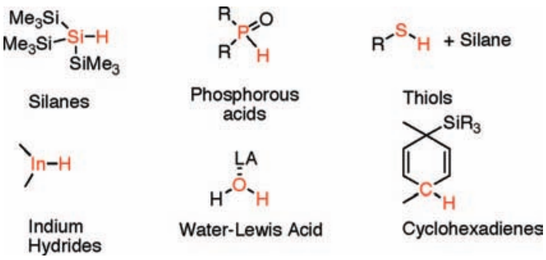


Figure 1. Alternate reagents for radical reactions.

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]

---

(1) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.

(2) For general reviews on alternate reagents to tin, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072–3082. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, 835–849. (c) Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794–802. (d) Studer, A.; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080–3082. (e) Parsons, A. *Chem. Br.* **2002**, *38*, 42–44.

(3) Fluorous tin hydrides: (a) Curran, D. P.; Hadida, S.; Kim, S-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607–6615. (b) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531–2532.

(4) Oragnosilanes: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188–194. (b) Chatgilialoglu, C. *Chem. Eur. J.* **2008**, *14*, 2310–2320. (c) Chatgilialoglu, C. *Organosilanes in Radical Chemistry*; Wiley: Chichester, 2004.

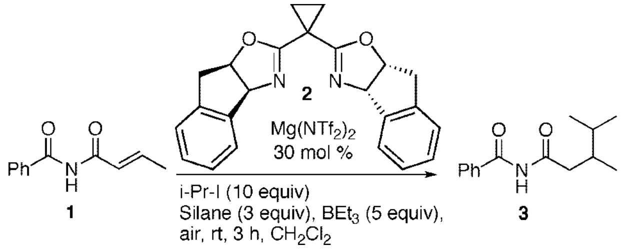
(5) (a) Hypophosphorous acid: Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) EPHP: Jang, D. O.; Cho, D. H. *Synlett* **2002**, 1523–1525. Francisco, C. G.; Gonzalez, C. C.; Herrera, A. J.; Paz, N. R.; Suarez, E. *Tetrahedron Lett.* **2006**, *47*, 9057–9060. (c) DEPO: Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971–2974. (d) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287–3289.

10.1021/ol802154d CCC: $40.75

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 phosphorus acids. The lower reactivity of the silicon and phosphorus 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 because of 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. Tristrimethylsilylsilane (TTMSS), the most well-known alternative to tinhydride, was evaluated first. The reaction gave the isopropyl addition product **3** in high yield and excellent enantioslectivity (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, tristrimethylsilyl silane is less atom economical (1H atom for a molecular weight of 252). However, it is more effective than hexyl silane (vide infra).

Table 1. Identification of Optimal Silane for Conjugate Radical Additions

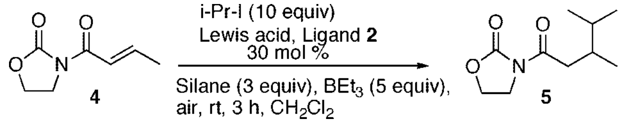


entry	silane	yield, %[b]	prod:ethyl[c]	ee, %[d]
1	$(TMS)_3SiH$	91	30:1	81
2	Ph_2SiH_2	86	15:1	78
3	Et_3SiH	31	12:1	80
4	Et_2SiH_2	53	12:1	80
5	$PhSiH_3$	75	12:1	79
6	$hexylSiH_3$	76	30:1	80
7		29	30:1	

[a] For experimental details see Supporting Information. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC.

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 $Mg(NTf_2)_2$/ligand **2** gave **5** in high yield and low ee (entry 1). An idential 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 $Zn(NTf_2)_2$/ligand **2** were not highly effective with either of the silanes (entries 3 and 4).

Table 2. Investigation of Oxazolidinone-Derived Crotonate[a]

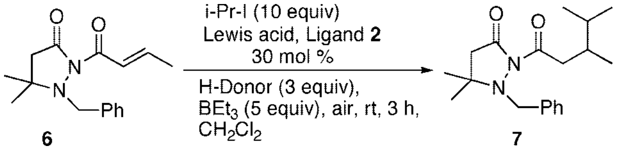


entry	silane	Lewis acid	yield[b]	prod:ethyl[c]	ee, %[d]
1	$(TMS)_3SiH$	$Mg(NTf_2)_2$	87	12:1	20
2	$hexylSiH_3$	$Mg(NTf_2)_2$	54	15:1	11
3	$(TMS)_3SiH$	$Zn(OTf)_2$	55	20:1	8
4	$hexylSiH_3$	$Zn(OTf)_2$	20[e]	10:1	7

[a] For experimental details see Supporting Information. [b] Isolated yields. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. [e] 62% of the starting material was recovered.

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

Table 3. Investigation of Pyrazolidinone-Derived Crotonate[a]



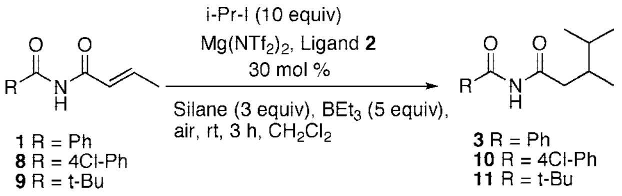
entry	H-donor	Lewis acid	yield, % (SM)[b]	ee, %[c]
1	$(TMS)_3SiH$	$Mg(NTf_2)_2$	56	51
2	$hexylSiH_3$	$Mg(NTf_2)_2$	33	54
3[d]	Bu_3SnH	$Cu(OTf)_2$	80	95

[a] For experimental details see Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction at −78 °C (data from ref 15b).

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 substitutent 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 equiv (entry 1) to 5 equiv (entry 6) to 3 equiv (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 precusor. Isopropyl radical addition to **9** using hexyl silane was slightly less efficient than that with TTMSS (compare entry 8 with entry 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).

Table 4. Optimization of the Imide Substituent

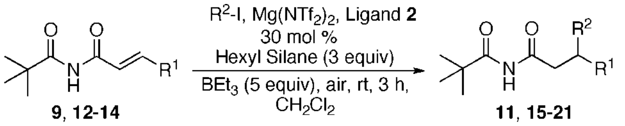


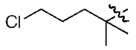
entry	R	silane	yield, %[b]	prod:ethyl[c]	ee (%)[d]
1	C_6H_5	$(TMS)_3SiH$	91	30:1	81
2	C_6H_5	$hexylSiH_3$	76	30:1	80
3	p-ClC_6H_4	$(TMS)_3SiH$	93	10:1	78
4	p-ClC_6H_4	$hexylSiH_3$	62	6:1	77
5	*t*-Bu	$(TMS)_3SiH$	83	>50:1	83
6[e]	*t*-Bu	$(TMS)_3SiH$	70	5:1	82
7[f]	*t*-Bu	$(TMS)_3SiH$	70	4:1	81
8	*t*-Bu	$hexylSiH_3$	76	10:1	83
9[e]	*t*-Bu	$hexylSiH_3$	70	5:1	82
10[f]	*t*-Bu	$hexylSiH_3$	70	3:1	81
11[g]	*t*-Bu	$hexylSiH_3$	72	15:1	87
12[h]	*t*-Bu	$hexylSiH_3$	56	20:1	90

[a] For experimental details see Supporting Information. [b] Isolated yields. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC. [e] Reaction with 5 equiv of *i*-PrI. [f] Reaction with 3 eq of i-PrI. [g] Reaction at 0 °C. [h] Reaction at −30 °C.

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 $Mg(NTf_2)_2$/ligand **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

Table 5. Breadth and Scope Studies[a]



ent	R^1	R^2I	yield (%)[b]	prod: ethyl[c]	ee (%)[d]
1	CH_3 (**9**)	Et (**15**)	64	-	43
2	CH_3 (**9**)	i-Pr (**11**)	73	10:1	83
3	CH_3 (**9**)	t-Bu (**16**)	81	>50:1	86
4	CH_3 (**9**)	Cyclohexyl (**17**)	60	2:1	70
5	CH_3 (**9**)	 (**18**)	95	>50:1	82
6	C_6H_5 (**12**)	t-Bu (**19**)	71	>50:1	91
7	4-Cl-C_6H_4 (**13**)	t-Bu (**20**)	89	>50:1	94
8	4-MeOC_6H_4 (**14**)	t-Bu (**21**)	88	>50:1	90

[a] For experimental details see Supporting Information. [b] Isolated yields. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC.

---

(6) Thiols: (a) Cai, Y.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *137*, 6–1386. (b) Dang, H-S.; Franchi, P.; Roberts, B. P. *Chem. Commun.* **2000**, 499–500. (c) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35. (d) Beaufils, F.; Denes, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563–2566.

(7) Triethylsilane-indium(III) chloride: Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981–4983.

(8) Water as a hydrogen atom source: (a) Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515. (b) Medeiros, M. R.; Schacherer, L. N.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2007**, *9*, 4427–4429. (c) Pozzi, D.; Renaud, P. *Chimia* **2007**, *61*, 151–154.

(9) (a) Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794–802. (b) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726–5733.

(10) (a) Cai, Y.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1376–1386. (b) Haque, M. B.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881–2890. (c) Gansaeuer, A.; Fan, C-A.; Piestert, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916–6917. (d) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293–1296.

(11) (a) Aechtner, T.; Dressel, M.; Bach, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5849. (b) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (c) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, 129. (d) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004.

(12) For recent reviews on enantioselective radical reactions, see: (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (b) Zimmerman, J.; Sibi, M. P. *Top. Curr. Chem.* **2006**, *263* (Radicals in Synthesis 1), 107–162. (c) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

(13) For details on reaction conditions and characterization data, see Supporting Information.

selectivity with minimal contamination from ethyl radical addition (entry 3). Interestingly, cyclohexyl radical addition to **1** proceeded 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 enantioselctive radical reactions.

Acknowledgment. We thank the NIH (GM-54656) for financial support of this work.

Supporting Information Available: Experimental procedures, characterization data, and proof of stereochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802154D

---

(14) Control experiments suggest that the reaction does not proceed through the formation of a boron enolate to any significant extent. Reaction using hexyl silane and CD_2Cl_2 as a solvent showed no deuterium incorporation in the product. Similarly, quenching the reaction with D_2O also showed no deuterium incorporation.

(15) For a full account on the use of pyrazolidinones in Diels−Alder reactions, see: (a) Sibi, M. P.; Stanley, L. M.; Venkatraman, L.; Nie, X.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395. For conjujate radical addition, see: (b) Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421.