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Crotylations of α-Carbonyl Radicals with Crotylstannane

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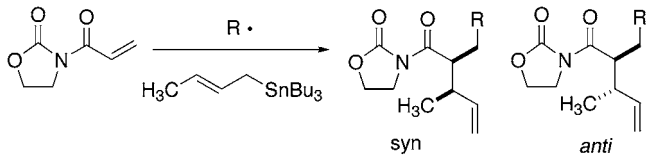
ABSTRACT



Electrophilic radicals undergo crotylation with crotylstannane with moderate to good efficiency. The reaction provides the syn isomer as the major product. The present methodology is complementary to Claisen protocols for the synthesis of γ,δ-unsaturated carboxylic acid derivatives. Details of the new radical methodology are presented.

Free radical fragmentation reactions have enjoyed immense popularity in organic synthesis.[1] Seminal work from the laboratories of Keck[2] and Curran[3] have firmly established convenient protocols for the installation of an allyl group using simple allylstannane as well as 2-substituted allylstannanes and a radical precursor.[1] However, reactions with 3-substituted allylstannanes are not well explored and have generally met with failure. Either they show low reactivity or they provide byproducts.[4] Some examples of successful allylations involving 3-substituted allylstannane[5] or alternatives[6] have been reported in the literature. Generally intermolecular radical addition to unactivated nonterminal alkenes is difficult.[7] The failure of reactions with crotylstannane may be attributed to the low reactivity of the radical partner, the reduced reactivity of crotylstannanes, the high temperatures used for the allylation reactions, and the isomerization to more reactive 1-substituted allylstannanes that can occur at high temperatures. We have previously shown that α-carbonyl radicals undergo highly selective allylation reactions with allylstannanes at low temperatures using catalytic amounts of a Lewis acid.[8] We surmised that the higher electrophilicity[9] of the Lewis acid-coordinated α-carbonyl radical in combination with low reaction temperature might allow for crotylation with the nucleophilic crotylstannane. This work reports successful examples of crotylation of α-carbonyl radicals in moderate to good yields (**1** to **2**, Scheme 1). Additionally, the stereoselectivity[10] (syn to anti

(1) For a recent review, see: Rosenstein, I. In *Radicals in Organic Synthesis*, Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, Chapter 1.4.

(2) (a) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(3) (a) Curran, D. P. *Synthesis* **1988**, 489. (b) Jasperse, C. P.; Fevig, T. L.; Curran, D. P. *Chem. Rev.* **1991**, *91*, 1237.

(4) (a) For general information, see: Clive, D. L. J.; Paul, C. C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028. (b) For formation of butadiene, see: Keck, G. E.; Yates, J. B. *J. Organomet. Chem.* **1983**, *248*, C21.

(5) Intermolecular reactions: (a) Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, 61, C33. (b) Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T. *J. Organomet. Chem.* **1973**, *56*, C11 (c) Easton, C. J.; Scharfbillig, I. M. *J. Org. Chem.* **1990**, *55*, 384. (d) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron* **1995**, *51*, 4183. Intramolecular reactions: (e) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917. (f) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345.

(6) Allylsufides: (a) Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442. Allylgallanes: (b) Usugi, S.-i.; Yorimitsu, Y.; Oshima, K. *Tetrahedron Lett.* **2001**, *42*, 4535.

(7) For information on rate data on intermolecular addition to nonterminal alkenes, see: *Free Radicals in Organic Chemistry*; Fossey, J., Lefort, D., Sorba, J., Eds.; Wiley: Paris, 1995, Chapter 12. Also see ref 9.

(8) (a) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (b) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472.

(9) Pereyre et al. (ref 5a) and Easton (ref 5c) have previously noted the higher reactivity of electrophilic radicals with 3-substituted allylstannanes.

(10) For diastereoselective radical allylation, see: (a) *Stereochemistry of Radical Reactions*; Curran, D. P., Porter, N. A., Giese, B.; VCH: Weinheim, 1995. (b) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (c) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (d) For recent reviews on enantioselective radical reactions, see: Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. Sibi, M. P.;

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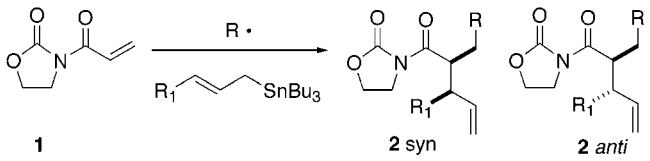
Scheme 1

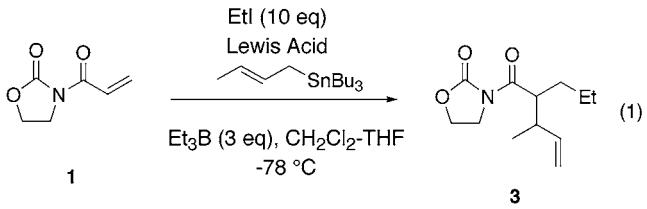


1 2 syn 2 *anti*

ratio) in the coupling of prochiral radicals with crotylstannane is also discussed.

Our experiments began with the establishment of reaction conditions for the addition/trapping reaction with acrylimide **1** (Table 1, eq 1). Reaction of the acrylimide with 2 equiv

Table 1. Effect of Lewis Acid on Radical Crotylations[a]



(1)

1 3

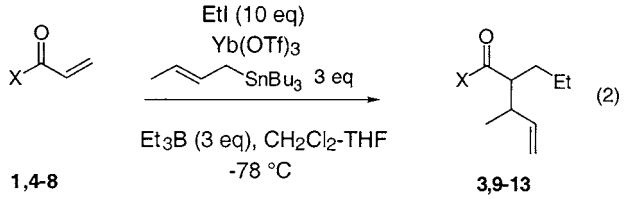
entry	Lewis acid (eqs)	allyltin (equiv)	yield (%)[b]	dr[c]
1	no Lewis acid	3	<5	
2	$Yb(OTf)_3$ (2)	2	55	3.6:1
3	$Yb(OTf)_3$ (1)	5	68	3.5:1
4	$Yb(OTf)_3$ (0.3)	5	70	3.5:1
5	$Zn(OTf)_2$ (1)	5	19	2.3:1
6	$Mg(ClO_4)_2$ (1)	5	22	3.2:1
7	$Hf(OTf)_4$ (1)	5	45	3.4:1

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Diastereomer ratio determined by ^{1}H NMR (500 MHz).

of the crotylstannane[11] and ethyl iodide in the absence of any Lewis acid gave none of the desired product (entry 1). In contrast, when ytterbium triflate was used as a Lewis acid for the reaction, the crotylated product **3** was obtained in 55% yield. The product was formed as a mixture of diastereomers in a ratio of 3.6:1 (entry 2). The reaction was effective using either stoichiometric or catalytic amounts of the Lewis acid and excess stannane (entry 3 and 4). Of the different Lewis acids examined, ytterbium triflate performed the best (compare entry 4 with 5−7).

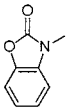
Two control experiments were conducted to establish that the crotylation reactions did indeed proceed via radical intermediates. Reaction in the absence of triethylborane as a radical initiator in the conversion of **1** to **3** gave no crotylated product. Similarly, carrying out the reaction in the presence of galvinoxyl, a radical inhibitor, gave none of the desired compound **3**. A minor amount of a 3 + 2

Table 2. Effect of Templates on Reactivity and Selectivity[a]



(2)

1,4-8 3,9-13

Entry	X =	SM	Product	Yield, (%)[b]	dr[c]
1		**1**	**3**	68	3.6:1
2		**4**	**9**	78	3.7:1
3		**5**	**10**	56	3.7:1
4		**6**	**11**	51	1.4:1
5		**7**	**12**	79	1.5;1
6		**8**	**13**	30	2.3:1

[a] Lewis acid (1 equiv) was used. For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Diastereomer ratio was determined by ^{1}H NMR (500 MHz).

cycloaddition product formed from crotylstannane, and the enone was obtained in the absence of an initiator. Porter and co-workers have also observed the formation of similar cyclopentanes in their work on enantioselective radical allylation reactions.[12] These clearly establish that reactions with crotylstannane and **1** occur via radical intermediates.

We have previously shown that achiral templates can have a significant impact on the outcome of conjugate radical addition reactions.[13] In light of this, we undertook a brief study on the effect of achiral templates on reactivity and selectivity in crotylations, and these results are tabulated in Table 2, eq 2.

Changing the oxazolidinone template (**1**) to a pyrrolidinone (**4**) gave a slight improvement in yield; however, there was no improvement in diastereoselectivity (compare entry 1 with 2). Similar levels of selectivity were observed with the *N*-phenylimidazolidinone template **5** (entry 3). In contrast, benzoxazolidinone (**6**)- and 3,5-dimethylpyrazole (**7**)-derived substrates gave much lowered selectivity (entries 4 and 5). We have recently shown 1,8-naphthosultam is a superior auxiliary in enantioselective H-atom transfer reactions.[13] However, compound **8** showed only moderate reactivity and the diastereoselectivity was lower than that observed with substrates **1** and **4** (compare entry 6 with 1 or 2).

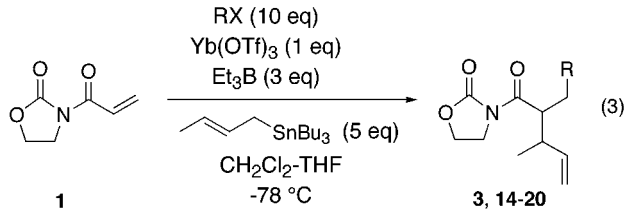
Rheault, T. R. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, Chapter 4.5. (e) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. (f) Nguyen, P. Q.; Schäfer, H. J. *Org. Lett.* **2001**, *3*, 2993.

(11) Crotylstannane was >98% (*E*)-configuration.

(12) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029.

(13) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984 and references therein.

Table 3. Effect of Substituents on Radical Allylation



entry	RX	product	yield (%)[a]	dr[b]
1	EtI	**3** R = Et	68	3.5:1
2	$MeOCH_2Br$	**14** R = $MeOCH_2$	48	2.0:1
3	*i*-BuI	**15** R = *i*-Bu	63	2.6:1
4	*n*-Bu	**16** R = *n*-Bu	58	3.4:1
5	*i*-PrI	**17** R = *i*-Pr	63	3.0:1
6	c-hexyl I	**18** R = c-hexyl	62	3.5:1
7	adamantyl I	**19** R = adamantyl	69	5.6:1
8	*t*-BuI	**20** R = *t*-Bu	75	5.4:1

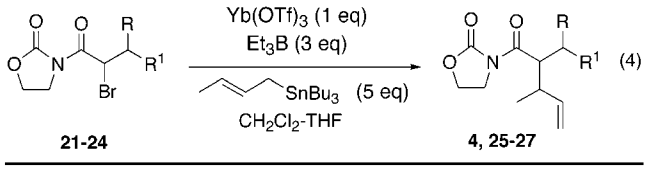
[a] Isolated yield. [b] Diastereomer ratio was determined by ^{1}H NMR (500 MHz).

With the reaction conditions for the crotylation established, the scope of the reaction was examined using various radical precursors, and these results are presented in Table 3, eq 3. As can be discerned form the table, primary, secondary, tertiary, and α-alkoxyalkyl radicals all gave the addition/trapping product in good yields (entries 1−8). It is interesting to note that the size of the radical precursor had a large impact on the diastereoselectivity: the adamantyl (entry 7) and *tert*-butyl radicals (entry 8) gave the highest selectivities of 5.6:1 and 5.4:1, respectively.[14]

To determine if the method of formation of the radical intermediate affects the reaction, we have examined the crotylation of the bromides **21**−**24** with crotylstannane (Table 4, eq 4). The allylation reactions proceeded with slightly better efficiency (entries 1−5) than those reported for reactions with **1**. The formation of **3** with comparable selectivity (3.5:1 vs 2.9:1; compare entry 1, Table 3, and entry 3, Table 4) from two different radical precursors suggests that the method of formation may have a small influence on the stereochemical outcome. Similarly, the substituent on the radical once again shows an impact on selectivity.[15] Interestingly, increasing bulk near the reaction center led to nearly equal amounts of diastereomers (entry 4) and temperature had little impact on the levels of selectivity (compare entry 4 with 5). The low selectivity in crotylations of **24** is in contrast to the formation of **3** with moderate selectivity.[16]

We have recently shown that steric effects play a minor role in determining the levels of diastereoselectivity in the addition of prochiral radicals to prochiral acceptors.[17] The stereochemistry for **16** and **26** was determined by hydrolysis to the corresponding carboxylic acids. The syn configuration for the major product was assigned by comparison of spectral characteristics of the acids with those of known compounds.[18] In the present work, the formation of the syn diastereomer with moderate selectivity as the major product can be rationalized through an open transition state **A** shown in Figure 1.[19] An alternative transition state **B** leading to the anti product has a slightly more severe gauche interaction between the methylene group of the allyl tin moiety and the

Table 4. Crotylations of α-Bromo Acyloxazolidinones



entry	starting material	temp °C	product	yield (%)[a]	dr[b]
1	**21** R = R^1 = H	−78	25	78	3.0:1
2	**22** R = H, R^1 = Me	−78	26	78	2.1:1
3	**23** R = H, R^1 = Et	−78	3	85	2.9:1
4	**24** R = R^1 = Me	20	27	74	1:1
5	**24** R = R^1 = Me	−78	27	82	1.2:1

[a] Isolated yield. [b] Diastereomer ratio was determined by ^{1}H NMR (500 MHz).

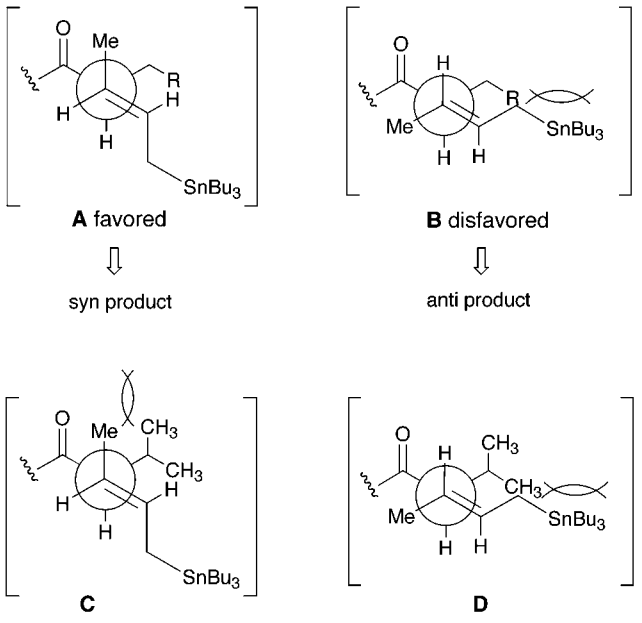


Figure 1. Transition states for diastereoselective crotylations.

(14) (a) The size of the exocyclic substituent has been shown to have an impact on H-atom transfer reactions: Giese, B.; Damm, W.; Witzel, T.; Zeitz, H.-G. *Tetrahedron Lett.* **1993**, *34*, 7053. (b) For effect of radical size on enantioselective H-atom transfer, see: Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293. (c) For steric effects on enantioselective allylations, see: Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067.

(15) We have recently shown that temperature and precursor stereochemistry impact selectivity in allylation reactions. See: Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873. For variation in enantioselectivity with changes in the formation of the radical intermediate, see ref 14c.

(16) Tandem ethyl radical addition−crotylation to the analogue of **1** gave **29** (R = Et, R^1 = Et) with a similarly low 1.4:1 level of diastereoselectivity.

(17) Sibi, M. P.; Rheault, T. R.; Chandramouli, S. V.; Jasperse, C. P. *J. Am. Chem. Soc.* **2002**, *124*, 2924.

R substituent on the radical. This analysis is consistent with the observed higher selectivity with larger R groups: the *tert*-butyl and adamantyl radical additions gave 5.4:1 and 5.6:1 selectivities, respectively (entries 6 and 7, Table 3). In reaction with **24**, severe gauche interactions in both transition states **C** or **D** lead to nearly equal amounts of the syn and anti products. Thus, a secondary substituent on the radical gives better selectivity (increasing with the size of R)[14c] than a tertiary substituent (R and R^1 = alkyl). At the present, time we do not have a clear explanation for the selectivity dependence on the achiral template (contrast entries 1−3 with 4 and 5, Table 2).

In conclusion, we have shown that allylation of electrophilic radicals with crotylstannane is efficient and the diastereoselectivity in the reaction is modest. It is important to note that the present methodology is a complementary method to Claisen protocols for the synthesis of γ,δ-unsaturated carboxylic acid derivatives.[20] The extension of the present methodology to γ-alkoxy stannanes and the development of procedures for enantiocontrol in the crotylation reaction are underway in our laboratory.

Acknowledgment. This work was supported by a grant from the National Institutes of Health NIGMS-54656. Hideto Miyabe thanks JSPS for a postdoctoral fellowship.

Supporting Information Available: Characterization data for compounds **1**−**28** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026510A

(18) Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *46*, 12631.

(19) Both antiperiplanar and synclinal transition states have been proposed for Lewis acid-catalyzed addition of crotylstannanes to aldehydes. For recent reviews on this subject, see: (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Denmark, S. E.; Almstead, N. A. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10, pp 299−401.

(20) For Claisen rearrangements leading to products with structures similar to those reported here, see: (a) ref 18. (b) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158. (c) Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728.