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Intramolecular Aminyl and Iminyl Radical Additions to α,β-Unsaturated Esters. Diastereoselective Tandem Cyclofunctionalization and Hydrogen Transfer Reactions

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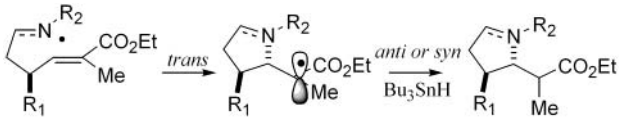
ABSTRACT



R_1 = electron-donating or electron-withdrawing group; no R_2 for iminyl radical

A tandem process featuring intramolecular aminyl radical cyclofunctionalization and hydrogen transfer affords 2,3-*trans*-disubstituted pyrrolidines with *anti* or *syn* diastereoselectivity. The extension of this strategy to iminyl radicals gives *trans-anti* pyrrolenines with high levels of 1,2-induction in both steps of the tandem process.

Diastereoselective radical processes involving acyclic substrates have attracted considerable interest in recent years.[1] Our group has focused in particular on atom and group transfer reactions of radicals flanked by an ester and a stereogenic center bearing an electron-withdrawing atom such as an oxygen.[2] We have shown that such carbon-centered radicals can be generated from the intramolecular delivery of an alkoxyl radical to an α,β-unsaturated ester.[3] This strategy, in combination with the hydrogen transfer reaction, has been effective in affording 2,3-*trans*-disubstituted tetrahydrofurans by the creation of two new contiguous stereogenic centers with high levels of 1,2-induction in both tandem steps.[3] The present study extends the tandem radical cyclofunctionalization/hydrogen transfer reactions for the preparation of five-membered azacycles using aminyl or iminyl radicals (Figure 1).[4] To determine the scope and limitations of this approach, different R_1 (allylic position of

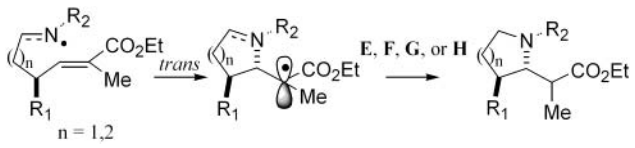


Figure 1. Tandem aminyl and iminyl radical cyclofunctionalization/hydrogen transfer reations.

(1) For reviews, see: (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296−304. (b) Smadja, W. *Synlett* **1994**, 1−26. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions − Concepts, Guidelines and Synthetic Applications*, VCH: New York, 1995. (d) *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: 2001; Vol. 1. (e) Stella, L. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: 2001; Vol. 2, pp 407−426.

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the olefin) and R_2 groups (on the nitrogen for the aminyl series only) are considered. Benzothiazolylsulfanylamines and benzothiazolylsulfanylimines,[5] which are stable enough for purification by flash chromatography and long-term storage, are used as precursors to generate the nitrogen-based free radicals.

The proposed transition states for the aminyl cyclofunctionalization reaction are illustrated in Figure 2. Preferred

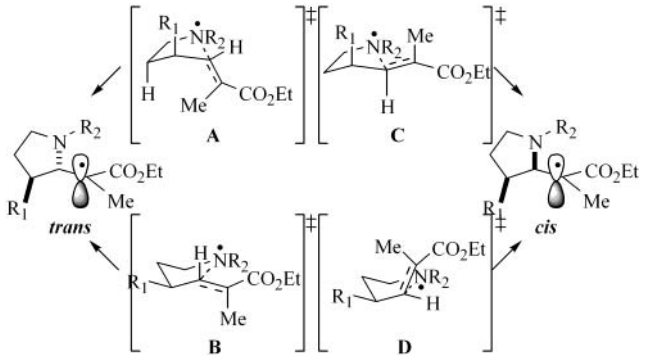

Figure 2. Proposed transition states for the aminyl cyclofunctionalization step.

trans diastereoselectivity originates from the minimization of allylic 1,3-strain imposed by the allylic R_1 and the methyl of the trisubstituted double bond. The transition states leading to the 2,3-*trans* pyrrolidine appear either only slightly disfavored by one gauche interaction in **A** or free of destabilizing interactions in **B**. The *cis*-predictive transition states are less favored. **C** suffers from two gauche interactions, while **D** is destabilized by allylic interaction between R_1 and the methyl group of the olefin. Similar transition states could be proposed for the cyclization with iminyl radicals.

Reduction of the carbon-centered radical, generated from the cyclization of either an aminyl or an iminyl radical, should proceed under the control of the exocyclic effect.[2a,6] The radical facial preference of the hydrogen transfer reaction is rationalized by *anti*-predictive transition states **E** (R_2 = H) and **F**, wherein allylic 1,3-strain and the dipole effect have been minimized (Figure 3). These transition states should be even more favored through σ-donation,[2b] when an electron-donating R_1 group is involved, allowing for a greater ratio favoring the *anti* product. An electron-withdrawing R_1 would have the opposite effect, increasing the energy of these *anti*-predictive transition states and thus decreasing the predominance of the *anti* product.

In the pyrrolidine series, a reversal of diastereoselectivity should be possible with a more sterically encumbered R_2,

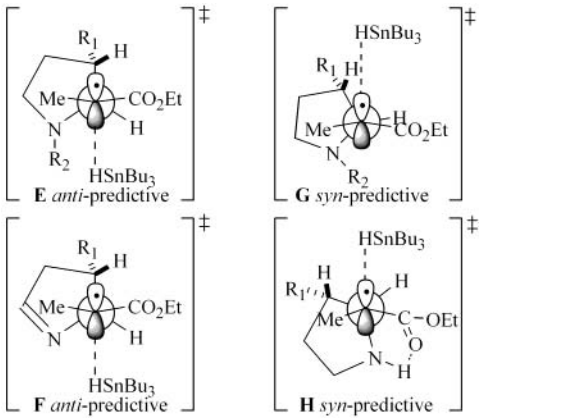

Figure 3. Proposed transition states for the hydrogen transfer step.

which can impede the tributyltin hydride (Bu_3SnH) attack on the bottom face of the molecule, thus favoring *syn* predictive transition state **G** (Figure 3).

Kinetic studies by Newcomb[7] and others[8] have indicated that 5-aminyl pentenes in the presence of Bu_3SnH have a slow rate of cyclization that is very similar to the rate of reduction of nitrogen radicals by Bu_3SnH. Poor yield is generally obtained in such reactions. The nucleophilic character of the aminyl radical seems to be at the origin of the slow rate of cyclization. It has been shown, for aminyl radicals, that the rate of cyclization can be increased very significantly by the addition of a Brönsted[9] or Lewis acid.[10] These agents, through protonation or complexation, contribute to an increase in the electrophilicity of the nitrogen, which results in a faster cyclization rate on an electron rich double bond.

A more favorable rate of cyclization was expected for the present study given the fact that electron poor olefins were involved, which would allow for a better match of reactivity with the nucleophilic nitrogen-based radical. Furthermore, the presence of the ester would stabilize the carbon-centered radical formed (Figure 2).[2] Of concern was whether the rate of cyclization would be accelerated enough to compete efficiently with the rate of nitrogen reduction by Bu_3SnH. To favor the cyclization, a low concentration of reducing agent was maintained in the reaction mixture for all of the reactions performed.[11]

The olefins needed for the tandem reactions in this study were realized using well-known chemistry.[12] The benzothia-

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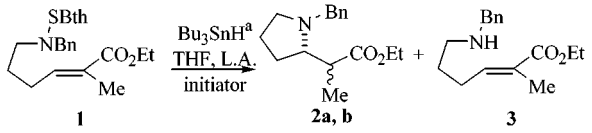
(10) Ha, C.; Musa, O. M.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 2704.
(11) Bu_3SnH was added slowly to the reaction mixture through a syringe-driven pump.
(12) See Supporting Information.

zolylsulfanylamines and benzothiazolylsulfanylimines were obtained by treatment of the corresponding amines or imines with benzothiazole chloride[13] and Et_3N in Et_2O at 0 °C. The tandem reactions were then performed by slow addition of Bu_3SnH to a THF solution of *N*-benzothiazolylsulfanylbenzylamine **1**, and Et_3B was used as the initiator of the free radical chain. The first result was very encouraging since the cyclized product was obtained, attesting to the importance of the electronic nature of the double bond involved in this reaction (Table 1, entry 1).

Table 1. Effects of the Radical Initiator and Lewis Acid (L.A.) on Radical Cyclization of Benzothiazole **1**



1 **2a, b** **3**

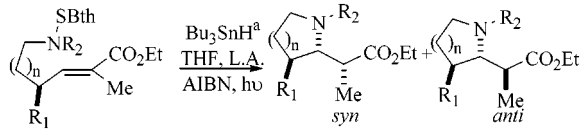
entry	initiator	L.A. (equiv)	ratio[b] **2a**,**b**:**3**	yield[c] (%)
1	Et_3B	none	3:1	54
2	Et_3B[d]	none	2:1	41
3	Et_3B	$BF_3{\cdot}OEt_2$ (1)[e]	1:>20	<5
4	AIBN, *hν*[f]	none	>20:1	74

[a] Conditions: to a solution of **1** (0.03M) in THF was slowly added 0.2 equiv of Bu_3SnH (0.3M) over 3 h via syringe pump. Initiation was accomplished using 0.2 equiv of Et_3B. [b] Ratios of crude product mixtures were determined by ^1H NMR. [c] Isolated yields of cyclized reduced products. [d] 1 equiv of Et_3B was used. [e] To substrate **1** in THF were successively added $BF_3{\cdot}OEt_2$, Bu_3SnH, and Et_3B. [f] Initiation was done using 0.15 equiv of AIBN/30 min, followed by 10 min irradiation (*hν*).

A close evaluation of the reaction indicated that a significant amount of benzylated amine **3**, the *N*-reduced product, was also present in the reaction mixture in a ratio of 3:1 favoring the cyclized product. Interestingly, increasing the amount of initiator altered the result from a 3:1 ratio with 0.2 equiv of Et_3B to a 2:1 ratio with 1 equiv of Et_3B (cf. entries 1 and 2). This suggested that the Et_3B, a weak Lewis acid, could have been responsible for increasing the electrophilicity of the aminyl radical through coordination of the nitrogen, thus accelerating the nitrogen reduction pathway. To determine the degree of impact of Lewis acid on this type of cyclization, 1 equiv of $BF_3{\cdot}OEt_2$ was added to the reaction mixture. As seen in entry 3, no cyclized product was observed, which indirectly supported the fact that Et_3B, by its Lewis acid nature, had had a deleterious effect on this reaction. This was further confirmed by the replacement of Et_3B with AIBN, which led to a significant increase in yield and a >20:1 ratio of cyclized:noncyclized products (entry 4).

We were then poised to study the effect of the R_1 and R_2 groups on the free radical hydrogen step. As seen in Table 2, only a modest 3:1 ratio in favor of the *syn* product was obtained when R_2 = Bn (entry 1). This suggested that the difference in energy between the two proposed transition

Table 2. Tandem Aminyl Radical Cyclofunctionalization and Hydrogen Transfer Reactions



entry	substrate	*syn*:*anti* product	*syn*:*anti* ratio[b]	yield[c] (%)
1	**1**, R_1 = H, R_2 = Bn, n = 1	**2a**:**2b**	3:1[d]	74
2	**4**, R_1 = H, R_2 = *i*Pr, n = 1			*e*
3	**5**, R_1 = H, R_2 = *t*Bu, n = 1			*e*
4	**6**, R_1 = H, R_2 = (1*S*)-phenylethyl, n = 1			*e*
5	**7**, R_1 = H, R_2 = Bn, n = 2			*e*
6	**8**, R_1 = Me, R_2 = Bn, n = 1[f]	**9a**:**9b**	1:1	74
7	**10**, R_1 = OMe, R_2 = Bn, n = 1[f]	**11a**:**11b**	2:1	56
8	**12**, R_1 = F, R_2 = Bn, n = 1[g]	**13a**:**13b**	2:1	67
		14a:**14b**	2:1	
9	**15**, R_1 = H, R_2 = H, n = 1	**2a**:**2b**	1:1[d,h]	68
10	**16**, R_1 = Me, R_2 = H, n = 1[f]	**9a**:**9b**	1:3[d,h]	74
11	**16**, R_1 = Me, R_2 = H, n = 1[f]	**9a**:**9b**	3:1[h,i]	85

[a] Conditions: to a solution of substrate (0.03M) in THF was slowly added 0.2 equiv of Bu_3SnH (0.3M) over 3 h via syringe pump. Initiation was accomplished using 0.15 equiv of AIBN/30 min, followed by 10 min irradiation (*hν*). [b] Ratios of crude product mixtures were determined by ^1H NMR. [c] Isolated yields of cyclized reduced products. [d] Reaction was performed at −23 °C. [e] Only noncyclized reduced product was observed. [f] Only *trans*-cyclized (20:1) product was obtained. [g] 4:1 ratio of *trans*-cyclized (**13a**,**b**):*cis*-cyclized (**14a**,**b**) products was determined by GC on the crude reaction mixture. [h] The crude mixture was treated with BnBr and Et_3N in CH_3CN, and the ratio was determined on the benzylated products. [i] The reaction was performed in cyclohexane.

states **E** and **G** was small (Figure 3) and further indicated that the presence of the benzyl moiety on the nitrogen had been able to raise the energy of, and thus disfavor, the *anti*-predictive transition state **G** by impeding the bottom face Bu_3SnH attack. Increasing the steric factor of R_2 in the pyrrolidine series to raise the energy of transition state **G** seemed, therefore, a plausible approach to increasing the ratio in favor of the *syn* product. Unfortunately, this hypothesis could not be verified because the *i*-Pr, *t*-Bu, and (1*S*)-phenethyl aminyl radicals did not cyclize (entries 2−4). The results pointed to the fact that, although an α,β-unsaturated ester was used, the rates of cyclization and nitrogen reduction had remained very close (Figure 2). Supporting this was the fact that the formation of the six-membered ring did not occur in the *N*-benzylpyrrolidine series (entry 5).[14]

In the same series, neither the electron-donating group Me (entry 6) nor the electron-withdrawing groups OMe or F (entries 7, 8) at the R_1 position significantly changed the *anti* or *syn* selectivity of the radical hydrogen transfer reaction. However, these results were significant as they confirmed the importance of R_1 in inducing the *trans* relative stereochemistry between the C−R_1 bond and the resultant C−N bond during the aminyl radical cyclofunctionalization

(13) The benzothiazole chloride was prepared with 2,2′-dithiobisbenzothiazole and oxalyl chloride. See ref 5.

(14) The 1,5-H transfer was not implicated in this reaction since the use of Bu_3SnD did not give deuteration of the carbon α to the double bond.

step. With Me or OMe as R_1 (entries 6 and 7), excellent ratios >20:1 in favor of the *trans* product were obtained. A lower *trans*:*cis* ratio of cyclized products was achieved when R_1 = F (4:1, entry 8), supporting our rationale that allylic 1,3-strain was the controlling factor of the relative stereoselectivity of the reaction. Indeed, this lower ratio can be accounted for by the size of the fluorine being only slightly bigger than that of a hydrogen, which in this case led to a less substantial difference in energy between transition states **A**, **B**, **C**, and **D** (Figure 2).

At this stage of the study, we knew that the cyclofunctionalization reaction occurred with excellent stereocontrol but that the *N*-benzyl substituent was not so effective in favoring the *syn* attack. To be determined next was whether an *anti* preference could be reestablished by decreasing the size of R_2, favoring transition state **E**. As seen in entries 9 and 10, reactions with R_2 = H gave disappointing *anti* diastereoselectivity when R_1 = H or Me. These results were very different from those of the tetrahydrofuran series where an *anti*:*syn* ratio of 16:1 was obtained at 23 °C.[3] A competitive pathway involving a H-bond between the hydrogen on the amine and the carbonyl of the ester[15] (*syn* predictive transition state **H**, Figure 3) was likely responsible for the lower diastereoselectivity observed in the pyrrolidine series. To support this hypothesis, we conducted a hydrogen transfer reaction using a less polar solvent aimed at favoring the formation of an intramolecular H-bond. With cyclohexane, a *syn*:*anti* ratio of 3:1 was obtained (entry 11), suggesting that the competition between the endocyclic (intramolecular hydrogen bonding, transition state **H**) and the exocyclic (transition state **E**) pathways might have occurred.

Considered next was the iminyl radical, a reactive intermediate that has emerged, in terms of application, mainly from the work of Zard.[16] This radical is known to be more electrophilic than the aminyl radical in cyclization reactions while being less susceptible to reduction by Bu_3SnH. We believed that the pyrrolenine, as a heterocycle, would offer the appropriate characteristics to promote *anti* diastereoselectivity during the reduction step, considering that the nitrogen bears no substituent nor the capacity to hydrogen bond with the ester as was the case with the pyrrolidine heterocycles.

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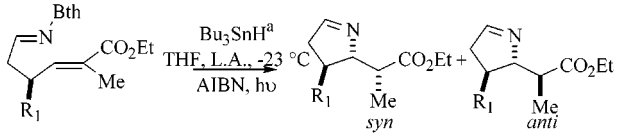
Table 3. Tandem Iminyl Radical Cyclofunctionalization and Hydrogen Transfer Reactions



		syn:*anti*		
entry	substrate	product	ratio[b]	yield[c] (%)
1	**17**, R_1 = H	**18a**:**18b**	1:9	83
2	**19**, R_1 = Me	**20a**:**20b**	1:16	84
3	**21**, R_1 = OMe	**22a**:**22b**	1:7	78

[a] Conditions: to a solution of substrate (0.03M) in THF was added slowly 2 equiv of Bu_3SnH (0.3M) over 3 h via syringe pump. Initiation was accomplished using 0.15 equiv of AIBN/30 min, followed by 10 min irradiation ($h\nu$). [b] Ratios of crude mixture products were determined by ^1H NMR. [c] Isolated yields of cyclized reduced products.

As seen in Table 3, the cyclization was successful in terms of both yield (entries 1−3) and the *trans* selectivity obtained (entries 2−3), attesting that the iminyl radicals could, like the aminyl radicals (with R_1 = Me or OMe), be analyzed using models derived from allylic 1,3-strain (Figure 2). The high *anti* ratio of the hydrogen transfer step indicated that transition state **F** (Figure 3) was clearly favored. As expected, this ratio had been increased by an electron-donating group (R_1 = Me, entry 2) and decreased by an electron-withdrawing group (R_1 = OMe, entry 3).[2b]

The iminyl radical is showing promise of being a very interesting intermediate in tandem reactions involving cyclofunctionalization and hydrogen transfer. We plan to take advantage of the properties of the iminyl radical in future studies involving other chemical transformations.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**2**, **4**−**22**; determination of relative configuration; and NMR spectra for compounds **1**, **7**, **15**, **17**, **2a**,**b**, **3a**, **14b**, **18a**,**b**, **20a**,**b**, and **22a**,**b**; and X-ray structure of **27b** derivatized from pyrrolenine **22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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