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Intermolecular Nonreductive Alkylation of Enamides via Radical−Polar Crossover

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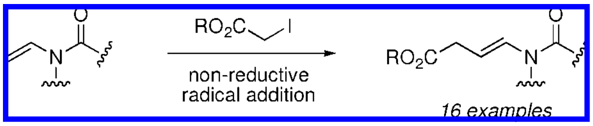
ABSTRACT



A carbon−carbon bond construction method is disclosed which involves radical addition of α-haloesters or iodoacetonitrile to enamides. Despite the presence of tri-*n*-butylstannane, nonreductive addition was predominant; H-atom transfer from tin hydride was not observed. Rapid iodine atom transfer to (or electron transfer from) the radical adduct, resulting in an iminium ion intermediate and radical chain propagation, is consistent with the observed reactivity.

Carbon−carbon bond constructions via free radical addition reactions offer practical advantages in chemoselectivity which complement ionic methods[1] and are amenable to development of tandem processes involving multiple bond-forming events.[2] Developments in the application of radical additions to synthesis of chiral amines have been progressing over the past few years, mainly through radical additions to the carbon of imino compounds.[3] An alternative approach could entail addition to enamines or enamides, such that the resulting α-amino- or α-amidoalkyl radical could be trapped to generate a chiral α-branched amine.[4] This process would generate two C−C bonds and a stereocenter (Figure 1), and more substituted cases with two or more stereocenters could also be easily envisioned with appropriate substitution of the enamine, R^1, and R^3. Proper matching of the electronic properties of the coupling components would be required, such that addition of R^1 to the enamine would occur, rather than direct reaction of R^1 with R^3 or polymerization.[5]

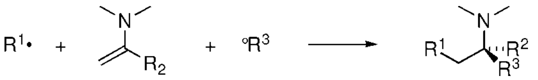


Figure 1. Hypothesized tandem C−C bond construction approach to chiral *tert*-alkylamines. The open circle of °R^3 denotes radical acceptor behavior.

Examples of intermolecular radical additions to enamines and enamides are known,[6] but with the exception of

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(1) (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: New York, 2001. (b) Zimmerman, J.; Sibi, M. P. In *Topics in Current Chemistry: Radicals in Synthesis I*; Gansauer, A., Ed.; Springer: Berlin, 2006; Vol. 263, pp 107−162.

(2) Reviews: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2225–2248. (b) Albert, M.; Fensterbank, L.; Lacote, E.; Malacria, M. In *Topics in Current Chemistry: Radicals in Synthesis II*; Gansauer, A., Ed.; Springer: Berlin, 2006; Vol. 264, pp 1−62. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186.

(3) Reviews: Friestad, G. K. *Eur. J. Org. Chem.* **2005**, *315*, 7–3172. Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140–1157. Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461–5496.

(4) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913–926.

(5) Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063–2066.

(6) (a) Renaud, P.; Schubert, S. *Synlett* **1990**, 624–626. (b) Russell, G. A.; Kulkarni, S. V.; Khannat, R. K. *J. Org. Chem.* **1990**, *55*, 1080–1086. (c) Russell, G. A.; Wang, K. *J. Org. Chem.* **1991**, *56*, 3475–3479. (d) Renaud, P.; Carrupt, P.; Schenk, K.; Schubert, S. *Synlett* **1992**, 211–213. (e) Renaud, P.; Schubert, S.; Carrupt, P.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473–2489. (f) Curran, D. P.; Eichenberger, E.; Collis, M.; Roepel, M. G.; Thoma, G. *J. Am. Chem. Soc.* **1994**, *116*, 4279–4288. (g) Chuang, C.-P.; Wu, Y.-L. *Tetrahedron* **2004**, *60*, 1841–1847. (h) Tsai, A.-I.; Chuang, C.-P. *Tetrahedron* **2006**, *62*, 2235–2239. (i) Aurrecoechea, J. M.; Coy, C. A.; Patiño, O. J. *J. Org. Chem.* **2008**, *73*, 5194–5197.

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numerous additions to dehydroalanine and related amino acids,[7] these reactions have rarely been applied in general synthetic methods. Two instructive precedents illustrate the potential for generating nitrogen-bearing stereocenters in the course of C−C bond construction (Figure 2). Renaud and Schubert examined the stereocontrol in additions of sulfonylmethyl radical to chiral enamines followed by H-atom transfer (Figure 2a)[6a] and Curran et al. reported addition of methylmalononitrile radical to *N*-vinylpyrrolidinone (Figure 2b) as part of a broader study of phenylselenenyl group transfer additions to electron-rich alkene acceptors.[6f]

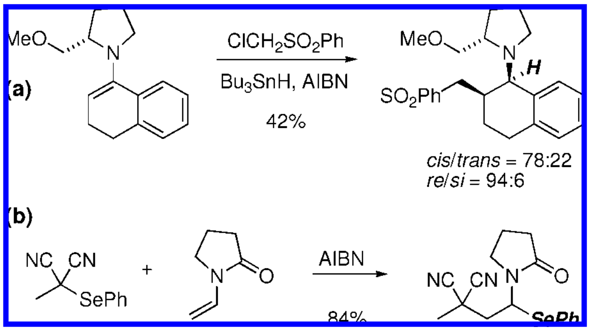
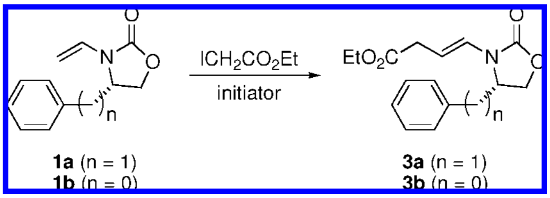


Figure 2. Instructive precedents: (a) addition to enamine followed by H-atom transfer;[6a] (b) addition to enamide followed by SePh group transfer.[6f]

Despite these precedents, our experiments directed toward the tandem C−C bond construction concept outlined in Figure 1 took a rather different course, leading to the discovery of an efficient nonreductive coupling of α-haloesters and enamides. The net result is reminiscent of the Heck reaction, essentially accomplishing a substitution of an alkenyl hydrogen of enamides by an organic halide. Here we report discovery and development of conditions to accomplish this interesting transformation, along with some mechanistic control experiments and a preliminary evaluation of the scope.

In considering potential substrates for an experimental test of Figure 1, we noted a considerable body of evidence regarding reactivity, conformation, and stereocontrol of alkenyl oxazolidinones,[8] as well as their ease of preparation.[9,10] Mindful of the electronic character of these enamides, for initial screening we selected the addition of the moderately electron-deficient radical derived from ethyl α-iodoacetate to *N*-vinyl-4-benzyloxazolidinone **1a**.[10]

Table 1. Initial Results for Radical Addition of Ethyl Iodoacetate to Vinyloxazolidinones

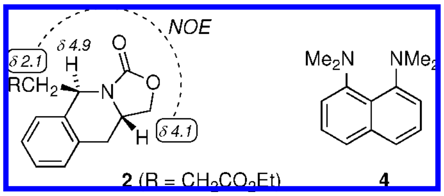


1a (n = 1)
1b (n = 0)
3a (n = 1)
3b (n = 0)

entry	alkene	method	base (equiv)	iodide, equiv	yield (%)
1	**1a**	A	none	3	0[b]
2	**1b**	A	none	3	31
3	**1a**	B	none	3	45
4	**1a**	B	NEt_3 (1)	3	69
5	**1a**	B	**4** (1)	3	69
6	**1a**	B	NEt_3 (0.5)	3	76
7	**1a**	B	NEt_3 (0.5)	10	63
8	**1a**	B	NEt_3 (0.5)	1.3	57
9	**1a**	B[c]	NEt_3 (0.5)	3	36
10	**1a**	B[d]	NEt_3 (0.5)	3	0
11	**1a**	B[e]	NEt_3 (0.5)	3	6

[a] Conditions: (method A) Et_3B, CH_2Cl_2, −78 °C, slow addition of O_2 over 5 h then warm to rt; (method B) slow addition of AIBN and Bu_3SnH over 10 h, PhH, reflux. [b] Cyclized product **2** (48% yield) was obtained. [c] Portionwise addition of AIBN and Bu_3SnH. [d] Bu_3SnH and AIBN omitted. [e] Galvinoxyl was added (1 equiv).

In the initial reactions, addition to **1a** with triethylborane as the initiator was accompanied by a substitution of the aromatic ring in the pendant benzyl group, leading to the cyclized product **2** as a single diastereomer (Table 1, entry 1). This cyclization was not observed with the phenyloxazolidinone **1b**;[10] instead this reaction gave nonreductive addition product **3b** in modest yield (entry 2). This differential reactivity for 5- versus 6-membered ring formation may be mechanistically relevant (vide infra).



2 (R = CH_2CO_2Et)
4

We next examined the typical reductive addition conditions using tri-*n*-butylstannane (Bu_3SnH). With 0.5 equiv of azobisisobutyronitrile (AIBN) and 2 equiv of Bu_3SnH as the initiating system, the addition of ethyl iodoacetate to **1a** gave **3a**, the product of nonreductive addition (Table 1, entry 3); the yield diminished to 26% using 1.2 equiv of Bu_3SnH. The modest yields appeared to be a consequence of hydroly-

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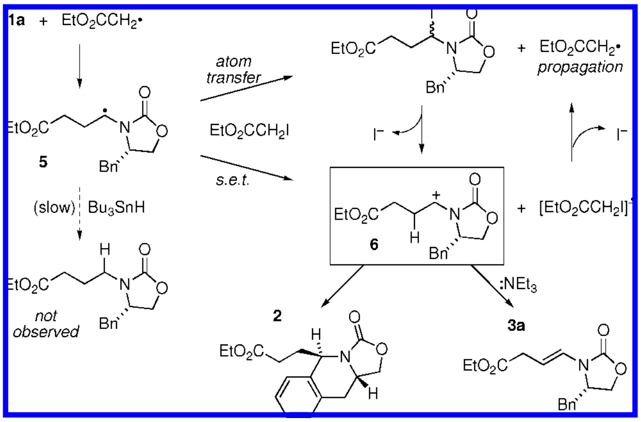
(7) For examples, see: Crich, D.; Davies, J. W. *Tetrahedron* **1989**, *45*, 5641–5654. Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1087–1088. Chai, C. L. L.; King, A. R. *Tetrahedron Lett.* **1995**, *36*, 4295–4298. Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron: Asymmetry* **2002**, *13*, 503–510. Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 385–393.

(8) For examples, see: Epoxidation: (a) Adam, W.; Bosio, S. G.; Wolff, B. T. *Org. Lett.* **2003**, *5*, 819–822. Hetero-Diels−Alder: (b) Dhal, R.; Dujardin, G. *Org. Lett.* **2007**, *9*, 211–214. Hydrogenation: (c) Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T *Tetrahedron Lett.* **2002**, *43*, 7941–7943. Oxidative cleavage: (d) Sivaguru, J.; Solomon, M. R.; Turro, N. J *Tetrahedron* **2006**, *62*, 6707–6717[2 + 2]-Cycloaddition: (e) Hegedus, L. S.; Bates, R. W.; Soderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923–927. Cyclopropanation: (f) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069–4072.

(9) (a) Jiang, L.; Job, G. E.; Klapers, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669. (b) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996–12997. (c) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848. (d) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809–1812.

(10) (a) Gaulon, C.; Gizecki, P.; Dhal, R.; Dujardin, G. *Synlett* **2002**, 952–956. (b) Gaulon, C.; Dhal, R.; Dujardin, G. *Synthesis* **2003**, 2269–2272.

Scheme 1



sis,[11] which suggested that an improved result might be obtained by buffering the reaction mixture with a basic additive. Indeed, a significant improvement, up to 76% yield, was observed in the presence of amine bases (triethylamine and proton sponge (**4**), entries 3−6). Larger or smaller excesses of iodide led to no improvement (entries 7 and 8), and slow addition of AIBN and Bu_3SnH afforded superior results (compare entries 6 and 9).

In all these reactions, there was no detected formation of the saturated adduct analogous to **3a**, predicted by the hypothesis in Figure 1 via H-atom abstraction from Bu_3SnH according to the precedent of Figure 2a. While this was unexpected, nonreductive addition to an enamide in the presence of Bu_3SnH has previously been observed in a radical cyclization.[12]

Control experiments examined whether a nonradical pathway could be involved. There was no reaction in the absence of AIBN and Bu_3SnH (entry 10) nor in the presence of AIBN and Bu_3SnH at ambient temperature. The presence of galvinoxyl suppressed the reaction; at 0.2 equiv of galvinoxyl, the yield was diminished to 40% (not shown), and at stoichioimetric quantities, galvinoxyl largely suppressed the reaction (entry 11).

The formation of the nonreductive addition product **3a**, together with the control experiments and observation of cyclized product **2**, suggests the mechanism proposed in Scheme 1. The addition of ethoxycarbonylmethyl radical to **1a** would afford α-amido radical **5**, which would then react with ethyl iodoacetate, either by iodine atom transfer[13] or by single electron transfer.[6b,c,12] Each of these alternatives would ultimately provide iminium ion **6** while propagating a radical chain. The absence of the saturated product of H-atom transfer from Bu_3SnH to **5** indicates this reduction is slow relative to either the iodine atom transfer or electron transfer. Common intermediate **6** can explain the formation of both **2** and **3a**: Intramolecular Friedel−Crafts reaction at the ortho position of the benzyl group of **6** would provide **2**,[12,14] and simple proton loss from **6** would afford **3a**. The differential reactivity of **1a** and **1b** (Table 1, entries 1 and 2) with respect to cyclization is consistent with precedent regarding iminium ions similar to **6**, produced by another means.[14a] This offers further support for the proposed Friedel−Crafts cyclization mode. Thus, the radical addition is followed by one of two polar reactions in a radical−polar crossover tandem process[15] which offers considerable potential for broadening the scope of the C−C bond constructions outlined here. In particular, formation of **2** accomplishes the general transformation hypothesized in Figure 1, albeit in an unexpected way. Other nucleophilic partners might be expected to serve the role of R^3 in Figure 1, and the fact that **2** forms as a single diastereomer is noteworthy in this broader synthetic context.

Expanding the scope of the nonreductive addition reaction was our next objective. For this purpose, various oxazolidinones **1a−d**[9,10] were subjected to the reaction with ethyl iodoacetate under the optimized conditions, and yields of **3a−d** ranged from 68 to 76% (Table 2, entries 1−4). In nearly the same yields, iodoacetonitrile was also effective in the coupling to furnish nitriles **3e** and **3f** (entries 5 and 6).

The wider availability of bromides could be advantageous to the scope of the reaction, prompting experiments to test whether α-bromoesters could be incorporated, but ethyl bromoacetate gave no reaction (Table 2, entry 7). Fortunately, however, the reaction accommodated the presence of tetrabutylammonium iodide, which conferred the desired reactivity upon ethyl bromoacetate (entry 8), presumably by in situ conversion of the bromide to iodide. A variety of α-bromo esters was then employed in the reaction, affording the nonreductive addition products **3a** and **3g−j** in good yield for primary and secondary halides (entries 9−12). A decreased yield of **3k** was observed with a tertiary bromide (entry 13); this is unsurprising since the added iodide ion

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(11) Loss of the *N*-vinyl group from **3a** was observed, along with byproducts which exhibited aldehyde signals in the ^{1}H NMR.

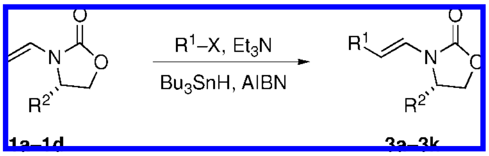
(12) Guerrero, M. A.; Miranda, L. *Tetrahedron* **2003**, *59*, 4953–4958.

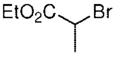
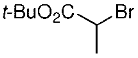
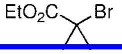
(13) (a) Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265–6276. (b) Thoma, G.; Curran, D. P.; Geib, S. V.; Giese, B.; Damm, W.; Wetterich, F. *J. Am. Chem. Soc.* **1993**, *115*, 8585–8591. (c) Curran, D. P.; Ko, S. B. *Tetrahedron Lett.* **1998**, *39*, 6629–6632.

(14) Closely related cyclizations have been observed previously, using a different method to access the iminium ion: (a) Mecozzi, T.; Petrini, M.; Profeta, R *Tetrahedron: Asymmetry* **2003**, *14*, 1171–1178. (b) Formation of **2** via radical cyclization of **5** followed by oxidative rearomatization by O_2 (method A) has not been ruled out. Cyclization to **2** was not observed with method B. (c) For a related discussion, see: Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706–13707. Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew Chem., Int. Ed.* **2004**, *43*, 95–98. (d) The possibility of AIBN as the oxidant of radical **5** was suggested by a reviewer and has not been rigorously excluded. However, this would be inconsistent with precedent (see ref 14c) as our optimal conditions use low concentrations of AIBN (0.5 equiv, syringe pump addition).

(15) For other types of radical−polar crossover reactions, see: Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A *J. Chem. Soc., Perkin Trans. 1* **1999**, *99*, 5–1001. Jahn, U.; Muller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212–5213. Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791–804. Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419–422. Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043–4046. Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261–4274. Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190–6193. Denes, F.; Cutri, S.; Perez-Luna, A.; Chemla, F. *Chem.—Eur. J.* **2006**, *12*, 6506–6513. Maruyama, T.; Suga, S.; Yoshida, J. *Tetrahedron* **2006**, *62*, 6519–6525. Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S. *J. Am. Chem. Soc.* **2007**, *129*, 1902–1903.

Table 2. Addition to Various *N*-Vinyloxazolidinones[a]



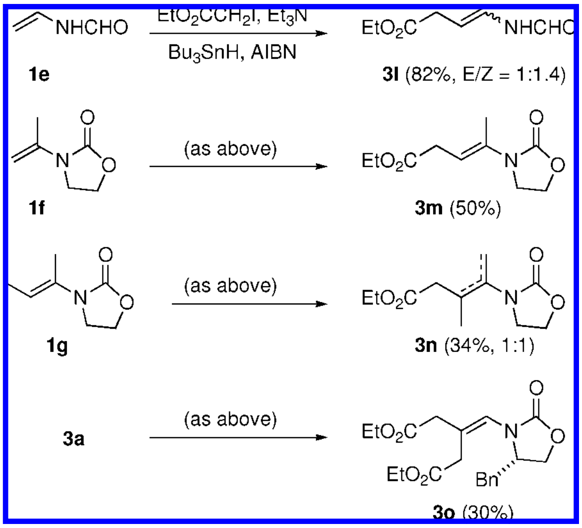
entry	R^1–X	enamide, R^2	product, yield
1	EtO$_2$CCH$_2$I	**1a**, Bn	**3a**, 76%
2	EtO$_2$CCH$_2$I	**1b**, Ph	**3b**, 69%
3	EtO$_2$CCH$_2$I	**1c**, *i*-Pr	**3c**, 72%
4	EtO$_2$CCH$_2$I	**1d**, H	**3d**, 68%
5	NCCH$_2$	**1a**, Bn	**3e**, 67%
6	NCCH$_2$	**1d**, H	**3f**, 66%
7	EtO$_2$CCH$_2$Br	**1d**, H	**3a**, 0%
8[b]	EtO$_2$CCH$_2$Br	**1d**, H	**3a**, 45%
9[b]	*t*-BuO$_2$CCH$_2$Br	**1d**, H	**3g**, 63%
10[b]	PhO$_2$CCH$_2$Br	**1d**, H	**3h**, 65%
11[b]		**1d**, H	**3i**, 58%
12[b]		**1d**, H	**3j**, 60%
13[b]		**1d**, H	**3k**, 22%

[a] Conditions: see Table 1, method B. In some cases, *i*-Pr$_2$NEt was substituted for Et$_3$N. [b] NBu$_4$I (1 equiv) was added.

may be ineffective with tertiary bromides, and the less electron-deficient tertiary radical may have a poorer SOMO–HOMO match with the enamide acceptor.

Finally, the substitution pattern of the alkene was varied (Scheme 2). Commercially available *N*-vinylformamide (**1e**) proved to be a very effective acceptor, furnishing 82% yield of adduct **3l** as a mixture of *E* and *Z* isomers (*E*/*Z* = 1:1.4). The 2-propenyl acceptor **1f**[16] led to adduct **3m** in 50% yield, whereas the (*Z*)-2-butenyl acceptor **1g**[16] gave a lower yield of **3n** (34%) as a mixture of alkene regioisomers. When adduct **3a** (from Table 1) was resubjected to the addition conditions, a second ethoxycarbonylmethyl group was added, leading to **3o**, albeit in only 30% yield. Thus, substitution at the α-carbon of the vinyl group was tolerated, but *β*-substitution diminished the yield.

Scheme 2



In conclusion, an unusual nonreductive coupling of enamides with α-haloesters and iodoacetonitrile is disclosed, a transformation of synthetic equivalence to alkylation of aldehyde enolate.[17] This C–C bond construction reaction appears to involve a radical–polar crossover from α-amidoalkyl radicals to *N*-acyliminium ions en route to the enamide products. Advantageous synthetic utility of the α-amidoalkyl radical and/or the *N*-acyliminium ion intermediate for further bond constructions may be envisioned.[4,13c,18]

Acknowledgment. We thank the University of Iowa and the NSF (CHE-0749850) for support of this work.

Supporting Information Available: Preparative details and characterization data for **2** and **3a–o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Copper-mediated coupling of vinyl halides afforded access to the enamides **1f** and **1g**. See ref 9d.

(17) The results disclosed herein appear to be mechanistically congruent with a remarkable asymmetric alkylation of aldehydes via radical addition to transient chiral enamines, reported in September 2008 during preparation of this manuscript. (a) Nicewicz, D. A.; MacMillan, D. W. C *Science* **2008**, *322*, 77–80. (b) A related radical α-oxidation has also been reported: Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124–4125.

(18) For examples of the synthetic utility of α-amidoalkyl radicals, see: Aurrecoechea, J. M.; Suerro, R.; de Torres, E. *J. Org. Chem.* **2006**, *71*, 8767–8778. Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610–11611. Khim, S.-K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7734–7736. Quirante, J.; Vila, X.; Escolano, C. *J. Org. Chem.* **2002**, *67*, 2323–2328. (b) For synthetic utility of *N*-acyliminimum ions see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.