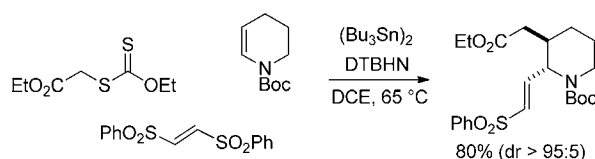# Free-Radical Carbo-alkenylation of Enamides and Ene-carbamates

Clément Poittevin, Virginie Liautard, Redouane Beniazza, Frédéric Robert, and
Yannick Landais*

*Institut des Sciences Moléculaires, Université de Bordeaux, UMR-CNRS 5255, 351,
cours de la libération, 33405 Talence Cedex, France*

y.landais@ism.u-bordeaux1.fr

ABSTRACT

The addition of xanthates and vinyldisulfones across the double bond of enamides and ene-carbamates provides access to the corresponding three-component adducts in good to excellent yields with a high level of diastereocontrol in cyclic systems. This strategy illustrates a complementary reactivity for these versatile olefins and extends their scope of application.

Enamides and ene-carbamates are versatile intermediates for the synthesis of heterocycles, amino acids, and other useful building blocks. Their functionalization using organic and organometallic catalysis has led to intensive research due to their unique reactivity.[1] The presence of an electron-withdrawing carbonyl group on the nitrogen center somewhat reduces the nucleophilicity of the olefinic moiety, as compared to that of their enamine analogues, thus expanding the reactivity scope of this class of olefins. Reactions of enamides and ene-carbamates **I** under ionic conditions generally follow route (a), where the C2 and C1 carbons exhibit, respectively, nucleophilic and electrophilic reactivities (Scheme 1).[2]

In a similar fashion, radical species are known to add efficiently to enamides[3] and ene-carbamates[4] both in intra- and

Scheme 1. Reactivity of Enamides and Ene-carbamates under Ionic and Radical Conditions
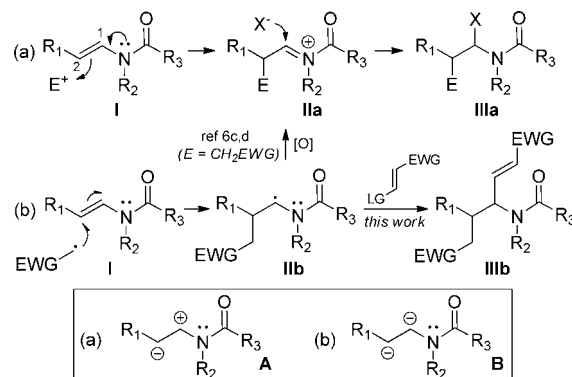
intermolecular fashions (path (b)). The resulting electron-rich radical **IIb** may simply react with a reducing agent (e.g., Bu$_3$SnH) or trap an halogen or a xanthate from the radical precursor in an atom-transfer process.[5] Recent studies have shown that **IIb** may also be oxidized to generate an iminium such as **IIa**, which then reacts following route (a).[6] On the

(1) (a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753–819. (b) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599–4657. (c) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292–301. (d) Gigant, N.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 3304–3307. (e) Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8588–8592. (f) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804–14813.

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(3) (a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84–91. (b) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922–1925. (c) Taniguchi, T.; Ishibashi, H. *Tetrahedron* **2008**, *64*, 8773–8779.

(4) (a) Parsons, A. F.; Williams, D. A. J. *Tetrahedron* **2000**, *56*, 7217–7228. (b) Parsons, A. F.; Williams, D. A. J. *Tetrahedron* **1998**, *54*, 13405–13420. (c) Curran, D. P.; Guthrie, D. B.; Geib, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 8437–8445. (d) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *7*, 1135–1138.

(5) (a) Curran, D. P.; Eichenberger, E.; Collis, M.; Roepel, M. G.; Thoma, G. *J. Am. Chem. Soc.* **1994**, *116*, 4279–4288. (b) Bryans, J. S.; Chessum, N. E. A.; Huther, N.; Parsons, A. F.; Ghelfi, F. *Tetrahedron* **2003**, *59*, 6221–6231. (c) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655–2657.

basis of these premises, it was foreseen that, under suitable (non-oxidative) conditions, the intermediate radical species **IIb** could also react with a third component, e.g., an electron-poor olefin, to generate an addition product **IIIb** in a process where the enamide or the ene-carbamate would exhibit formal polarity as in **B**, thus complementing the polarity **A** generally observed in reactions of these olefins.[2,6] Following our continuous interest in radical multi-component processes[7] and guided by recent progress in this field,[6,7b] we wish to report here on the development of a carbo-alkenylation of various acyclic and cyclic enamides and ene-carbamates, the reactivity of which follows pathway (b) above.

The study began with the examination of the three-component reactions (3-CR) starting from xanthate **1a,b** and acyclic ene-carbamates **2a–f** in the presence of vinyldisulfone **3**[8] (Table 1). The reaction was initiated using di-*tert*-butyl hyponitrite (DTBHN) and (Bu₃Sn)₂ in 1,2-dichloroethane.[7c] Preliminary experiments showed that better results were obtained using 1 equiv of xanthate,[9] 4 equiv of the olefin, and 1.2 equiv of the disulfone. Yields of the 3-CR process were generally good but decreased with the presence of bulky and/or electron-withdrawing substituents on the carbamate moiety (entries 5 and 6, Table 1). Introduction of a substituent α to the nitrogen center as in trisubstituted ene-carbamate **2g** led to no reaction, illustrating the detrimental effect of steric hindrance α to the carbamate moiety.[10] In all cases, the diastereocontrol was very low, contrasting with the observations made during addition of similar radicals to enamines (vide infra).[11]
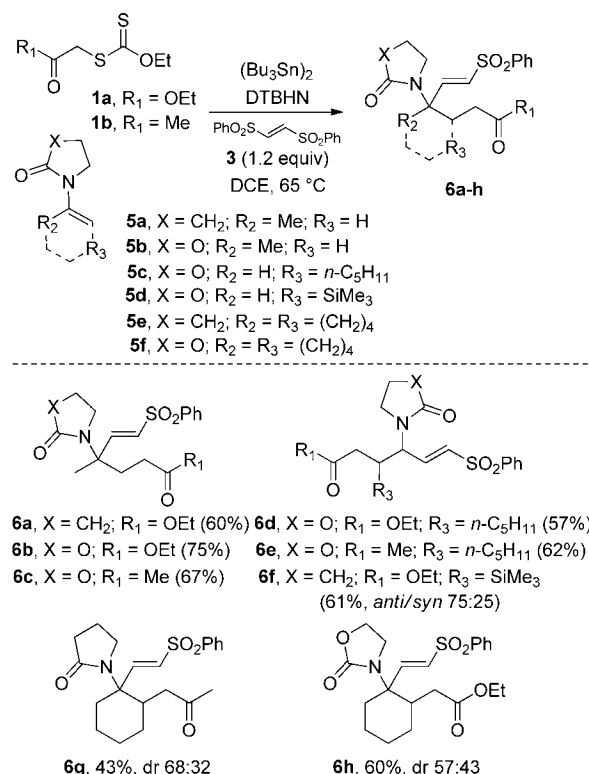
The study was then extended to vinyloxazolidinones and -pyrrolidinones **5a–f** (Scheme 2). We were pleased to observe that the three-component reaction led to the expected products **6a–h** in good yields, whatever the substitution pattern of the olefinic backbone, in contrast with observations made with acyclic systems above (e.g., **2g**). For instance, reaction between **1a**, **3** and **5a,b** led to **6a** and **6b** in 60 and 75% yield, respectively, indicating that the steric hindrance at the proximity of the nitrogen center was reduced with oxazolidinones and pyrrolidinones. As above, no stereocontrol was observed during the formation of **6d–e**. The presence of a bulky SiMe₃ as in **5d** slightly improved the diastereocontrol with the formation of the major *anti* diastereomer **6f**, whose relative configuration was determined on the basis of X-ray diffraction studies on the minor *syn*-isomer (Supporting Information). The reaction was also applied to cyclohexenecarbamates **5e** and amides **5f**, which afforded the corresponding disubstituted cyclohexanes **6g–h** in moderate yields and low stereocontrol.

Scheme 2. Carbo-alkenylation of Vinyloxazolidinones and -pyrrolidinones **5a–f**

5a, X = CH₂; R₂ = Me; R₃ = H
5b, X = O; R₂ = Me; R₃ = H
5c, X = O; R₂ = H; R₃ = *n*-C₅H₁₁
5d, X = O; R₂ = H; R₃ = SiMe₃
5e, X = CH₂; R₂ = R₃ = (CH₂)₄
5f, X = O; R₂ = R₃ = (CH₂)₄

6a, X = CH₂; R₁ = OEt (60%) **6d**, X = O; R₁ = OEt; R₃ = *n*-C₅H₁₁ (57%)
6b, X = O; R₁ = OEt (75%) **6e**, X = O; R₁ = Me; R₃ = *n*-C₅H₁₁ (62%)
6c, X = O; R₁ = Me (67%) **6f**, X = CH₂; R₁ = OEt; R₃ = SiMe₃ (61%, *anti/syn* 75:25)

6g, 43%, dr 68:32

6h, 60%, dr 57:43

Table 1. Radical Carbo-alkenylation of Ene-carbamates **2a–f**

2a, R₂ = R₃ = H; R₄ = OEt
2b, R₂ = Me; R₃ = H; R₄ = OMe
2c, R₂ = Me; R₃ = Me; R₄ = OMe
2d, R₂ = Me; R₃ = Boc; R₄ = OMe
2e, R₂ = Me; R₃ = COPh; R₄ = OMe
2f, R₂ = Me; R₃ = Phen; R₄ = OMe

entry	R₁	R₂	R₃	R₄	4[a]	yield[b] (%)
1	OEt	H	H	OEt	**4a**	86
2	OEt	Me	H	OMe	**4b**	80
3	OEt	Me	Me	OMe	**4c**	91
4	Me	Me	Me	OMe	**4d**	88
5	OEt	Me	Boc	OMe	**4e**	38
6	OEt	Me	COPh	OMe	**4f**	0
7	OEt	Me	Phen[c]	OMe	**4g**	62
8	Me	Me	Phen[c]	OMe	**4h**	82

[a] Compounds **4** were obtained essentially as a 1:1 mixture of diastereomers (measured by ¹H NMR of the crude reaction mixture). [b] Isolated yield after column chromatography. [c] Phen: 2-phenylethyl.

(6) (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11. (b) Friestad, G. K.; Wu, Y. *Org. Lett.* **2009**, *11*, 819–821. (c) Courant, T.; Masson, G. *Chem.—Eur. J.* **2012**, *18*, 423–427. (d) Jiang, J.; Huang, C.; Zeng, C.; Zhang, Y.; Yu, S. *Chem.—Eur. J.* **2012**, *18*, 15158–15166.

(7) (a) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662–12663. (b) Godineau, E.; Landais, Y. *Chem.—Eur. J.* **2009**, *15*, 3044–3055. (c) Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *10*, 2658–2661 and references cited therein.
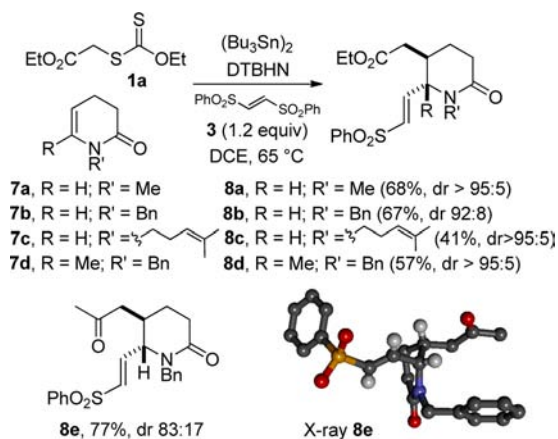
(8) (a) Kim, S.; Kim, S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809–822. (b) Bertrand, F.; Le Guyader, F.; Liguori, L.; Ouvry, G.; Quiclet-Sire, B.; Seguin, S.; Zard, S. *Z. C. R. Acad. Sci.* **2001**, *4*, 547–555.

(9) Quiclet-Sire, B.; Zard, Z. S. *Top. Curr. Chem.* **2006**, *264*, 201–236.

The methodology was extended to the functionalization of cyclic enamides **7a−d** (Scheme 3). In contrast with the three-component reaction involving acyclic precursors, a high level of diastereocontrol was observed (^{1}H NMR) with the *trans*-isomer generally predominating, as shown by the X-ray structure determination of compound **8e** obtained from xanthate **1b** and amide **7b**. In line with previous observations, yields dropped with the introduction of a chain α to the nitrogen center (e.g., **8d**). Reaction with amides **7a−d** allowed various substituents on the nitrogen. Reaction of amide **7c** afforded the addition product **8c**, albeit in modest yield but high diastereocontrol, without a trace of the 5-*exo-trig* cyclization product, indicating that the intermolecular trapping of the radical intermediate **IIb** (Scheme 1) by sulfone **3** is faster than the cyclization onto the butenyl fragment. The matched polarity between radical **IIb** and vinylsulfone **3** is likely at the origin of this reactivity (vide infra).

Carbo-alkenylation of cyclic ene-carbamates led to similar observations (Scheme 4). For instance, the presence of an alkyl chain α to nitrogen in **9a,b** led to modest yields of the three-component adducts **10a,b**, having the *trans*-relative configuration (^{1}H NMR). Varying the size of the ene-carbamate ring led to contrasting results.

Scheme 3. Carbo-alkenylation of Cyclic Enamides **7a−d**

7a, R = H; R' = Me	**8a**, R = H; R' = Me (68%, dr > 95:5)
7b, R = H; R' = Bn	**8b**, R = H; R' = Bn (67%, dr 92:8)
7c, R = H; R' = ⌇⟋⟍	**8c**, R = H; R' = ⌇⟋⟍ (41%, dr>95:5)
7d, R = Me; R' = Bn	**8d**, R = Me; R' = Bn (57%, dr > 95:5)

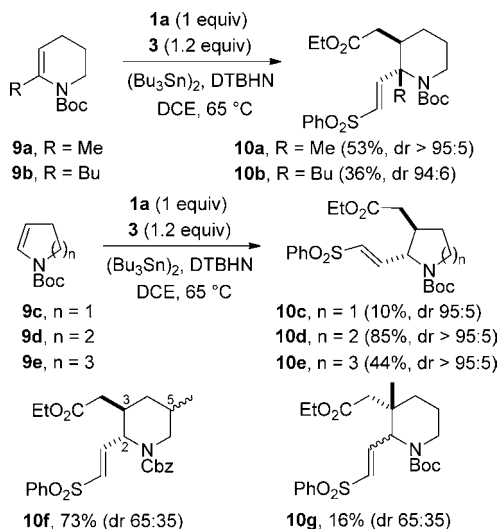**8e**, 77%, dr 83:17   X-ray **8e**

While excellent yield was obtained with 6-membered ring carbamate **9d**, modest and low yields were observed respectively for the 7- and 5-membered ring systems **9e** and **9c**. The formation of **10f** indicates that the presence of a substituent (Me) at C5 is not sufficient to control the diastereofacial selectivity during the attack of the xanthate precursor, while the *trans*-configuration between C2 and C3 is again observed. Finally, the formation of **10g**, albeit in low yield, is noteworthy and is the result of the addition of a radical species at the most sterically hindered site of a trisubstituted olefin, indicating that a strong driving force

overbalance the natural tendency of the C-centered radical to react at the less hindered site.

Scheme 4. Carbo-alkenylation of Cyclic Ene-carbamates **9a−e**

|	
9a, R = Me	**10a**, R = Me (53%, dr > 95:5)
9b, R = Bu	**10b**, R = Bu (36%, dr 94:6)
9c, n = 1	**10c**, n = 1 (10%, dr 95:5)
9d, n = 2	**10d**, n = 2 (85%, dr > 95:5)
9e, n = 3	**10e**, n = 3 (44%, dr > 95:5)

10f, 73% (dr 65:35)   **10g**, 16% (dr 65:35)

As mentioned above, enamides and ene-carbamates are electron-rich olefins that favor the addition of electron-deficient radical species such as those derived from xanthates **1a,b**. These additions generate a reactive radical such as **IIb**,[12] which possesses an allylic character[13] as shown by the canonical forms below (Scheme 5). Ab initio calculations at the DFT level[14] indicates that spin density in **IIb** is mainly concentrated α to the nitrogen as in **IIb-*i***. The free rotation around the C·−N bond and thus the absence of allylic strain ($A_{1,3}$), as in resonance form **IIb-*ii***, would thus explain the low level of stereocontrol observed in acyclic series (Table 1 and Scheme 2). This contrasts with the high stereocontrol observed in radical addition to related enamine systems,[11] where $A_{1,3}$ was invoked. Computational studies have also been performed on the reaction between radical intermediate **IV** (arising from the addition of **1b** onto olefin **9d**) and vinylsulfone **3** (Scheme 5). The lowest energy conformation, which exhibits a nearly planar C·NC=O system, clearly shows that the top face is hindered by the ketone chain (pseudoaxial), forcing the sulfone to approach through the bottom face. This transition state proved to be in excellent agreement with experiment, as **10h** arising from the three-component reaction between **9d**, **1b**, and **3** was formed with complete diastereocontrol (Scheme 6).

(10) Olefin **2g** may have also lost its enamide character (overlap between the olefin and the nitrogen lone pair) as a result of $A_{1,3}$ strain (we thank a reviewer for this comment).

(11) (a) Renaud, P.; Schubert, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433–435. (b) Schubert, S.; Renaud, P.; Carrupt, P.-A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473–2489.

(12) Electron-rich radicals such as **IIb** react very rapidly with vinyl-sulfone **3**, leading to the expected adduct, without a trace of the xanthate transfer product (e.g., quenching the reaction between **1a**, **3** and **9d** after 10 min led to 30% of the expected **10d** and no xanthate transfer product; see the Supporting Information). Such transfer products are occasionally found[7c] and are likely intermediates in these reactions when using less reactive olefins.

(13) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279–3282.

(14) DFT calculations were performed with the Gaussian09 software package (Supporting Information). The M06-2X exchange correlation functional was used with a standard double-ζ 6-31+G(d,p) basis set.
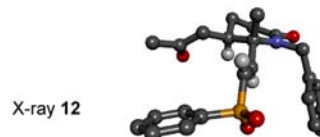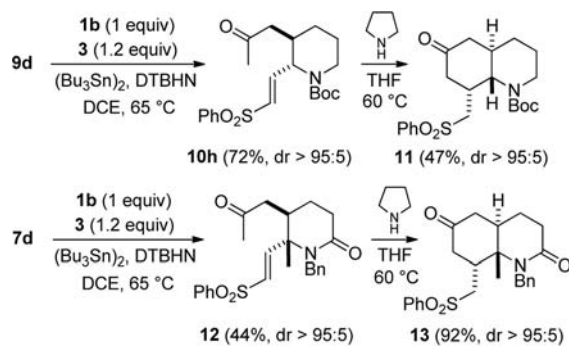
Scheme 5. Canonical Forms of Radical **IIb** and Transition State for the Addition of Radical Intermediate **IV** onto Sulfone **3**

Scheme 6. Functionalization of Carbamate **10h** and Amide **12**
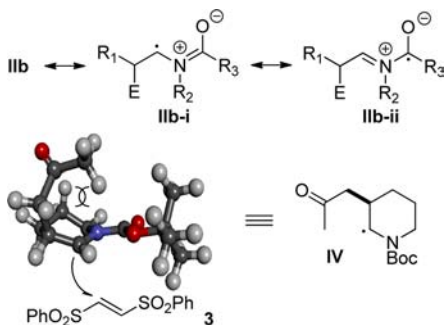
The compounds resulting from the free-radical carbo-alkenylation are valuable intermediates in organic synthesis, as illustrated by the pyrrolidine-mediated cyclization of ketone **10h** into aza-decalone **11**, which was obtained as a single diastereomer and may be regarded as a potent building block in the synthesis of alkaloids of the lycopodium family (Scheme 6).[15] Similarly, cyclization of amide **12**, whose structure was unambiguously determined through X-ray diffraction studies, led to the corresponding bicyclic amide **13** with complete diastereocontrol.

As a summary, we reported here the carbo-alkenylation of enamides and ene-carbamates. This three-component reaction proceeds through the addition of a radical species derived from a xanthate, and a vinylsulfone across the olefinic backbone of enamides and ene-carbamates. Good yields and high level of stereocontrol in the cyclic series are observed, leading to valuable intermediates for organic synthesis. This study illustrates a new reactivity pattern for enamides and ene-carbamates and demonstrates that these olefins are efficient traps for electron-poor radical species. Further elaboration of cyclic sulfones such as **8**, **10**, and **12** into advanced intermediates for alkaloid synthesis is now underway and will be reported in due course.

Supporting Information Available. Representative experimental procedures including product characterization and CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Ma, X.; Gang, D. R. *Nat Prod. Rep.* **2004**, *21*, 752–772.

The authors declare no competing financial interest.