Experimental Section

The procedure for the asymmetric alder–ene reaction of **1b** catalyzed by rhodium (**2b**):[4] In a dried Schlenk tube, [{Rh(cod)Cl}$_2$] (4.9 mg, 0.01 mmol) and (*S*)-BINAP (13.8 mg, 0.022 mmol) were dissolved in freshly distilled 1,2-dichloroethane (2 mL), then freshly prepared **1b** (37.2 mg, 0.2 mmol) was added to the solution at room temperature under nitrogen. After the mixture had been stirred for 1 min, AgSbF$_6$ (0.04 mmol) was added, and the reaction was complete within 5 min. The reaction mixture was directly subjected to column chromatography. Compound **2b** (35.8 mg, 96% yield, $>99.9\%$ *ee*) was obtained. The *ee* value was determined by GC with chiral select 1000 at 150°C. $[\alpha]_D = 23.85$ ($c = 0.5$, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.33$–7.29 (m, 2H), 7.22–7.18 (m, 1H), 7.12–7.10 (m, 2H), 6.24(s, 1H), 5.70–5.65 (m, 1H), 5.2–5.16 (m, 2H), 4.77 (d, $J = 14.0$ Hz, 1H), 4.64 (d, $J = 14.0$ Hz, 1H), 4.15 (t, $J = 7.7$ Hz, 1H), 3.60–3.48 ppm (m, 2H); ^{13}C NMR (90 MHz, CDCl$_3$): $\delta = 144.1$, 137.6, 137.1, 128.9, 128.3, 127.1, 122.5, 118.1, 72.8, 70.7, 51.1 ppm.

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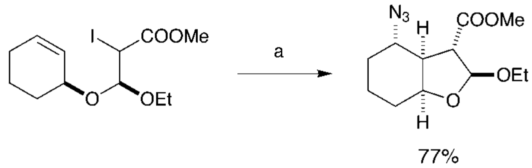
[6] Using [{Rh(BINAP)Cl}$_2$] as catalyst precursor and AgSbF$_6$ as additive, the reaction of **1a** yielded **2a** in less than 5% conversion within 20 min at room temperature. This was consistent with the low reactivity observed in ref. [4b].

[7] Compared with our earlier system, [{Rh(dppb)Cl}$_2$] and [{Rh(dppbo)Cl}$_2$] were effective catalytic precursors for the Alder–ene reaction.[4] This clearly indicates the differences between our previous catalyst and the new catalytic system.

Radical Carboazidation of Alkenes: An Efficient Tool for the Preparation of Pyrrolidinone Derivatives**

Philippe Renaud,* Cyril Ollivier, and
Philippe Panchaud

The use of free radical reactions in multistep synthesis has steadily increased over the last years, mainly because of their compatibility with a large number of functional groups and their high potential for performing sequential transformations.[1] Recently, we developed a novel method that allows the efficient formation of carbon–nitrogen bonds by reaction of radicals with sulfonyl azides.[2,3] Since sulfonyl azides possess an electrophilic character, this azidation process is particularly efficient with nucleophilic radicals and does not occur with ambiphilic or electrophilic radicals. For instance, the cyclization depicted in Scheme 1 can be performed by mixing all the reagents at once under relatively concentrated conditions (0.5 M substrate) without the formation of even traces of noncyclized products.



Scheme 1. Radical cyclization–azidation process. a) PhSO$_2$N$_3$ (3 equiv), (Bu$_3$Sn)$_2$ (1.5 equiv), *t*BuON=NO*t*Bu (3 mol%), benzene.

This observation let us speculate that the reaction could also be accomplished in intermolecular processes. Here we report our first results on the intermolecular addition of radicals to unactivated alkenes followed by azidation. This reaction sequence represents a formal carboazidation of alkenes, and it is the key process for an efficient three-component synthesis of pyrrolidinone, pyrrolizidinone, and indolizidinone derivatives.

In a first series of experiments, we tested the feasibility of the reaction starting from terminal alkenes and different radical precursors that are known to be efficient in radical atom or group transfer reactions (Scheme 2, see also Table 1).[4] A one-pot procedure similar to that used for intramolecular reactions gave promising results: The radical precursors are treated with phenylsulfonyl azide (3 equiv),

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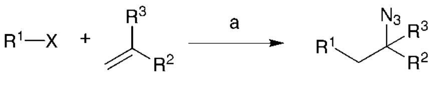

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Scheme 2. Reaction of terminal alkenes with various radical precursors. a) $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), tBuON=NOtBu (3–21 mol %), benzene.

Table 1. Radical carboazidation of terminal alkenes according to Scheme 2.[a]

Entry	X	R^1	R^2, R^3	Product	Yield [%]
1	I	$EtOOCCH_2$	C_6H_{13}, H	**1**	79
2	I	$EtOOCCH_2$	$(CH_2)_5$	**2**	89
3	I	$EtOOCCH_2$	$(CH_2)_3$OTBDMS, H	**3**	77
4	Br	$EtOOCCH_2$	C_6H_{13}, H	**1**	66
5	SC(S)OEt	$EtOOCCH_2$	C_6H_{13}, H	**1**	70
6	SC(S)OEt	$EtOOCCH_2$	CH_2SiMe_3, H	**4**	80
7	I	(EtOOC)(Me)CH	C_6H_{13}, H	**5**	75[b]
8	Br	$(COOEt)_2CH$	C_6H_{13}, H	**6**	46[c]
9	SePh	$(COOEt)_2CH$	C_6H_{13}, H	**6**	50[d]
10	SC(S)OEt	$(COOEt)_2CH$	C_6H_{13}, H	**6**	76
11	Br	Cl_3C	$(CH_2)_5$	**7**	40[e]

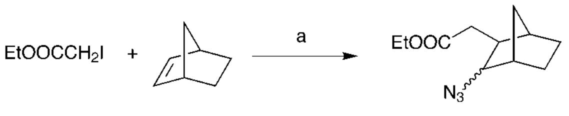
[a] See the Experimental Section for the reaction conditions. [b] 1:1 Mixture of diastereomers. [c] 26 % of Br transfer. [d] 34 % of PhSe transfer. [e] 36 % of Br transfer. TBDMS = *tert*-butyldimethylsilyl.

terminal olefins (2 equiv), hexabutyldistannane (1.5 equiv), and di-*tert*-butylhyponitrite (DTBHN, 3–21 mol %) as initiator in refluxing benzene.[5] Slow addition of the benzenesulfonyl azide is not necessary because this electrophilic reagent does not react with the initial ambiphilic or electrophilic radicals, such as enolate radicals and the trichloromethyl radical.

Reactions of 1-octene, methylenecyclohexane, and silylated 5-pentene-1-ol with ethyl iodoacetate give the expected azides **1**, **2**, and **3** in good yields (Table 1, entries 1–3). Reactions of ethyl bromoacetate and ethyl 2-ethoxythiocarbonylsulfanylethanoate with 1-octene (entries 4, 5) furnish the azide **1** in 66 and 70 % yield, respectively.[6] Reaction of the same dithiocarbonate with allyltrimethylsilane delivers the addition–azidation product **4** in 80 % yield (entry 6). As expected, other enolate radicals react with similar efficiency, as demonstrated by the reaction of ethyl 2-iodopropionate with 1-octene, affording **5** in 75 % yield (entry 7). The reaction of the malonyl radical, generated from either diethyl bromomalonate or diethyl phenylselenomalonate, with 1-octene gives the carboazidation product **6** in only 46 or 50 % yield, respectively (entries 8, 9). The products of bromine atom and phenylseleno group transfer were identified as the major side products. Interestingly, when the malonyl radical is generated from diethyl ethoxythiocarbonylsulfanylmalonate, the carboazidation product **6** is obtained in higher yield (76 %, entry 10). Finally, the use of bromotrichloromethane, a reagent known to be very efficient for bromine atom transfer reactions, was investigated. Reaction with methylenecyclohexane furnishes the azide **7** in 40 % yield (entry 11). In this last example, the only identified side product was again the product of bromine atom transfer.

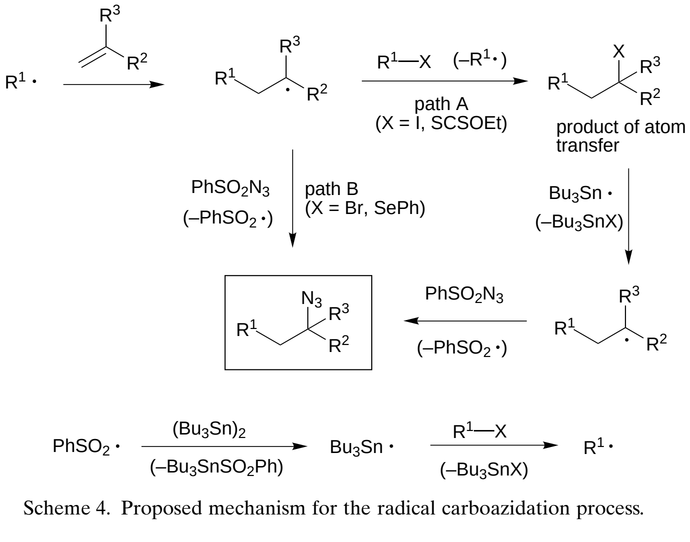
By analogy to iodine atom transfer, we were expecting that the radical addition–azidation process would be limited to terminal alkenes. Indeed, Curran and co-workers showed that olefins substituted at both carbon atoms give low yields in atom transfer processes with iodoacetate derivatives.[7] We tested the reaction with dimethyl cyclohex-4-ene-1,2-dicarboxylate, and observed only traces of the desired azide.[8] Interestingly, norbornene, a more reactive 1,2-disubstituted alkene, reacts cleanly with ethyl iodoacetate to afford the azide **8** in 74 % yield as a 85:15 *exo*:*endo* mixture of isomers (Scheme 3).

From a mechanistic point of view, the reaction is expected to occur in a stepwise manner involving carbon–carbon bond formation by an atom or group transfer reaction followed by an azidation process (Scheme 4, path A). This mechanism is supported by the detection of the intermediate product of iodine or dithiocarbonate transfer. However, in the case of diethyl bromomalonate, diethyl phenylselenomalonate, and bromotrichloromethane, the products of bromine and phenylselanyl transfer are not efficiently converted into azides.[2,9]



8 (74%, *exo*:*endo* 85:15)

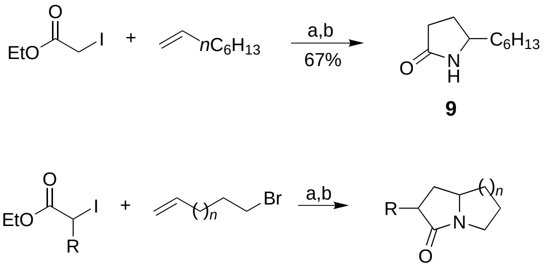
Scheme 3. Reaction of norbornene with ethyl iodoacetate. a) $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), tBuON=NOtBu (6 mol %), benzene.



Scheme 4. Proposed mechanism for the radical carboazidation process.

Therefore, the observed azides are presumably issued from a direct mechanism of radical addition–azidation (path B). The rate of azidation of the intermediate radical competes with the rate of bromine atom and phenylseleno group transfer.[10,11] Path A contributes only marginally to the formation of the azide due to the inefficient azidation of the intermediate alkylbromide and selenide.

The radical carboazidation of alkenes with 2-iodoesters can be coupled with the reduction of azides to afford 3-amino esters that spontaneously cyclize to pyrrolidinones (Scheme 5). For example, 5-hexylpyrrolidinone (**9**) is prepared in 67 % overall yield from 1-octene and ethyl iodoacetate. The intermediate 3-azidoester is reduced with indium in ethanol.[12] Spontaneous cyclization to **9** is observed, but it is slow. The lactamization process can be promoted by adding triethylamine and by heating the crude reaction mixture under reflux. Starting from 5-bromopent-1-ene and 6-bromohex-1-ene, the reduction of the azide initiates a double cyclization leading to pyrrolizidinones **10** and **11** as well as indolizidinones **12** and **13** (Scheme 5). It is interesting to note that, even in the presence of primary bromides, the carboazidation process with iodoesters proceeds in good yields.



10 $n = 1$, R = H: a) 77% b) 82%
11 $n = 1$, R = Me: a) 72% b) 84%*
12 $n = 2$, R = H: a) 74% b) 72%
13 $n = 2$, R = Me: a) 69% b) 83%*

* 1:1 mixture of diastereomers

Scheme 5. Two-step preparation of mono- and bicyclic lactams from terminal alkenes. a) $PhSO_2N_3$ (3 equiv), $(Bu_3Sn)_2$ (1.5 equiv), *t*BuON=NO*t*Bu (3–21 mol %), refluxing benzene. b) 1. Indium 1 equiv), NH_4Cl (1 equiv), refluxing EtOH. 2. Et_3N (5 equiv), refluxing EtOH.

In conclusion, a one-pot intermolecular radical addition–azidation procedure has been developed. Remarkably, this reaction is efficient with nonactivated terminal alkenes and takes advantage of the radical atom or group transfer processes. In order to illustrate the utility of the reaction, the preparation of pyrrolidinones, pyrrolizidinones, and indolizidinones starting from phenylsulfonyl azide, terminal alkenes, and 2-iodoesters was developed. This reaction is expected to be of great importance for the total synthesis of alkaloids. Such applications are currently underway in our laboratory and will be reported in due course.

Experimental Section

Carboazidation reaction: DTBHN (5 mg, 0.03 mmol) was added every 2 h to a solution of ethyl 2-iodoacetate (214 mg, 1.0 mmol), benzenesulfonyl azide (550 mg, 3.0 mmol), olefin (2.0 mmol), and Bu_6Sn_2 (0.76 mL, 1.5 mmol) in dry benzene (2.0 mL) at reflux under N_2. The reaction was monitored by thin-layer chromatography. Upon completion of the reaction (4–12 h), the solvent was removed under reduced pressure and the crude product was filtered through silica gel. Elution with hexane allowed the removal of unchanged Bu_6Sn_2, and then elution with hexane/Et_2O gave a crude product that was purified by flash chromatography (hexane/Et_2O).

Reductive lactamization: Indium powder (230 mg, 2.0 mmol) and NH_4Cl (107 mg, 2.0 mmol) were added to a solution of the azide (2.0 mmol) in dry ethanol (6.0 mL). The reaction mixture was stirred under reflux for 2 h. Then Et_3N (1.4 mL, 10.0 mmol) was added, and the reaction mixture was stirred under reflux for 4 h. The cooled reaction mixture was diluted with EtOAc (10 mL), stirred for 10 min, and filtered through a short pad of celite. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH).

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