CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Title: Free-radical Carbo-cyanation of Olefins

Authors: Yannick Landais, Vincent Pirenne, Haitham Hassan, Frédéric Robert, Maren Wissing, Chahinaz Khiar, and Ashique Hussain

To be cited as: *Chem. Eur. J.* 10.1002/chem.201605946

Link to VoR: http://dx.doi.org/10.1002/chem.201605946

Supported by
ACES

WILEY-VCH

Chemistry - A European Journal 10.1002/chem.201605946

WILEY-VCH

FULL PAPER

Free-radical Carbo-cyanation of Olefins.

Haitham Hassan,[‡][a] Vincent Pirenne,[‡][a] Maren Wissing,[a] Chahinaz Khiar,[a],[b] Ashique Hussain,[a]
Frédéric Robert,[a] and Yannick Landais*[a]

Abstract: The free-radical 3-component carbo-cyanation of electron-rich olefins has been investigated using *p*-tosyl cyanide as a cyanide source. Scope and limitation of the process was established varying the nature of the alkene and that of the radical precursor. Carbocyanation of chiral allylsilanes was shown to occur with high diastereocontrol, leading to *syn* β-silyl nitriles. The origin of the stereocontrol was rationalized through a Felkin-Anh type transition state model. Finally, a tin-free carbocyanation process was also devised, based on the use of a new alkylsulfonyl cyanide incorporating both carbon fragments to be added across the olefinic π-system.

Introduction

The regioselective addition of two carbon fragments onto olefins gives rise to useful intermediates for organic synthesis starting from readily available starting materials. Organometallic but also free-radical additions of carbon moieties across the olefinic π-system have thus been thoroughly studied and applied to a broad range of electron-rich and electron-deficient olefins.[1] In this context, this laboratory has recently developed several radical processes relying on such additions, providing original substrates bearing two new C-C bonds along with two additional functional groups.[2] Amongst these reactions, one-pot 3-component carbo-oximation of olefins proved to be particularly efficient,[2a,2e] allowing the incorporation on the carbon backbone of an oxime functional group which was later hydrolyzed into an aldehyde or reduced into an aminomethyl substituent, as illustrated recently in the total synthesis of Eucophylline alkaloid.[3] However, further use of this carbo-oximation as a formal carbo-formylation process with more hindered substrates (*i.e.* **2a**, Figure 1) led to less satisfactory yields, underlining the limitation of the process.[3] In the search for a better formyl or aminomethyl surrogate, it was envisioned that a cyano group might be particularly well suited as it may be selectively reduced into an aldehyde (with DIBAL-H) or fully hydrogenated into an amine using H_2 and Raney-Nickel under mild conditions.[4] Moreover, the small size of the CN substituent should allow the elaboration of acyclic systems bearing quaternary centers with a nitrile function, ready for further transformation.[5] While organometallic intra- and intermolecular carbo-cyanation of alkenes and alkynes have been well developed using Ni and Pd-catalysis,[6] free-radical carbocyanation of olefins has been more scarcely studied. 1,2-Cyanocarbofunctionalization of alkenes has thus been limited to copper-catalyzed cyano-trifluoromethylation.[7] Recently, Inoue[8] disclosed an interesting intramolecular cyanide transfer process during the addition of Cl_3CCN onto an olefin catalyzed by a copper complex. Zhu[9a] and Liu[9b] also developed an elegant cyano-functionalization of olefins relying on an intramolecular cyano migration strategy. However, in all these cases, the scope is restricted to olefins bearing specific functional groups or substituents. Fang *et al*[10] described earlier the addition of *p*-$TolSO_2CN$ across olefins π-bonds to afford the corresponding β-sulfonyl cyanides. Various reports have also described the use of sulfonyl cyanides as efficient cyanating agents in radical processes,[11] but none of them have reported on the consecutive incorporation of a carbon fragment and a cyano substituent on an olefinic backbone.

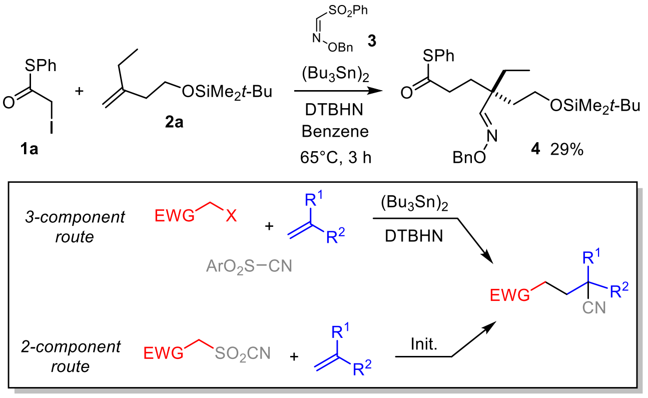


Figure 1. Free-radical carbo-oximation and carbo-cyanation of olefins.

Based upon previous work on carbo-azidation,[12] carbo-alkenylation[2b,c] and carbo-oximation,[2a,e] we describe here an efficient 3-component free-radical carbo-cyanation of electron-rich olefins.[13] Optimization of the process also led us developing a tin-free (two-component) version of this carbo-cyanation using

---

[a] Dr. H. Hassan, V. Pirenne, C. Khiar, M. Wissing, Dr. F. Robert, Prof. Dr. Y. Landais
Institute of Molecular Sciences, UMR-CNRS 5255
University of Bordeaux
351, Cours de la libération
33405 Talence cedex, France
E-mail: y.landais@ism.u-bordeaux1.fr

[b] C. Khiar
Laboratoire de Chimie Appliquée et du Génie Chimique (LCAGC)
Université Mouloud Mammerie de Tizi-Ouzou
15000, Tizi-Ouzou, Algeria

[‡] These authors contributed equally to this work.

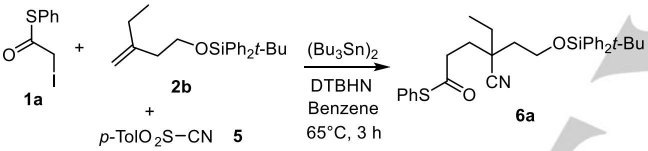
Supporting information for this article is given via a link at the end of the document a readily available sulfonyl cyanide incorporating both functional groups which will be added onto the olefin.

Results and Discussion

3-component carbo-cyanation of olefins

Preliminary studies were carried out using iodide **1a** and olefin **2b** respectively as radical precursor and olefin, and *p*-TolSO$_2$CN as a commercially available cyanating agent, using first optimal conditions set up for the carbo-oximation process[2e] (Table 1, entry 1). (Bu$_3$Sn)$_2$ (1.5 equiv.) was used as a chain carrier and di-*t*butyl hyponitrite (DTBHN) as an initiator. Pleasingly, under these conditions, the carbocyanation product **6a** was formed in an excellent 79% yield. Lowering both the amount of olefin and that of **5** slightly lowered the yield, which however remained satisfactory (Table 1, entry 2). A further decreased of the quantity of olefin to 1.1 equiv. led to only 50% yield of **6a**. Finally, the scaling up of the reaction using conditions in entry 2 led to an acceptable yield and showed that such multicomponent process could be used for further synthetic purposes.

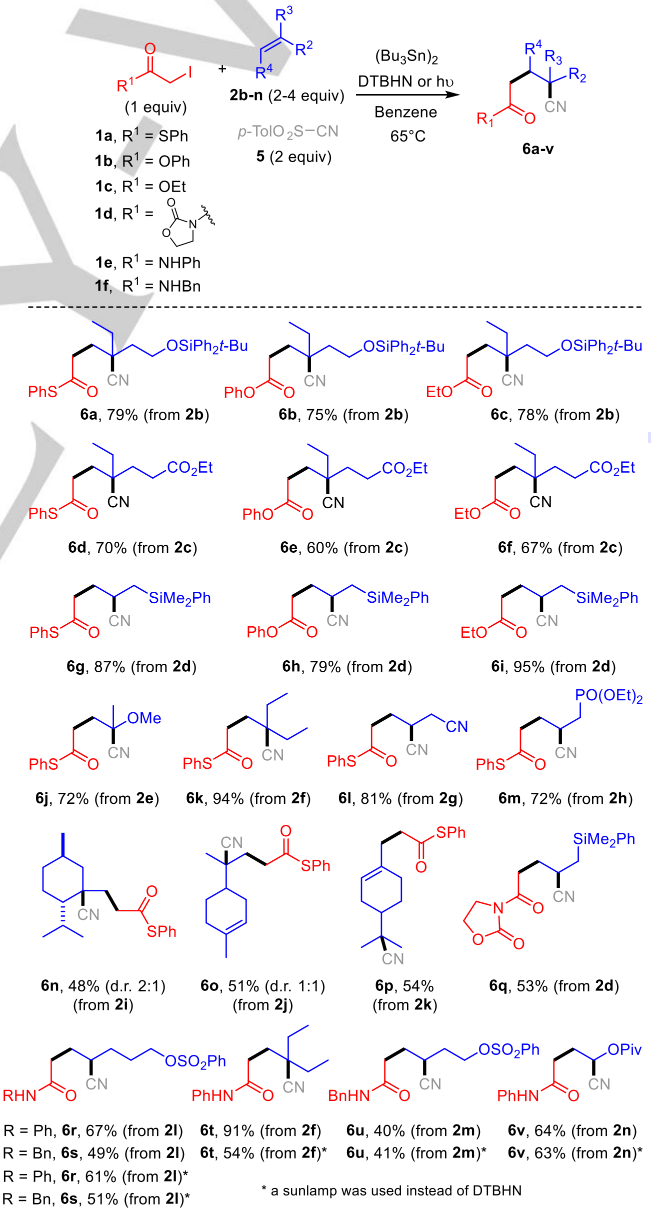
Table 1. Optimization of the carbocyanation conditions.



Entry	Olefin **2b** (eq.)	*p*-TsCN **5** (eq.)	Yield [%][a]
1	4	2	79
2	2	1.2	68
3	1.1	1.2	50
4[b]	2	1.2	60

[a] Yield of isolated products. [b] Scaling up experiment starting from 20 mmol of **2b**.

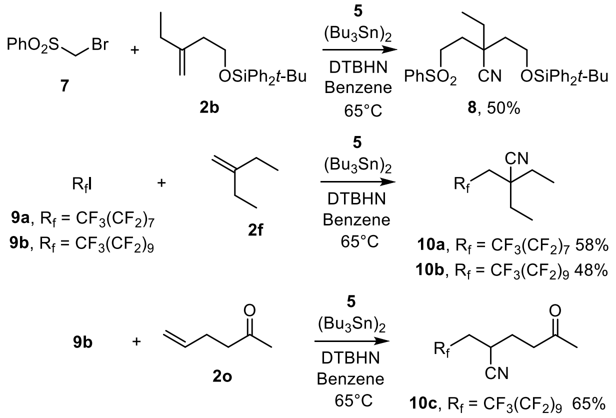
These preliminary studies showed that tin-mediated carbo-cyanation of olefin is efficient even with substrates for which the carbo-oximation led to poor yield. Best conditions (Table 1, entry 1) were then applied to the carbocyanation of a series of olefins as summarized in Scheme 1. It is worth noticing that for large scale synthesis and for costly olefins, the use of 2 equivalents of olefin (Table 1, entry 2 and 4) gave generally suitable yields. As already observed before,[2b-c] electron-rich olefins (enol ethers, enamides, allylsilanes, …..) being more reactive, 2 equivalents is usually sufficient to attain reasonable yields. α-Iodoesters **1b-c** were also tested and led to the expected 3-component adducts **6b-c**, **6e-f** and **6h-6i** with yields similar to those obtained from thioester **1a** (Scheme 1). The latter generally led to faster and cleaner reactions. Moreover, the presence of the reactive orthogonal thioester group allows for further manipulation in the presence of esters as in **6d**.[3] As observed in carbo-alkenylation and oximation reactions,[2b,c,e] electron-richer olefins reacted faster and led to higher yields as illustrated with the formation of silane **6i** or enol ether **6j**. In contrast with carbo-oximation reaction, which led to moderate yields with sterically hindered substrates, carbo-cyanation allowed the incorporation of the cyano group on tertiary center and thus the generation of all-carbon quaternary centers as in **6a-f**. The reaction conditions were also compatible with functional groups as exemplified with esters (**6d-f**), nitrile (**6l**), phosphonate (**6m**) and substituted olefins (**6o**). Finally, the nature of the radical precursor was varied including α-iodoimides and amides **1d-f**. 3-component adducts **6q-v** were thus obtained in moderate to good yields. Interestingly, useful O-protecting groups such as OPiv, but also OTs as in **6r-s** and **6v** were also tolerated in these reactions. Finally, we also tested the efficiency of the photochemical initiation. For instance, 3-component adducts **6r-6v** were prepared under similar conditions, but using a sunlamp instead of DTBHN. Moderate to good yields were obtained, suggesting that this protocol may be suitable for reactions on a larger scale as to avoid the use of costly DTBHN.



* a sunlamp was used instead of DTBHN

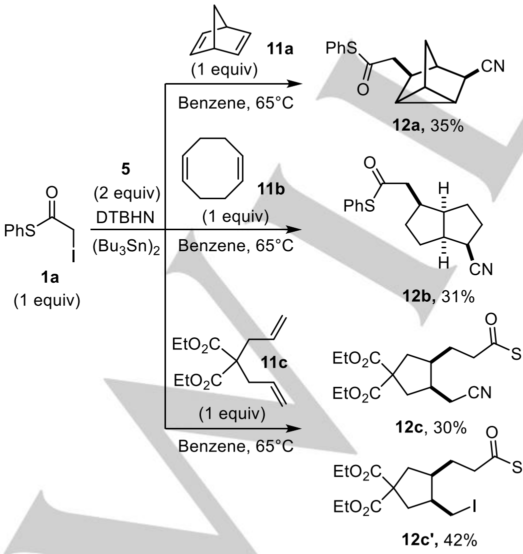
Scheme 1. Carbo-cyanation of olefins using *p*-tosyl cyanide **5**.

Other radical precursors than α-iodoesters **1a-c** were tested, including α-bromosulfone **7**, which proved to be less reactive than its ester counterpart, however providing the desired compounds **8** in moderate yield (Scheme 2). Fluorinated alkyl iodide chains are also competent radical precursors in these reactions, as shown by the addition of **9a-b** onto olefins **2f** and **2o**, which led to **10a-c** in reasonable yields.[14] Pyramidal C-centered fluorinated radicals are known to add efficiently onto double bonds.[15]



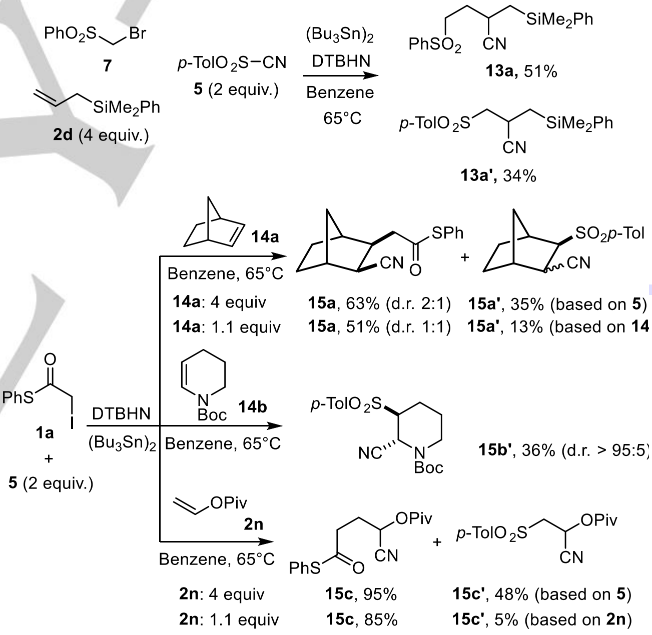
Scheme 2. Carbo-cyanation of olefin **2a**, **2f** and **2o** with α-sulfonyl bromide and fluorinated alkyl chains.

In these multi-component processes, dienes were shown to behave differently than normal olefins,[16] leading to higher amounts of sulfonyl addition products (*vide infra*).[10] In order to suppress these side-reactions, the radical process is carried out using only 1 equivalent of olefin. These conditions were used here to access carbo-cyanation products in modest yields (Scheme 3). In the reaction of diene **11c**, the expected product **12c** was thus obtained in 30% yield along with a large amount of the iodide transfer product **12c'**.



Scheme 3. Carbo-cyanation of dienes **11a-c**.

With reactive electron-rich olefins, we observed along with the expected carbo-cyanation product, various amount of sulfonyl-cyanation product.[10] For instance, addition of sulfone **7** onto allylsilane **2d** led to the desired adduct **13a**, along with the sulfonyl cyanide by-product **13a'**, resulting from the facile addition of the electrophilic *p*-tosyl radical onto the double bond.[17] Similarly, addition to the strained norbornene **14a** (4 equiv) led to compound **15a** as 2:1 mixture of separable diastereomers, along with a high percentage of sulfonylated cyanide **15a'**. Repeating the reaction with only 1.1 equivalent of norbornene however led to a reduced amount of **15a'**. The same behavior was observed during the carbo-cyanation of vinyl pivalate **2n**. Sulfonyl-cyanation[10] is thus observed when excess of both **5** and olefins are present in the medium, and thus occurs after the limiting iodide substrate has been consumed. This side-reaction is observed on these particular cases, as **2d** and **14a-b** are electron-rich and thus particularly reactive. This was not observed with less reactive alkenes. Limiting the quantity of olefin disfavors the addition of the electrophilic tosyl radical.[18] The fast reaction of the tosyl radical with ditin then allows an efficient propagation of the radical chain and prevents the formation of side products **13a'**, **15a'**, **15b'** and **15c'**.[19]

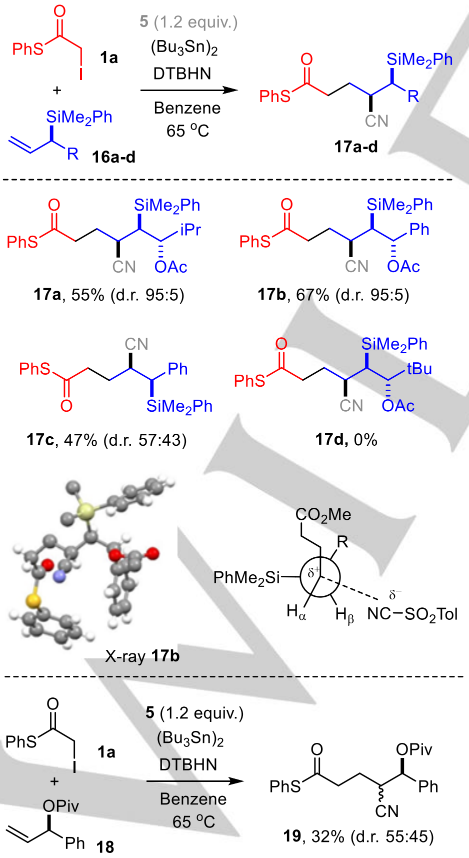


Scheme 4. Carbo-cyanation and competing sulfonyl-cyanation of electron-rich olefins.

The carbo-cyanation reaction was also applied to chiral olefins in order to study the level of 1,2-stereocontrol in these reactions. Previous studies have shown that carbo-azidation of chiral allylsilanes could be highly stereoselective with d.r. ranging between 80:20 and 100:0.[20] Extension of this study to carbo-oximation was plagued by the low reactivity of the β-silyl radical species with the sulfonyloxime due to steric hindrance.[21] It was anticipated that the small size of the cyano group would allow the reaction of the β-silyl radical intermediate with the *p*-tosyl cyanide **5** and provide the carbo-cyanation product. The reaction was thus

10.1002/chem.201605946

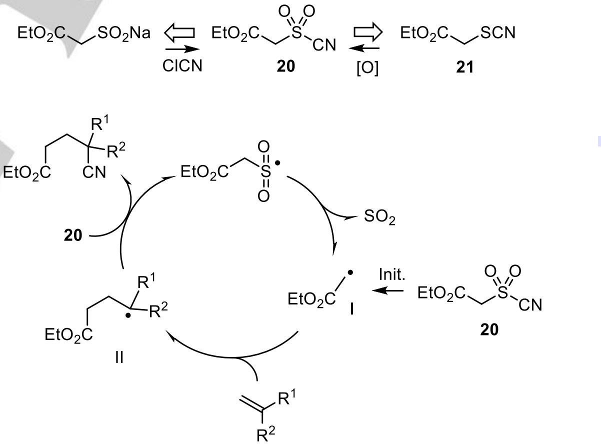
performed with a series of chiral allylsilanes **16a-d** prepared following reported procedures.[20] The 3-component carbo-cyanation was found to be highly diastereoselective when sufficient steric bulk was present on the β-carbon, as in allylsilanes **16a-b** affording **17a-b** in good yield (Scheme 5). The sole presence of a phenyl group as in **16c** (leading to **17c**) on the stereogenic center was surprisingly not sufficient to induce the stereocontrol, in contrast with our previous observations in carbo-azidation on the same substrate. With sterically hindered allylsilane **16d** having a *t*-Bu substituent on the β-center, no reaction was observed. Finally, we extended the study to the carbo-cyanation of a chiral allylic ester **18**, which led to the desired compound **19**, albeit in low yield and no stereocontrol, in good agreement with precedent in carbo-azidation and carbo-alkenylation processes.[16,20] The relative configuration of the major diastereomer was determined through X-ray diffraction studies of the crystalline nitrile **17b**, which was shown to possess the *syn*-configuration, similarly to azidosilanes prepared through carbo-azidation.[20] The origin of the diastereocontrol was thus rationalized invoking a similar transition state model as depicted in Scheme 5. In this Felkin-Anh-type model, the *p*-tosyl-cyanide is believed to approach the nucleophilic radical *anti* relative to the bulky silicon group on the side of the small hydrogen substituent, with the bulkiest substituents ($SiMe_2Ph$ and CH_2CH_2COSPh) orthogonal to each other. When the size of the substituents on the stereogenic center was decreased as in **16c** (R = Ph), the diastereocontrol decreased dramatically. This may be explained by the now alternative approach of the cyanide group from the side of the medium-sized phenyl group (R = Ph).



Scheme 5. Carbocyanation of chiral allylsilanes **16a-d** and ester **18**.

"Tin-free" carbo-cyanation of olefins

Examples above thus showed that three-component carbo-cyanation of olefins using commercially available *p*-tosyl cyanide has a rather broad scope, providing polyfunctional substrates in satisfying to excellent yields. However, such a process would be really useful for synthetic purposes, if a "tin-free" version was made available, as in certain cases, complete removal of tin residues may be tedious. Based on literature precedents,[22] it was intended to develop an access to a sulfone such as **20** having both an ester functional group as in radical precursors **1a-c** and a cyano substituent (Scheme 6). An initiation step should generate electrophilic radical **I**, the addition of which onto the olefin would afford a new nucleophilic radical **II**. Reaction of the latter with **20** would give the product along with an alkylsulfonyl residue ($EtO_2CCH_2SO_2$), which α-scission (and loss of SO_2) would regenerate **I** and thus sustain the radical chain.[23] Although Kim and co-workers have developed a general procedure to access alkylsulfonyl cyanides from alkylsulfinyl salts and ClCN,[24] the use of volatile and highly toxic ClCN prompted us to test the alternative oxidation of a thiocyanate such as **21**.[25] This approach is usually limited to arylthiocyanate[26] and only one report mentioned a good yield for an oxidation of an alkylthiocyanate using *m*-CPBA.[27]

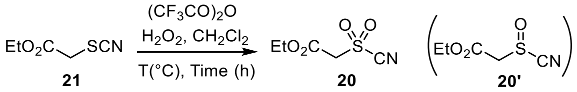


Scheme 6. Synthesis of sulfonyl cyanide **20** and radical chain in the 2-component process.

Preliminary attempts at oxidizing **21** using oxone,® but also MnO_2 or $KMnO_4/MnO_2$ failed to afford satisfying yields of the desired sulfonyl cyanide **20**, leading instead to the formation of the corresponding carbamothioate ($EtO_2CCH_2S(C{=}O)NH_2$), through hydrolysis of **21** (see supporting information). With *m*-CPBA, formation of **20** was observed, but excess peracid was difficult to remove, which prompted us to use a more soluble oxidizing agent. More encouraging results were thus obtained using CF_3CO_3H prepared from $(CF_3CO)_2O$ and H_2O_2.[28] Optimization of this oxidation process is summarized in Table 2.

10.1002/chem.201605946

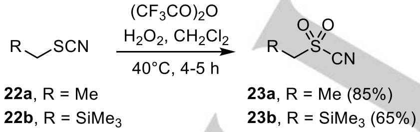
Table 2. Optimization of the oxidation conditions of **21**.



Entry	H_2O_2[a] (equiv)	$(CF_3CO)_2O$ (equiv)	T(°C)	Time (h)	**20**/**20'** (%)[b]	Yield [%][c]
1	5	5	20	15	44:56	-
2	5	5	40	16	80:20	-
3	7.5	7.5	35	18	70:30	-
4	13	20	20	7	100:0	32
5	10	10	40	16	>95:<5	75
6	2	2	40	3	5:95	-[d]

[a] H_2O_2 50%wt in water was used. [b] **20**/**20'** ratio was estimated through ^1H NMR of the reaction mixture. [c] Crude yield of **20-20'** after washing with H_2O and evaporation of the solvent (> 95:5 purity). [d] **20'** was isolated with 20% unreacted **21**.

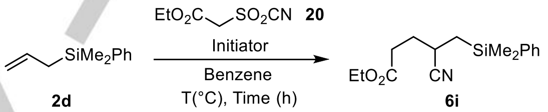
The use of a 5-fold excess of both reagents to ensure the formation of CF_3CO_3H and the complete oxidation of **21** led to a mixture of the sulfone **20** and sulfinyl cyanide **20'** (Table 2, entry 1). **20'** could be easily detected through ^1H NMR, showing two sets of peaks at 4.5 and 4.7 ppm for diastereotopic CH_2 protons.[29] A higher conversion into **20** was obtained using 5- then 7.5-fold excess of reagents and increasing the temperature (entries 2-3). A still higher amount of reagent led to a complete conversion into **20**, but afforded a low yield after work-up (entry 4). Finally, a good compromise was found by using 10 equiv. of both reagents at 40°C. A simple washing of the reaction mixture with H_2O and evaporation of the solvent led to good and reproducible yields of **20** (68-75%) with > 95:5 purity. This procedure was repeated and scaled up to 30 mmol of **21** (affording ~ 4g of **20**). Sulfinyl cyanide **20'** (*vide infra*) could also be isolated using only 2 equiv. of peracid (along with 20% unreacted **21**) (entry 6). This method was also found suitable to prepare other volatile alkylsulfonyl cyanides **23a-b** in good yields.



Scheme 7. Synthesis of sulfonyl cyanides **23a-b**.

With **20** in hands, the radical carbo-cyanation was then studied with allylsilane **2d** as a model compound. The reaction was studied using first an excess of olefin **2d** (2 equiv.). Thermal initiation at 65°C led to no reaction (Table 3, entry 1). Several initiation protocols were thus tried, which are summarized in Table 3. DTBHN and dilauroyl peroxide (DLP) led to modest yields of **6i** with three consecutive additions (3 x 0.1 eq.) (entries 2-3). Di-*t*-butyl peroxide (DTBP) under thermal conditions led to no conversion (entry 4). Reaction using Et_3B and oxygen at room temperature was effective, leading to full conversion of **20**, but to isolation of **6i** in only moderate yield (entry 5). Di-*t*-butyldiazene (DTBD) under photochemical conditions[22f] afforded an encouraging yield, which could not be increased using additional amount of initiator (entry 6). The cheaper AIBN also led to full conversion of **20** and moderate to good yields of **6i** depending on the amount of initiator which was added (entries 7-9). Although good yields of **6i** were obtained using AIBN (entry 8), large amount of initiator was required. Moreover, when less reactive olefins such as 1-octene was used under these conditions, the carbocyanation product was formed in low yield (47%). We thus turned our attention to V-40 (1,1'-azobis(cyclohexane-1-carbonitrile)), known to decompose at a higher temperature, which should also facilitates the fragmentation (α-scission) of **20**.[24] At this temperature (120°C), and using a low amount (2 x 0.05 mol%) of V-40 in chlorobenzene, satisfying yield of **6i** was obtained (entry 10). Reversing the ratio of **2d** and **20** (entry 11), we finally observed that although the conversion was still complete, the yield of **6i** slightly decreased. These conditions are however useful when the starting olefins are less reactive than allylsilane and their preparation requires several steps.

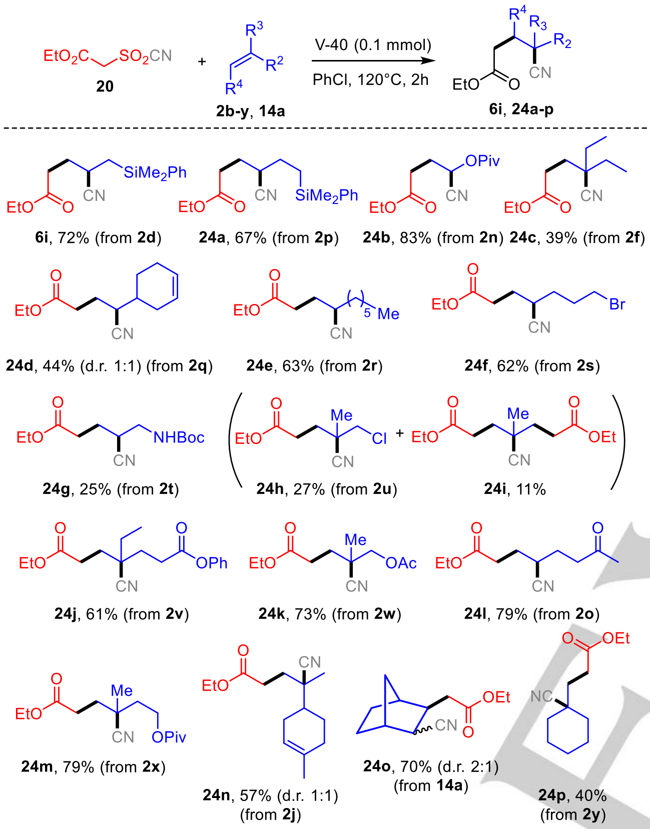
Table 3. Optimization of the reaction conditions for the carbo-cyanation of **2d** with **20**.



Entry	Init.	Init. (equiv.)	T(°C)	Time (h)	Conv. (%)[f]	Yield [%][g]
1[a]	-	-	65	14	0	-
2[a]	DTBHN	3 x 0.1	65	4.5	nd	49
3[a]	DLP	3 x 0.1	80	6	nd	32
4[a]	DTBP[c]	3 x 0.1	120	6	< 15	-
5[a]	Et_3B[d]	2	20	5	100	50
6[a]	DTBD[e]	0.5	80	6	100	58
7[a]	AIBN	3 x 0.1	80	6	nd	47
8[a]	AIBN	2	65	14	100	74
9[a]	AIBN	3 x 0.25	80	6	100	75
10[a]	V-40[c]	2 x 0.05	120	2	100	83
11[b]	V-40[c]	0.1	120	2	100[h]	72

[a] **2d** (2 equiv) and **20** (1 equiv). [b] **2d** (1 equiv) and **20** (2 equiv). [c] PhCl was used as a solvent. [d] Et_3B 1.0 M in hexane. [e] $h\upsilon$ (sunlamp) and benzene were used. [f] Conversion of **20**. [g] Isolated yield of **6i** after chromatography. [h] Conversion of **2d**.

These optimized conditions (entry 11) were then applied to a series of olefins as summarized in Scheme 8. The "tin-free" carbo-cyanation reaction proved to be efficient with a broad range of olefins, leading to the final nitriles in moderate to excellent yields. Functional groups such as esters, ketones, olefins and substituents such as halides, silanes, were found compatible with the reaction conditions. Modest yields were in turn obtained with acid-sensitive olefins (*i.e.* **24g**), likely due to the presence of SO_2 in the reaction medium. Attempts at using a base to trap the acid resulting from the reaction of SO_2 with traces of moisture failed to improve yields. Methallyl chloride was found to be a competent partner, providing nitrile **24h** albeit in modest yield. Interestingly, this olefin is also an allylating agent[30] under these conditions, providing a new olefin (not shown) which reacted further with **20** to give compound **24i**. The same reaction carried out with methallyl bromide led to no product. This carbo-cyanation also opens a straightforward access to **24j** a precursor of Kuehne's aldehyde, a key synthon in the synthesis of important monoterpene indole alkaloids.[31] Finally, the carbo-cyanation of allylsilane **2d** and 1-octene was also attempted with the sulfinyl cyanide **20'** (~70-80% pure), using respectively AIBN at 80°C and V-40 at 120°C. In both cases, only traces of the nitriles **6i** and **24e** were observed, showing that **20'** is not an efficient cyanide transfer agent.



Scheme 8. "Tin-free" carbocyanation reaction.

Conclusions

In summary, we reported a comprehensive study on the free-radical carbo-cyanation of olefins. This process can be applied to a broad range of electron-rich olefins, leading to functionalized nitriles. The process is compatible with many functional groups including ketones, esters, double bonds, amides, nitriles, phosphonates and sulfonates. With very reactive olefins (strained olefins, enol ethers,…), sulfonyl-cyanation products may be formed, a problem which can be solved by decreasing the amount of olefin in the medium. An efficient "tin-free" version was also devised, relying on a new sulfonyl cyanide incorporating the radical precursor, and easily available through oxidation of the corresponding thiocyanate. Overall, the 3-component carbo-cyanation of olefins which uses, as a cyanide source, commercially available *p*-TsCN, nicely complements the carbo-oximation process, requiring a sulfonyloxime (*i.e.* **3**), which must be prepared through a 5 steps sequence. From a practical point of view, carbo-cyanation products were more easily separated from tin residues than in carbo-oximation. Carbo-cyanation was also found to be more efficient than carbo-oximation for the incorporation of a CN substituent on a quaternary center. Finally, on a broader context, this work also complements recent studies reported on the use of sulfone and sulfinate derivatives as radical traps.[32]

Experimental Section

General procedure for the 3-component carbo-cyanation process

To a solution of the bromide or iodide (1.0 equiv) in dry benzene (1.0 M), olefin (2.0 or 4.0 equiv), *p*-toluenesulfonyl cyanide **5** (2.0 equiv), bis(tributyltin) (1.5 equiv) were added. The reaction mixture was degassed for 20 min with argon and the process was initiated by adding DTBHN (20 mol%). The mixture was then stirred for 1.5 h at 65°C. The reaction progress was monitored by TLC and another addition of DTBHN (20 mol%) was performed when necessary, then the reaction mixture was stirred for another 1.5 h at 65 °C. After 3 h, the reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel.

General procedure for the "tin-free" carbo-cyanation process using sulfonyl cyanide 20.

In a sealed tube, sulfonyl cyanide **20** (2 equiv) and alkene (1 equiv) were diluted in distilled chlorobenzene. The mixture was degassed for 15 minutes with argon and 1,1'-Azobis(cyclohexanecarbonitrile) (0.1 equiv) was added in one portion. The flask was tightly closed and the reaction mixture was stirred at 120°C for 2 h. The chlorobenzene was then partially evaporated under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel.

Acknowledgements

H.H., V.P. and A.H. thank respectively the Erasmus-Mundus Green IT program (3772227-1-2012-ES-ERA MUNDUS-EMA21), the *"Fondation pour le développement de la Chimie des substances Naturelles et ses applications"* and the Shaheed Benazir Bhutto University for PhD grants. The Erasmus+ and Algerian PNE programs are also acknowledged for financial support respectively to M.W. and C.K. The CNRS and the University of Bordeaux are thanked for financial help. M. Stephane Massip (IECB, University of Bordeaux) is acknowledged for X-ray diffraction studies.

Keywords: Radical • carbo-cyanation • multicomponent • α-scission • sulfones

[1] (a) B. Giese, *Radical Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986; Chapter 2, pp 4-35; (b) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820; (c) G. J. Rowlands *Tetrahedron* **2010**, *66*, 1593; (d) N. A. Porter, B. Giese, D. P. Curran, *Acc. Chem. Res.* **1991**, *24*, 296; (e) H. Subramanian, Y. Landais, M. P. Sibi in Comprehensive Organic synthesis, Eds. G. A. Molander, P. Knochel, 2nd ed., Vol. 4, Oxford: Elsevier, **2014**, pp. 699-741.

[2] (a) E. Godineau, Y. Landais, *J. Am. Chem. Soc.* **2007**, *129*, 12662; (b) V. Liautard, F. Robert, Y. Landais, *Org. Lett.* **2011**, *13*, 2658; (c) C. Poittevin, V. Liautard, R. Beniazza, F. Robert, Y. Landais, *Org. Lett.* **2013**, *15*, 2814; (d) B. Ovadia, F. Robert, Y. Landais, *Org. Lett.* **2015**, *17*, 1958; (e) Y. Landais, F. Robert, E. Godineau, L. Huet, N. Likhite, *Tetrahedron* **2013**, *69*, 10073; (f) B. Ovadia, F. Robert, Y. Landais, Chimia, **2016**, *70*, 34.

[3] H. Hassan, S. Mohammed, F. Robert, Y. Landais, *Org. Lett.* **2015**, *17*, 4518.

[4] M. Rabinovitz, *Reduction of the cyano group* in *The chemistry of the cyano group*, Z. Rappoport Ed., John Wiley & Sons Ltd, 1970, Chap. 7, pp 307-340.

[5] A-value for the CN group has been estimated to be 0.21. E.L. Eliel, S.H. Wilen and L.N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York (1994).

[6] (a) M. Tobsiu, N. Chatani, *Chem. Soc. Rev.* **2008**, *37*, 300; (b) N. Yoshiaki, *Bull. Chem. Soc. Jpn* **2012**, *85*, 731; (c) A. Yada, T. Yukawa, Y. Nakao, T. Hiyama, *Chem. Comm.* **2009**, *26*, 3931; (d) C. Najera, J. M. Sansano, *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. *Angew. Chem.,* **2009**, *121*, 2488; (e) Z. Zhuang, W.-W. Liao, *Synlett* **2014**, *25*, 905; (f) Y. Nishihara, Y. Inoue, M. Itazaki, K. Takagi, *Org. Lett.* , **2005**, *7*, 2639; (g) Y. Nishihara, Y. Inoue, S. Izawa, M. Miyasaka, K. Tanemura, K. Nakajima, K. Takagi, *Tetrahedron* , **2006**, *62*, 9872; (h) Y. Nishihara, M. Miyasaka, Y. Inoue, T. Yamaguchi, M. Kojima, K. Takagi, *Organometallics*, **2007**, *26*, 4054; (i) Y. Nakao, Y. Hirata and T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 7420.

[7] (a) N. O. Ilchenko, P. G. Janson, K. J. Szabo, *J. Org. Chem.* **2013**, *78*, 11087; (b) Y.-T. He, L.-H. Li, Y.-F. Yang, Z.-Z. Zhou, H.-L. Hua, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 270; (c) Z. Liang, F. Wang, P. Chen, G. Liu, *J. Fluor. Chem.* **2014**, *167*, 55. Photocatalysis using Ru catalyst was also disclosed, see: (d) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240.

[8] S. Kamijo, S. Yokosaka, M. Inoue, *Tetrahedron Lett.* **2012**, *53*, 4324.

[9] (a) Z. Wu, R. Ren, C. Zhu, *Angew. Chem., Int. Ed.* **2016**, *55*, 10821. *Angew. Chem.,* **2016**, *128*, 10979; (b) N. Wang, L. Li, Z.-L. Li, N.-Y. Yang, Z. Guo, H.-X. Zhang, X.-Y. Liu *Org. Lett.* **2016**, *18*, 6026.

[10] J.-M. Fang, M.-Y. Chen, *Tetrahedron Lett.* **1987**, *28*, 2853.

[11] (a) D. H. R. Barton, J. S. Jaszberenyi, E. A. Theodorakis, *Tetrahedron* **1992**, *48*, 2613; (b) S. Kim, H.-J. Song, Synlett **2002**, 2110; (c) A.-P. Schaffner, V. Darmency, P. Renaud *Angew. Chem., Int. Ed.* **2006**, *45*, 5847. *Angew. Chem.,* **2006**, *118*, 5979; (d) S. Kim, S. Kim, N. Otsuka, I. Ryu, *Angew. Chem., Int. Ed.* **2005**, *44*, 6183. *Angew. Chem.,* **2005**, *117*, 6339; (e) S. Kim, C. H. Cho, S. Kim, Y. Uenoyama, I. Ryu, *Synlett* **2005**, 3160; (f) S. Kim, S. Kim, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809; (g) R. Ren, Z. Wu, Y. Xu, C. Zhu, *Angew. Chem., Int. Ed.* **2016**, *55*, 2866. *Angew. Chem.* **2016**, *128*, 2916.

[12] (a) P. Renaud, C. Ollivier, P. Panchaud, *Angew. Chem., Int. Ed.* **2002**, *41*, 3460. *Angew. Chem.* **2002**, *114*, 3610; (b) P. Panchaud, P. Renaud, *J. Org. Chem.* **2004**, *69*, 3205.

[13] For a specific example of carbo-cyanation of cyclopropenes, see: N. S. Dange, F. Robert, Y. Landais, *Org. Lett.* **2016**, *18*, 6156.

[14] For a recent report on addition of alkylfluorinated chains onto olefins, see: P. Dudzinski, A. V. Matsnev, J. S. Thrasher, G. Haufe, *Org. Lett.* **2015**, *17*, 1078.

[15] (a) A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8950. *Angew. Chem.,* **2012**, *124*, 9082; (b) D. Leifert, A. Studer, *Angew. Chem., Int. Ed.* **2016**, *55*, 11660. *Angew. Chem.,* **2016**, *128*, 11832.

[16] R. Beniazza, V. Liautard, C. Poittevin, B. Ovadia, S. Mohammed, F. Robert, Y. Landais, *Chem. Eur. J.* **2017**, DOI: 10.1002/chem.201605043.

[17] (a) C. Chatgilialoglu in *The chemistry of sulfones and sulfoxides: sulfonyl radicals*, S. Patai, S. Rappoport, C.M.J. Stirling, Eds. Chap. 25, Wiley, New-York, 1988, pp 1089-1113; (b) For rate constant of sulfonyl radical addition onto olefins, see: C. Chatgilialoglu, O. Mozziconacci, M. Tamba, K. Bobrowski, G. Kciuk, M. P. Bertrand, S. Gastaldi,, V. I. Timokhin, *J. Phys. Chem. A* **2012**, *116*, 7623.

[18] Addition of sulfonyl radicals onto olefins is however a reversible process, see: (a) P. J. Wagner, J. H. Sedon, M. J. Lindstrom, *J. Am. Chem. Soc.* **1978**, *100*, 2579; (b) V. I. Timokhin, S. Gastaldi, M. P. Bertrand, C. Chatgilialoglu, *J. Org. Chem.* **2003**, *68*, 3532.

[19] As pointed out by one of the reviewer, Bu_3Sn radical might also react with *p*-TsCN to afford Bu_3SnCN, a possible cyanation reagent. However, when iodide **1c** and allylsilane **2d** were allowed to react with Bu_3SnCN (instead of ditin and *p*-TsCN) and V-40 as an initiator, no trace of the desired product was observed, thus ruling out this hypothesis.

[20] L. Chabaud, Y. Landais, P. Renaud, F. Robert, F. Castet, M. Lucarini, K. Schenk, *Chem. Eur. J.* **2008**, *14*, 2744.

[21] B. Ovadia, PhD Thesis dissertation, University of Bordeaux (2015).

[22] (a) J. Gong, P. L. Fuchs, *J. Am. Chem. Soc.* **1996**, *118*, 4486; (b) F. Le Guyader, B. Quiclet-Sire, S. Seguin, S. Z. Zard, *J. Am. Chem. Soc.* **1997**, *119*, 7410; (c) F. Bertrand, F. Leguyader, L. Liguori, G. Ouvry, B. Quiclet-Sire, S. Seguin, S. Z. Zard, *C. R. Acad. Sci. Paris,* **2001**, *4*, 547; (d) F. Bertrand, B. Quiclet-Sire, S. Z. Zard, *Angew. Chem., Int. Ed.* **1999**, *38*, 1943. *Angew. Chem.,* **1999**, *111*, 2135; (e) S. Kim, C. J. Lim, *Angew. Chem., Int. Ed.* **2002**, *41*, 3265. *Angew. Chem.,* **2002**, *114*, 3399; (f) K. Weidner, A. Giroult, P. Panchaud, P. Renaud, *J. Am. Chem. Soc.* **2010**, *132*, 17511; (g) B. Ovadia, F. Robert, Y. Landais, *Org. Lett.* **2015**, *17*, 1958; (h) J. Lei, X. Wu, Q. Zhu, *Org. Lett.* **2015**, *17*, 2322.

[23] Sulfonyl cyanides **5** and **20** serve here as UMCT (UniMolecular Chain Transfer) reagents. See: D. P. Curran, J. Xu, E. Lazzarini, *J. Chem. Soc., Perkin Trans 1*, **1995**, 3049.

[24] S. Kim, K.-C. Lim, S. Kim, *Chem. Asian J.* **2008**, *3*, 169.

[25] **21** was prepared in 83% by reaction of ethyl α-bromoacetate with NH_4SCN in ethanol under reflux. See: U. Burkard, F. Effenberger, *Chem. Ber.* **1986**, *119*, 1594.

[26] R. G. Pews, F. P. Corson *J. Chem. Soc. Chem. Commun.* **1969**, 1187.

[27] J. M. Blanco, O. Caamanio, F. Femandez, G. Gomez, C. Lopez, *Tetrahedron: Asymmetry* **1992**, *3*, 749.

[28] (a) C. Fehr, *Angew. Chem.* **1998**, *110*, 2509. *Angew. Chem. Int. Ed.* **1998**, *37*, 2407; (b) B. A. McKittrick, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 4895.

[29] A. Boerma-Markerink, J. C. Jagt, H. Meyer, J. Wildeman, A. M. van Leusen, *Synth. Commun.* **1975**, *5*, 147.

[30] H. Jasch, Y. Landais, M. R. Heinrich, *Chem. Eur. J.* **2013**, *19*, 8411.

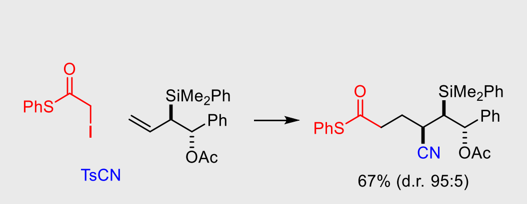
[31] J.-B. Gualtierotti, D. Pasche, Q. Wang, J. Zhu, *Angew. Chem., Int. Ed.* **2014**, *53*, 9926. *Angew. Chem.* **2014**, *126*, 10084.

[32] (a) T. Hoshikawa, S. Kamijo, M. Inoue, *Org. Biomol. Chem.* **2013**, *11*, 164; (b) V. A. Vasin, Y. Y. Masterova, V. V. Razin, N. V. Somov, *Can. J. Chem.* **2013**, *91*, 465; (c) B. Du, P. Qian, Y. Wang, H. Mei, J. Han, Y. Pan, *Org. Lett.* **2016**, *18*, 4144; (d) R. K. Quinn, V. A. Schmidt, E. J. Alexanian, *Chem. Sci.* **2013**, *4*, 4030; (e) S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu, A. Lei, *Chem. Commun.,* **2014**, *50*, 4496; (f) Y. Amaoka, M. Nagatomo, M. Watanabe, K. Tao, S. Kamijo, M. Inoue, *Chem. Sci.* **2014**, *5*, 4339; (g) T. Hoshikawa, S Kamijo, M. Inoue, *Org. Biomol. Chem.* **2013**, *11*, 164; (h) Z. Huang, Q. Lu, Y. Liu, D. Liu, J. Zhang, A. Lei, *Org. Lett.* **2016**, *18*, 3940; (i) A. U. Meyer, K. Strakova, T. Slanina, B. König, *Chem. Eur. J.* **2016**, *22*, 8694; (k) T. Rawner, M. Knorn, E. Lutsker, A. Hossain, O. Reiser, *J. Org. Chem.* **2016**, *81*, 7139; (l) S. K. Pagire, S. Paria, O. Reiser, *Org. Lett.* **2016**, *18*, 2106.

10.1002/chem.201605946

Entry for the Table of Contents

FULL PAPER



The free-radical 3-component carbo-cyanation of electron-rich olefins has been investigated using *p*-tosylcyanide as a cyanide source. Scope and limitation of the process was established varying the nature of the alkene and that of the radical precursor. A "tin-free" carbo-cyanation process was also devised, relying on the use of a new alkylsulfonyl cyanide incorporating both carbon fragments which will be added across the olefinic π-system.

H. Hassan,[a] *V. Pirenne,*[a] *W. Missing,*[a] *C. Khiar,*[a],[b] *A.Hussain,* [a] *F. Robert,*[a] *and Y. Landais**[a]

Page No. – Page No.

Free-radical Carbo-cyanation of Olefins.