

Palladium-Catalyzed Alkylation of Allylic Nitrates Derived from Ceric Ammonium Nitrate Promoted Oxidative Addition of Trimethylsilyloxy-cyclopropanes to 1,3-Butadiene

Anna Belli Paolobelli, Fabio Gioacchini, Renzo Ruzziconi *

Dipartimento di Chimica, Università di Perugia, 06100-Perugia, Italy

Abstract: Silyloxycyclopropanes are easily oxidized by ceric ammonium nitrate to generate β -carbonylalkyl radicals which are able to add to 1,3-butadiene to give a mixture of 4-(γ -carbonylalkyl)-substituted 3-nitroxy-1-butenes and 4-(γ -carbonylalkyl) substituted (E)-1-nitroxy-2-butenes (1,2- and 1,4-adducts) in ca. 1:1 molar ratio. The crude mixture, subjected to palladium-catalyzed alkylation by a variety of carbon nucleophiles, affords mainly δ , ϵ -unsaturated carbonyl compounds with high regio- and stereoselectivity and in satisfactory overall yield.

Cyclopropanol, like enol derivatives, can be easily oxidized by monoelectronic metal oxidants to generate β -carbonylalkyl radicals in very mild conditions. Recently, oxidative addition to electron rich alkenes has been successfully exploited both in intra- and intermolecular carbon-carbon bond formation making use of $\text{Mn}(\text{pic})_3^1$ and $\text{Cu}(\text{BF}_4)_2^2$ as the oxidizing species.

Previously we reported that ceric ammonium nitrate (CAN) is an efficient one electron oxidant in generating α -carbonylalkyl radicals from silyl enol ethers, oxidative addition of the resulting α -ketoalkyl radical to electron rich alkenes allowing the access to a variety of polyfunctionalized carbonyl compounds.³ In virtue of the strict similarity in the chemical behaviour of silyloxycyclopropanes with trimethylsilyl enol ethers, we have considered worthwhile to extend our investigation to CAN promoted oxidative addition of silyloxycyclopropanes to electron rich carbon-carbon double bonds. In the initial approach, we investigated the reaction with 1,3-butadiene. Since we expected that the reaction would lead to a mixture of 1,2- and 1,4-nitroxy adducts, analogously to what was previously reported by us on the CAN promoted oxidative addition of carbonyl compounds to 1,3-butadiene,⁴ our principal aim was to increase the synthetic potentiality of the process by looking for a procedure allowing the conversion of the regioisomeric mixture into unsaturated regio- and stereoselectively substituted carbonyl derivatives through the nucleophilic replacement of the allylic nitroxy group. We wish now to report that a tandem procedure based on the CAN promoted oxidative addition and palladium catalyzed allylic substitution allows the goal to be attained.

Accordingly, when a mixture of trimethylsilyloxycyclopropane and 1,3-butadiene is treated with CAN in acetonitrile at room temperature, a fast reaction occurs to give a mixture of 4-(γ -carbonylalkyl) substituted 3-nitroxy-1-butene and 4-(γ -carbonylalkyl) substituted-1-nitroxy-2-butene (1,2- and 1,4-adduct respectively) in nearly equimolar amount. Moreover, we found that when the crude mixture, coming from the above reaction, is subjected to nucleophilic attack by a variety of carbon nucleophiles, in THF at room temperature and in the presence of $\text{Pd}(\text{PPh}_3)_4$ as the catalyst, then alkylated unsaturated carbonyl compounds are obtained in satisfactory overall yields and in very short time (0.5-5 min). Some results are reported in the Table.

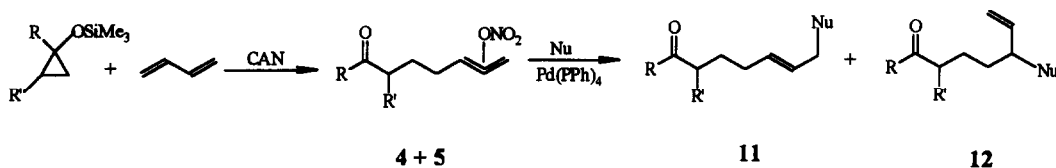
In this condition the nitroxy group, which up to now, has never been involved in palladium catalyzed allylic substitution, proves to be a very good leaving group, at least as much as alkyl carbonate, acethoxy or other groups frequently employed in such processes, whereas, in the absence of catalyst, alkylation involves exclusively the 1,4-adduct and the product is obtained in only 30% of yield after 24 h.

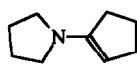
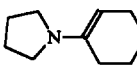
Interestingly, Palladium(0)-catalyzed reaction exhibits a very high regioselectivity, attack at the primary

allylic carbon accounting for at least 94% of the alkylated product.

Moreover, on the basis of $^1\text{H-NMR}$ coupling constants and IR spectra, in all cases, a *trans* geometry for the carbon-carbon double bond has been assigned which make this procedure suitable for the synthesis of highly functionalized (*E*)-7-alkyl-substituted δ,ϵ -unsaturated carbonyl compounds.

Table. Products from Palladium Catalyzed Alkylation of Allylic Nitrates Obtained by CAN Promoted Oxidative Addition of Trimethylsilyloxycyclopropanes to 1,3-Butadiene.



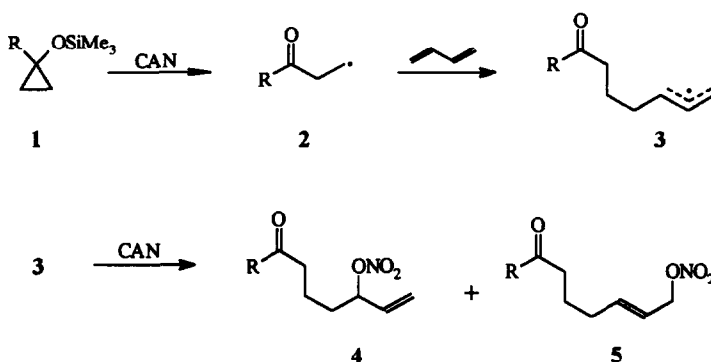
Entry	Trimethylsilyloxy-cyclopropane	Nucleophile	Product composition, 11:12 ^a	Overall yield, % ^b
1	R = OEt, R' = H	$\text{-CH}(\text{COOMe})_2$	95 : 5	68
2		$\text{-CH}(\text{COMe})\text{COOMe}$	95 : 5	63
3		$\text{MeC}(\text{COOEt})_2$	97 : 3	87
4		$\text{MeC}(\text{SO}_2\text{Ph})\text{COMe}$	97 : 3	59
5		 ^c	96 : 4	53
6		 ^c	97 : 3	58
7	R = Ph, R' = H	$\text{-CH}(\text{COOMe})_2$	91 : 9	59
8	R,R' = $\text{-(CH}_2\text{)}_3\text{-}$	$\text{-CH}(\text{COOMe})_2$	96 : 4	17 ^d

^a Determined by g.l.c. analysis of the crude reaction product. ^b Yield of isolated regioisomeric mixture calculated with respect to CAN. ^c In the product, Nu = 2-oxocycloalkyl after hydrolysis in 5% aqueous H_2SO_4 . ^d In this case, 3-oxocyclohexene (34%) was also recovered.

In a typical experiment, a solution of silyloxycyclopropane (10 mmol) and 1,3-butadiene (60 mmol) in acetonitrile (5 mL) was added dropwise to a vigorously stirred suspension of CAN (18 mmol) and powdered calcium carbonate (63 mmol) in the same solvent (100 mL). The mixture was allowed to react, at room temperature, until complete reduction of CAN (by iodometric titration, 10 min). The solid was then removed

by filtration on celite, washed with CHCl_3 (50 mL) and the filtrate was poured into water. The organic phase was separated and the aqueous phase was further extracted with CHCl_3 (3 x 50 mL). The collected extracts were washed with water (100 mL), dried over sodium sulphate and the solvent was evaporated at reduced pressure (15 mmHg). The residual yellow oil was dissolved in anhydrous THF (20 mL), $\text{Pd}(\text{PPh}_3)_4$ (50 μmol) was added and the mixture was stirred for 30 min, at room temperature under nitrogen, before addition, at once, to a clear solution of the carbon nucleophile in THF (20 mL) prepared by reacting the carbonyl compound (18 mmol) with pentane washed sodium hydride (10 mmol). The mixture was stirred until disappearance of the nitroxy adducts (g.l.c. analysis, 0.5-5 min depending on the nature of the nucleophile), then it was poured into water (100 mL) and extracted with CHCl_3 (3 x 50 mL). The collected extracts were washed with water (150 mL), dried on sodium sulphate and the solvent was evaporated in vacuum. Chromatography of the residual brown oil on silica gel (1:1 diethyl ether-petroleum ether as the eluent) allowed recovery of the regioisomeric mixture from which pure products were isolated by HPLC and characterized by their $^1\text{H-NMR}$, IR and MS spectra. All products had correct C, H analysis.

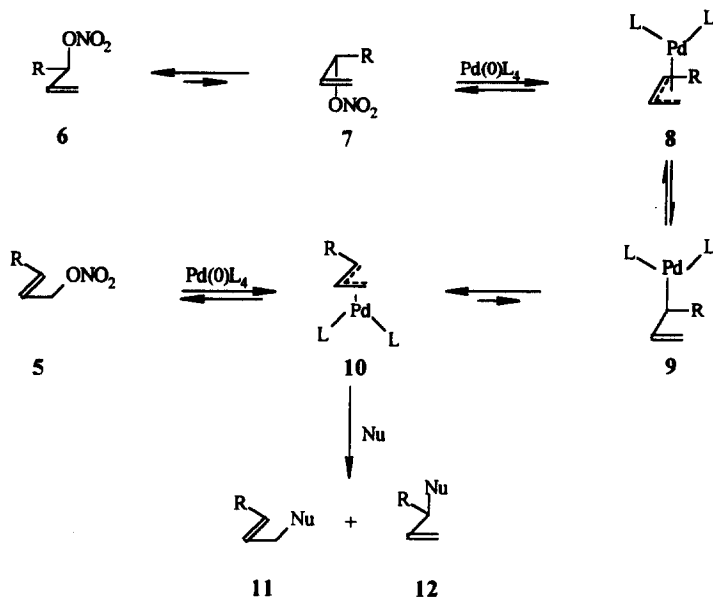
From a mechanistic point of view, the overall process could be rationalized considering that oxidation of trimethylsilyloxycyclopropane (1) by CAN generates β -carbonylalkyl radical 2, an electrophilic species, which adds to 1,3-butadiene to give δ -carbonylallyl radical 3 (Scheme 1). The latter, now a nucleophilic species, undergoes a fast oxidation by CAN leading to a mixture of 1,2- and 1,4-nitroxy adducts (4 and 5 respectively), probably through a ligand transfer process. Interestingly, the carbon-carbon double bond of the 1,4-adduct possesses an exclusively *trans* geometry according to what is usually observed in free radical additions to conjugated dienes.⁵



Scheme 1

The high regio- and stereoselectivity observed in the Pd(0) catalyzed allylic alkylation clearly indicates that products 11 and 12 (Scheme 2) are formed from both regioisomers 4 and 5 through the common η^3 palladium complex 10 which undergoes nucleophilic attack near exclusively at the primary allylic carbon. In turn, 10 could be formed both directly from the more stable conformer 6 and from 7. In the latter case, an η^3 complex 8 is first formed which converts into 10 probably through the η^1 complex 9 before undergoing nucleophilic attack which would lead to the *cis* alkene.⁶

It should be noted that, when the above procedure is applied to 2-substituted silyloxycyclopropanes, α,β -unsaturated carbonyl compounds are obtained as the main reaction product. Thus, 1-trimethylsilyloxy-bicyclo[3.1.0]hexane affords predominantly 3-oxocyclohexene, the expected product being formed in very poor yield (entry 8 in the Table). Most probably, cleavage of the cyclopropane ring preferentially generates the secondary 3-oxocyclohexyl radical which undergoes fast oxidative elimination by CAN.⁸



Scheme 2

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- See for example Oswald, A.A.; Griesbaum, K.; Thaler, W.A.; Hudson, Jr.B.E. *J.Am.Chem.Soc.* **1962**, *84*, 3897-3904.
- Accordingly, complete Z to E isomerization has been observed in Pd(PPh₃)₄ catalyzed alkylation of 4-acetoxy-2-buten-1-yl carbonate which should inevitably involve an $\eta^3 \rightleftharpoons \eta^1$ equilibrium.⁷
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- A similar trend has been observed in the oxidation of bicyclo[4.1.0]heptan-1-ol by Mn(pic)₃.¹ However, in this case, oxidative addition of the preferentially formed 3-oxocycloheptyl radical to electron rich alkenes occurs faster than its oxidation, confirming the scarce ability of Mn(III) in oxidizing secondary alkyl radicals.

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