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Very Important Publication

Synthetic Approaches to the Challenging Direct C-Alkylation and C-Allylation of Unactivated Nitroalkanes

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Abstract: The limited nucleophilic character and the bidentate nature of unactivated nitroalkane anions (nitronates) makes the corresponding alkylation and allylation procedures rather troublesome. This aspect is in sharp contrast with other commonly employed processes involving nitronate anions such as conjugate additions or nitroaldol reactions. This review summarizes the most rewarding approaches that along the years have been devised to overcome this limitation. Efficient methods are nowadays mainly based on metal-catalyzed processes involving purely ionic or mixed ionic-radical intermediates including photoenzymatic reactions.

Keywords: alkylation; allylation; nucleophilic substitution; organometallic catalysis; radicals

1. Introduction

The activating properties of the nitro group are mainly associated to its remarkable electron-withdrawing character. In nitroalkanes this feature enables a prompt deprotonation of the α-carbon with consequent formation of a stabilized carbanion.[1–3] The close similarity of this behavior with the flourishing chemistry of enolate systems is supported by the existence of a keto-enol type equilibrium involving the nitroalkane and its nitronic acid tautomer (*aci*/nitro equilibrium) (Scheme 1). Thus, considering the low pKa values evidenced for simple nitroalkanes (7–10), conversion of the nitronic acid into the corresponding nitronate anion can be readily pursued using basic reagents of moderate strength. This aspect has favored the success of nitroalkanes as easy to handle carbanionic reagents amenable of generating new C–C bonds in the reaction with carbon centered electrophiles. The interest in nitro-embedding structural entities is further boosted

Scheme 1. Tautomeric equilibrium of nitroalkanes and base assisted deprotonation.

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by the manyfold synthetic manipulation of the nitro group which can be reduced to a primary amine,[4,5] converted into a carbonyl system,[6–8] or definitively removed by reductive methods (denitrations) or exploiting base-induced elimination processes.[9–11] The nitronate anion **1**, once generated from the corresponding nitroalkanes, can be involved in several reactions with different electrophilic species as portrayed in Scheme 2. The nucleophilic addition of **1** to aldehydes known as the nitroaldol (Henry) reaction is a very effective process which can be catalyzed by a plethora of basic catalysts/promoters leading to nitro alcohols **2**.[12–14] Similarly, the conjugate addition of **1** to electron-poor alkenes occurs with outstanding levels regioselectivity generating adducts **3**.[15,16] Nowadays, the utilization of chiral catalysts in these reactions allows the asymmetric synthesis of adducts **2** and **3**

Scheme 2. Carbon-carbon bond forming processes of nitroalkanes.

with excellent levels of stereocontrol. The involvement of nitronate anions **1** in nucleophilic substitution reactions aimed at the preparation of *C*-alkylated nitroalkanes **4** represents a truly challenging process among those described in Scheme 2. The observed weak reactivity displayed by **1** is mainly due to the limited nucleophilic strength of the carbanion making the corresponding S_N2 process rather sluggish and thus favoring the competitive and regiocomplementary *O*-alkylation leading to nitronate esters **5**.[17] The synthetic strategies to improve the efficiency of nitroalkane alkylations include an increase of the nucleophilicity of the generated nitronate anions or the exploitation of different reaction mechanisms involving metal catalyzed processes or radical intermediates.

The utilization of α-functionalized nitroalkanes bearing electron-withdrawing groups (activated nitroalkanes) can be also pursued since the additional nitronate stabilization provided by these groups has a beneficial effect in the alkylation process increasing the nucleophilic character of the doubly stabilized anion. This review is aimed to discuss the main synthetic protocols that along the years have been devised to introduce simple or functionalized alkyl/allyl chains at α position of unactivated primary and secondary nitroalkanes.

2. Nitroalkane Dianions

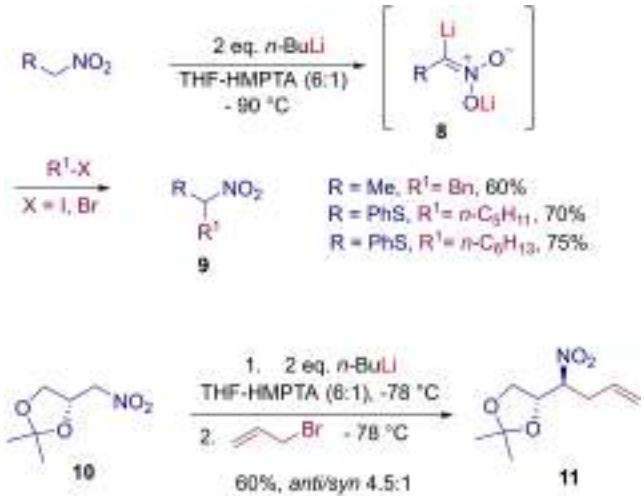
The reduced nucleophilic character of simple nitronate anions has been nicely demonstrated by Seebach almost fifty years ago in the reaction of doubly deprotonated 2-arylnitroethanes with electrophiles (Scheme 3).[18] The dianions of **6** reacts with alkyl halides in a regioselective fashion leading to 2-

Scheme 3. Selective alkylation of 2-aryl nitroethane dianions.

alkylated nitroalkanes **7** in satisfactory yield. This trend has been also demonstrated for the reaction of the same dianions with other sp^2-type C-electrophiles such as aldehydes, ketones and nitroalkenes.[18,19]

The application of this approach to other simple or functionalized nitroalkanes lacking acidic β hydrogen atoms leads to the formation of dianions of type **8** with enhanced nucleophilicity at the α carbon atom (Scheme 4).[20]

This feature enables the corresponding alkylation to be carried out even at very low temperature efficiently leading to secondary nitroalkanes **9**. Despite these results, this protocol has found a very limited application for practical purposes because of the complicated reaction conditions required. The only significant application of this approach has been found in the allylation of optically active nitroalkane **10** which product **11** has been obtained in satisfactory yield and diastereoselectivity.[21]



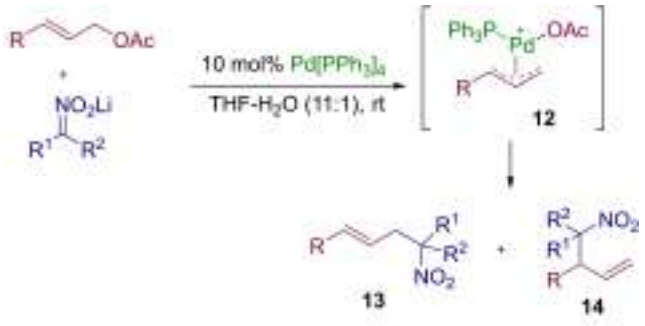
Scheme 4. Alkylation of α-lithiated nitronate dianions.

3. Metal-Catalyzed Reactions

3.1. Palladium-Catalyzed Reactions

The limited nucleophilic character of nitronate anions, coupled with the relatively modest reactivity of most haloalkane derivatives in S_N2 reactions, has suggested the use of stronger electrophiles generated from allylic substrates. Palladium catalyzed reactions of allylic acetates or carbonates with methylene active compounds including nitroalkanes have been envisaged as a valid alternative to the classical bimolecular nucleophilic substitutions.[22] This process, also referred as the Tsuji–Trost reaction, is based on the generation of a π-allyl complex **12** by interaction of an allyl acetate/carbonate with a Pd(0)-complex (Scheme 5).[23] Complex **12** smoothly reacts with nitronate anions leading to regioisomeric couples of products **13** and **14**. The α-substituted product **13** is usually predominant unless the two electrophilic sites are poorly differentiated from a stereoelectronic standpoint. Doubly stabilized nitronate anions, even when significantly hindered, give excellent results but a remarkable yield lowering is observed using the 2-nitropropane anion. This result has been ascribed to the extensive *O*-alkylation of the nitronate probably caused by the steric crowding at the nucleophilic carbon.

Under related reaction conditions allylic alcohols, their acetate derivatives and allylphenyl ethers **15** have been proved effective as allylating agents toward various secondary nitroalkanes (Scheme 6).[24] The reaction was carried out in methanol in the presence of a variable amount of sodium methoxide. Allyl acetates and allylphenyl ethers **15** were almost equally reactive in the reaction with 2-nitropropane. Allyl alcohols gave modest results but the addition of one equivalent



R	R¹	R²	yield (%)	13:14
Ph	Me	H	54	87:13
Me	Ph	H	81	49:51
Ph	CO_2Et	Et	89	97:3
Ph	Me	Me	29	93:7

Scheme 5. Pd-catalyzed reaction of allyl acetates with nitronate anions.

Scheme 6. Pd-catalyzed reaction of various allylic alcohol derivatives **15** with nitroalkanes.

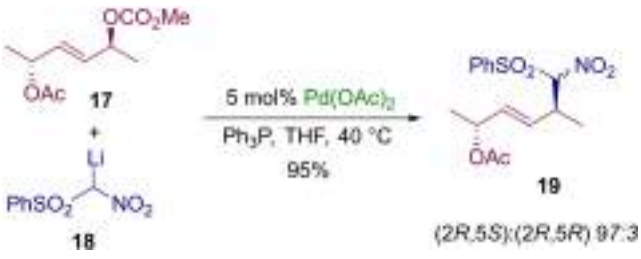
of ethyl acetate provided a remarkable increase in the chemical yield probably because of an *in situ* transesterification. The reactivity of substituted primary allylic alcohols with 2-nitropropane was satisfactory showing an almost exclusive preference for the α-substituted products **16**. Secondary allylic alcohols gave very modest chemical yields (11–31%). Finally, variable results were obtained with other secondary nitroalkanes. Nitrocyclohexane was quite effective in the allylation reaction but linear derivatives other than 2-nitropropane gave modest results.

The initially employed allyl acetates have been subsequently replaced by allyl carbonates showing a superior reactivity profile.[25] The chemoselective substitution of the carbonate moiety is thus possible even in the presence of the acetate group as demonstrated for the reaction of chiral allyl derivative **17** with lithiated nitrosulfone **18** (Scheme 7).[26] The substitution also occurs with substantial retention of the original configuration in **19** although the notable acidity of the further enolizable α hydrogen atom does not allow any stereocontrol of the third stereocenter.

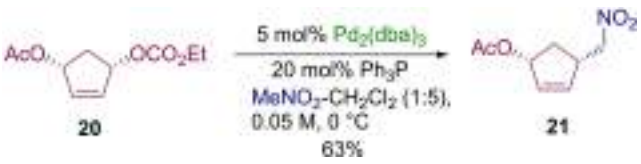
A related process has been observed in the reaction of cyclic derivative **20** with nitromethane under solvolytic conditions (Scheme 8).[27] The nitromethylated product **21**, prepared as single diastereomer, is obtained in lower yield compared to similar reactions involving α-functionalized nitro derivatives. This is a general trend very often observed in these metal catalyzed processes.

The first successful enantioselective nitromethylation of symmetrical carbonates **22** has been carried out using chiral phosphine ligand **23** in the presence of a strong excess of nitromethane for a prolonged time (Scheme 9).[28] A poor enantiocontrol was evidenced using alkenyl derivatives (R = alkyl) although improved *E/Z* diastereoselection has been observed by chain elongation. Conversely, phenyl substituted carbonates **22** were converted into nitrometylated derivatives **24** practically as single *E* stereoisomers with excellent enantioselectivity.

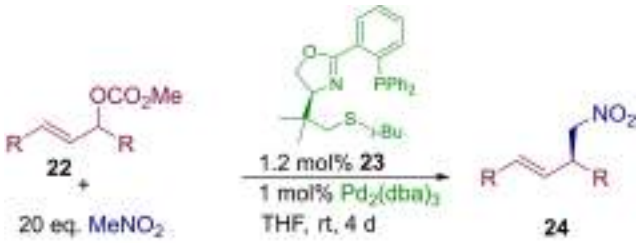
Later on, a truly effective diphosphine ligand **25** has been devised for the Pd-catalyzed allylation of primary nitroalkanes to carbonate **26** (Scheme 10).[29] Interestingly, nitromethane as well as 2-nitropropane are poorly effective in this process which generally affords the corresponding adducts **27** with excellent diastereo- and enantioselectivity. A strong excess of nitroalkane (8 eq.) is usually required for an appropriate conversion but the utilization of functionalized nitro compounds asks for a reduction of this amount (2 eq.) at the expense of the chemical yield. In this context it should be observed that the corresponding yields based on the recovery of the starting material



Scheme 7. Chemoselective Pd-catalyzed reaction of lithiated nitrosulfone **18** with allyl diester **17**.

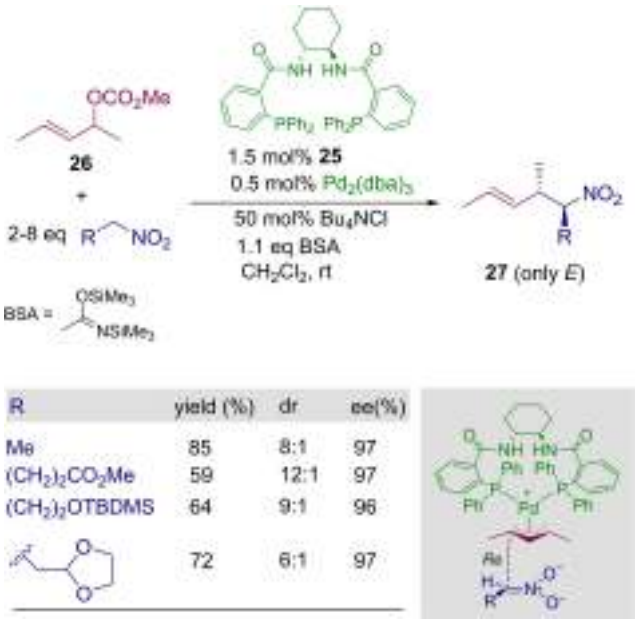


Scheme 8. Chemoselective Pd-catalyzed nitromethylation of diester **20**.

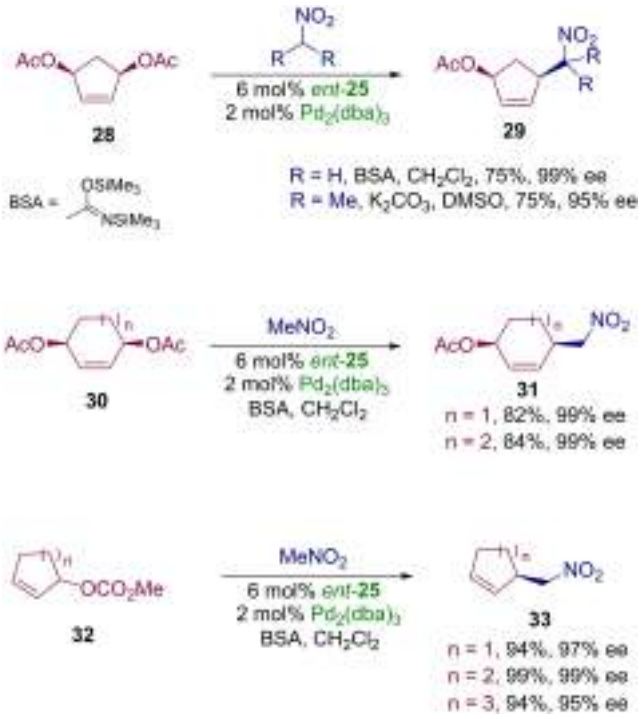


R	*E*:*Z*	yield (%)	ee(%)
Me	74:26	85	76
Et	98:2	83	71
Ph	>99:1	87	>99

Scheme 9. Enantioselective nitromethylation of allyl carbonates **22** assisted by a chiral Pd-complex.



Scheme 10. Diastereo- and enantioselective allylation of nitroalkanes by carbonate **26**.



Scheme 11. Desymmetrization of cyclic diacetates and racemic carbonates.

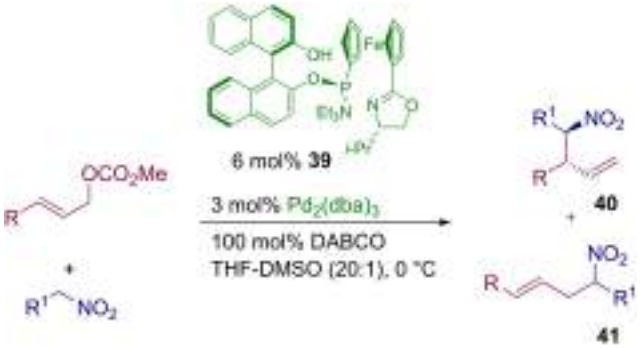
Scheme 12. Pd-catalyzed nitroalkylation of cyclic hydroxyesters **34**.

are well over 90%. The origin of the observed diastereoselectivity has been tentatively ascribed to the basket-shape of the Pd-complex favoring the attack by the *Re* face of the nitronate anion to the π-allyl intermediate. A related approach has been used for the desymmetrization of cyclic diacetates and racemic carbonates using diphosphine ligand *ent*-**25** under similar reaction conditions (Scheme 11).[30]

According to the nature of the substrate, and the nitroalkane employed, slightly different base/solvent combinations have been applied as in the conversion of *meso* diacetate **28** into nitro derivatives **29**. Different ring sized *meso* diacetates **30** can be used for this transformation leading to nitromethylated products **31** in excellent yield and enantioselectivity. Finally, racemic carbonates **32** have been efficiently used in the reaction with nitromethane affording products **33**. The latter reaction has been also carried out on the acetate analogs of **32** using 2-nitropropane with similar levels of enantioselectivity. The palladium catalyzed reaction of monoacetate **34** with nitroalkanes results in the formation of 3-nitroalkylcyclopentanones **35** similarly to the products obtained by a conjugate addition to cyclopentenone. (Scheme 12).[31]

This process can be rationalized considering that the initially formed π-allylic complex **36** upon isomerization is converted into **37** which reacts with nitronates leading to enol **38**. Tautomerization of **38** to the more stable carbonyl systems completes the transformation. The remarkable results obtained in these Pd-catalyzed allylations led to the development of other ligands working under more sustainable conditions. The nitromethylation of cycloalkenyl carbonates has been efficiently carried out in water using as palladium ligand a polymer bound chiral imidazoindolephosphine.[32] The enantioselectivity in this process is notable only using cycloheptenone carbonates (98% ee) since smaller rings give only modest results (70–80% ee). Similarly, an aspartic acid-derived P-chirogenic diaminophosphine oxide has been successfully employed for the nitromethylation of 1,3-diaryl allyl carbonates giving the corresponding products in high yields and excellent enantioselectivity (92–98% ee).[33] Further synthetic efforts have been

especially directed toward the regio- and diastereocontrol of the allylated nitro derivatives. A successful chiral ligand to this scope has been found in the binaphthyl-ferrocenyl compound **39** which palladium complex is very active in the reaction of allyl carbonates with linear nitroalkanes (Scheme 13).[34,35] A notable regiocontrol toward the γ-allylation product **40** is observed which is also generated with high diastereo- and enantioselectivity. An optically pure homoallylnitro compounds **40** (R = 4-ClC_6H_4; R^1 = H) prepared following this procedure has been used for the synthesis of the antidepressant drug (*R*)-baclofen or as in the example reported in Scheme 14, to access α,β-disubstituted amino acid derivatives. The oxidative demolition of the terminal double bond followed by methyl esterification of optically pure compound **42** allowed the introduction of a carboxylate moiety leading to β-nitroester **43**. Chemoselective reduction of the nitro group and reductive amination of the latter compound finally gave the amino acid derivative **44**.



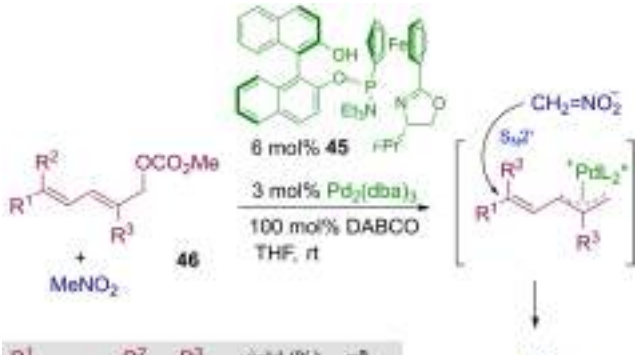
R	R^1	yield (%)	40:41	dr 40	ee (%)
Ph	H	61	92:8	-	97
4-FC_6H_4	H	88	94:6	-	96
Ph	Me	96	97:3	94:6	99
Ph	*n*-Bu	86	96:4	95:5	99
4-$MeOC_6H_4$	Et	94	96:4	97:3	99
3-ClC_6H_4	Et	94	87:13	92:8	98

Scheme 13. Regioselective asymmetric nitroalkylation of allylic carbonates.

Scheme 14. Synthesis of optically active α-amino acid derivative **44** from allylated nitro derivative **42**.

An interesting study on the regioselectivity achievable using dienyl carbonates **46** has been carried out using ferrocenyl based palladium ligand **45** (Scheme 15).[36] Despite the use of the chiral ligand **45**, the enantioselectivity evidenced in this process is practically negligible. However, the palladium complex is able to address a regioselective S_N2' attack of the nitronate anion to the π-allyl intermediate leading to the efficient formation of nitrodienes **47**. As expected, an increase of the steric hindrance around the preferred reaction center leads to a sensible lowering of the observed regioselectivity.

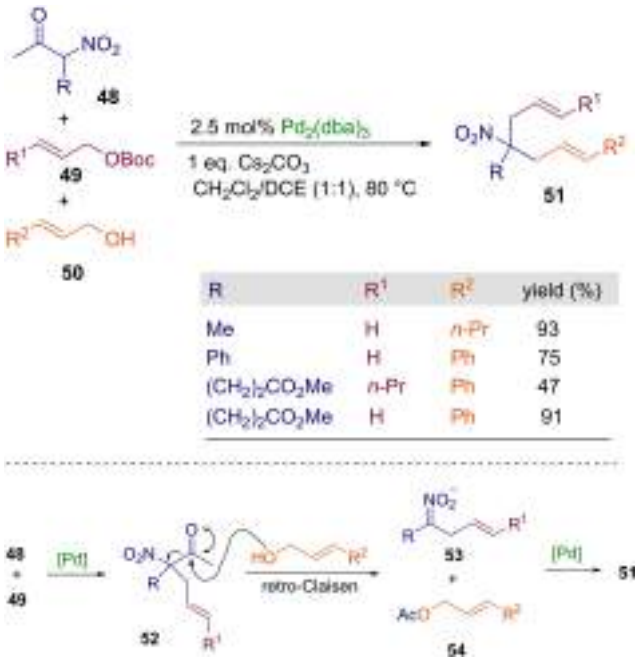
A truly clever transformation has been devised in the palladium-catalyzed three-component coupling of nitro ketones **48** with allyl carbonates **49** and allylic alcohols **50** leading to tertiary bishomoallyl nitroalkanes **51** (Scheme 16).[37] The chemoselective reaction of nitro ketone **48** with carbonate **49** occurs following the usual mechanism giving the allylated derivative **52**. At this point, allylic alcohol **50** reacts, under basic conditions, with **52** by a retro-Claisen process generating the nitronate anion **53** and the allyl acetate **54**. In the presence of the palladium catalyst these intermediates undergo a further allylation which ultimately leads to the bisallylated product **51**. Activation of allylic alcohols can be also realized performing the process under carbon dioxide atmosphere (Scheme 17).[38] The interaction of allylic alcohol **55** with carbon dioxide initially affords an allyl monocarbonate which is activated toward the formation of a π-allylic palladium complex and thus can give the usual reaction with nitronate anions. The latter



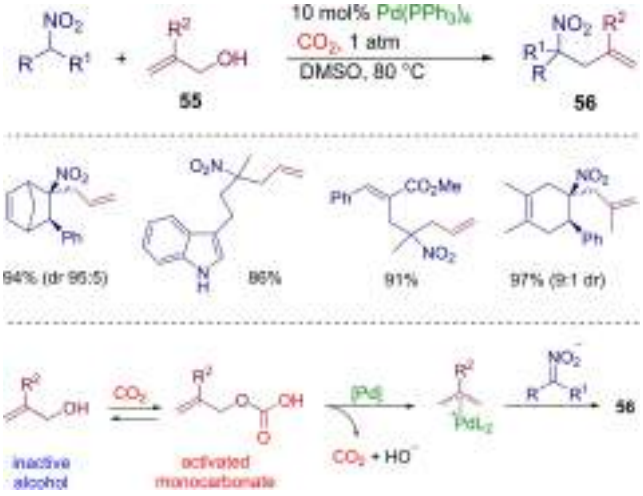
R^1	R^2	R^3	yield (%)	π[a]
Ph	H	H	87	95:5
Ph	H	Me	56	97:3
4-BrC_6H_4	H	H	96	97:3
-$(CH_2)_5$-	H		64	80:20

[a] 47 (sum of other regioisomers)

Scheme 15. Pd-catalyzed regioselective nitromethylation of dienyl carbonates **46**.



Scheme 16. Synthesis of bishomoallyl nitroalkanes by three-component coupling.



Scheme 17. Pd-catalyzed nitroalkylation of allylic alcohols activated by carbon dioxide.

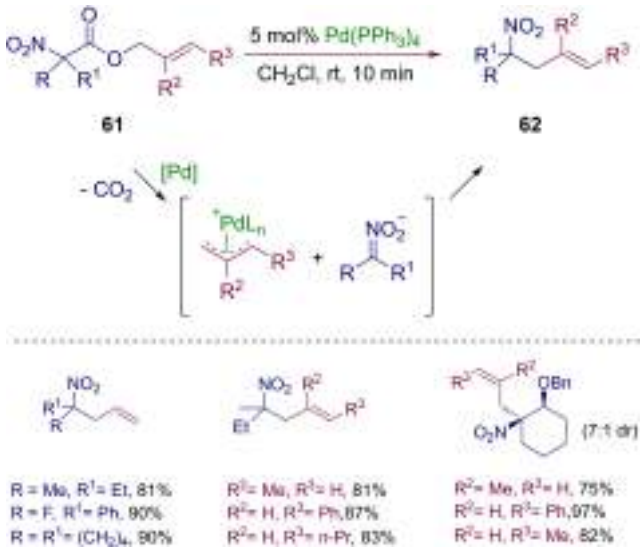
nucleophilic reagents are apparently generated by reaction of secondary nitrocompounds with the hydroxide anions released upon decomposition of the monocarbonate. Functionalized tertiary nitroalkanes **56** are efficiently produced in this process which can be however extended to other stabilized enolate systems including nitriles and carbonyl derivatives. More recently, the allylic alcohol activation has been attained using titanium tetraisopropoxide under similar reaction conditions (Scheme 18).[39] Formation of an allyltitanium alkoxide intermediate provides the required

Scheme 18. Pd-catalyzed nitroalkylation of allylic alcohols activated by titanium tetraisopropoxide.

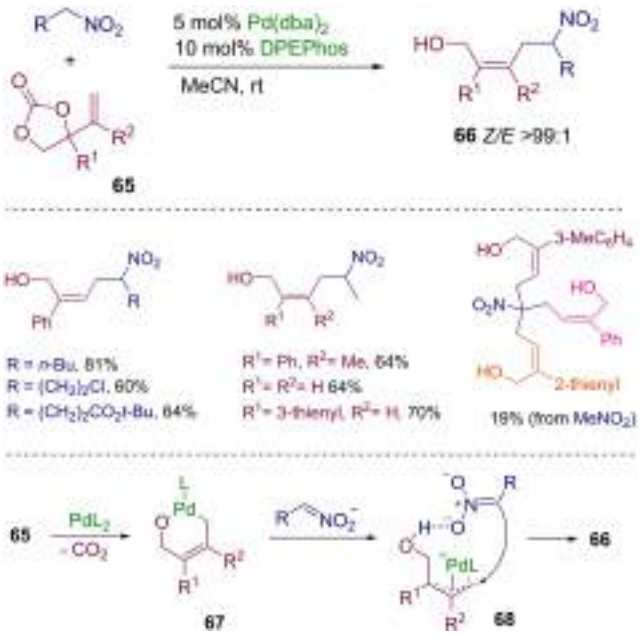
species enabling the generation of the required π-allylic palladium complex. Formation of homoallyl nitro derivatives **57** is less efficient compared to the carbon dioxide usage especially with 3-substituted allyl alcohols as substrates. The effectiveness of this method has been demonstrated in the racemic synthesis of the piperidine alkaloid adalinine **60** (Scheme 19). The allylated nitro derivative **58** was initially converted into ketoester **59** by double ozonolysis and Fisher esterification. The selective reduction of the nitro group was proved rather challenging because of the concomitant elimination of nitrous acid commonly observed in β-nitro ketone derivatives under basic conditions.[6] Thus, the utilization of zinc powder in acetic acid was demonstrated the best method for the reduction-lactamization step leading to adalinine **60**.

Compounds embedding both functional groups like allyl α-nitroesters **61** can be involved in a decarboxylative palladium-catalyzed process which simultaneously generates the π-allylic complex and the nitronate anion (Scheme 20).[40] A fast coupling of these two species leads to homoallyl nitro derivatives **62** in very good yields and satisfactory diastereoselectivity. This synthetic approach was previously anticipated in a general procedure using allylic esters of methylene

Scheme 19. Synthesis of adalinine from homoallyl nitro derivative **58**.



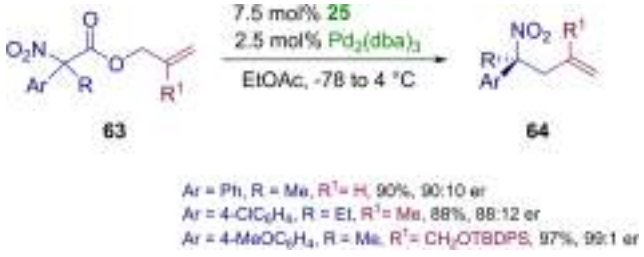
Scheme 20. Pd-catalyzed decarboxylative allylation of *O*-allyl α-nitroesters.



Scheme 22. Stereoselective synthesis of (*Z*)-homoallylic nitroalkanes **66**.

active compounds but in the original reaction conditions, substrates of type **61** gave an almost equimolar mixture of regioisomeric products arising from *C*- and *O*-alkylation (*cf.* Scheme 2).[41] Later on, the asymmetric version of this transformation was carried out using the same catalytic system employed for the intermolecular version of this process (*cf.* Scheme 10). Conversion of allylic esters **63** into homoallyl nitroalkanes **64** is quite efficient but the obtained enantioselectivity is not particularly high except for some particular examples (Scheme 21).[42] Reaction of cyclic carbonates **65** with nitroalkanes under palladium catalyzed conditions affords homoallylic nitroalkanes **66** with outstanding *Z* stereoselectivity (Scheme 22).[43]

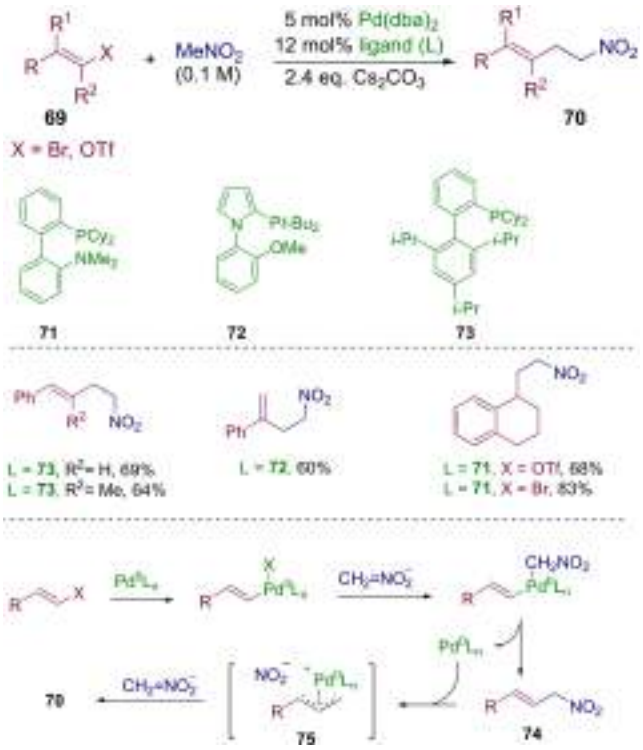
Primary functionalized nitroalkanes efficiently react under the devised reaction conditions while 2-nitropropane requires the utilization of a stronger base such as DBU. Interestingly, the triple reiteration of the same reaction starting from nitromethane and different carbonates **65** allows the preparation of unsymmetrical tertiary nitroalkanes embedding multiple homoallylic frameworks. This transformation entails a preliminary



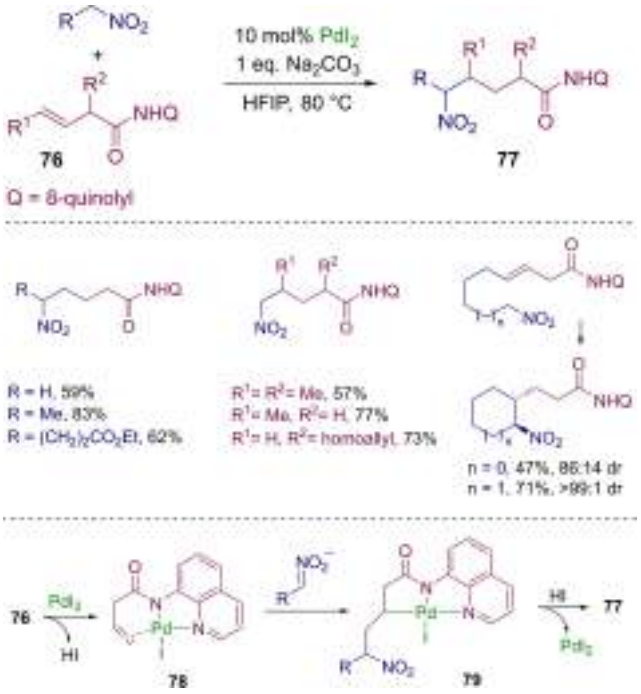
Scheme 21. Enantioselective Pd-catalyzed decarboxylative allylation of *O*-allyl α-nitroesters.

formation of a *Z*-palladacyclic intermediate **67** also supported by DFT analysis. Interaction of **67** with nitroalkane generates the π-allyl palladium complex **68** in which the nitronate anion is induced to attack the terminal carbon leading to the regioselective formation of **66**. Compounds **66**, after conversion into the corresponding carbonates, have been transformed into isoxazoline *N*-oxides by an intramolecular palladium-catalyzed reaction involving the usual π-allylic complex and the nitronate anion oxygen atom.[44]

The well documented aptitude of the nitro group to be eliminated as nitrite anion, has been successfully exploited in the double coupling of nitromethane with vinyl bromides or triflates **69** under palladium catalysis assisted by phosphine ligands **71**–**73** (Scheme 23).[45] The yield of the obtained homoallylic nitro derivatives **70** is strongly affected by the nature of the ligand employed and is generally higher using vinyl bromides as substrates. Formation of products **70** can be easily rationalized accounting for the formation of allylnitro compounds **74** through a mechanism involving a vinylpalladium intermediate. Interaction of **74** with the Pd^0-complex generates the π-allylic complex **75** which reacts with the methanenitronate anion leading to the target compound **70**. Interestingly, the direct utilization of allylnitro compounds **74** in this process does not provide the homologues **70** with the same level of efficiency displayed by the double coupling starting from vinyl derivatives **69**. Thus, slow formation of intermediate **74** appears mandatory for an appropriate overall catalytic cycle of the process. Unactivated alkenes such as β,γ-unsaturated amides **76** can be used



Scheme 23. Pd-Catalyzed double coupling of nitromethane with vinyl bromides and triflates.



Scheme 24. Nitroalkylation of β,γ-unsaturated amides bearing an internal Pd-ligand.

as alkylating agents toward nitroalkanes providing that a suitable chelating group on the amide moiety is able to coordinate the palladium salt (Scheme 24).[46] The 8-quinolyl appendage enables an easy formation of the palladium complex **78** which undergoes a regioselective addition of the nitronate anion leading to a further intermediate **79**. Protodepalladation of **79** by the initially released HI completes the formation of the target adduct **77**. The highly ionizating solvent haxafluoroisopropanol (HFIP) assists the addition of the sodium nitronate to the complex **78** through hydrogen bonding also involving the iodine atom as demonstrated by DFT computational studies. Nitromethane as well as primary nitroalkanes can be used in this process that can be also carried out intramolecularly with formation of five and six membered ring functionalized nitrocycloalkanes.

3.2. Iridium-Catalyzed Reactions

Alternative methods for the allylation of unactivated nitroalkanes using metal complexes other than those of palladium are rather scanty. In a recently reported procedure, unactivated nitroalkanes have been made to react with allyl acetates in the presence of chiral iridium complex **80** (Scheme 25).[47] The reaction is highly regioselective in favor of the branched adduct **81** and shows very good levels of enantioselectivity

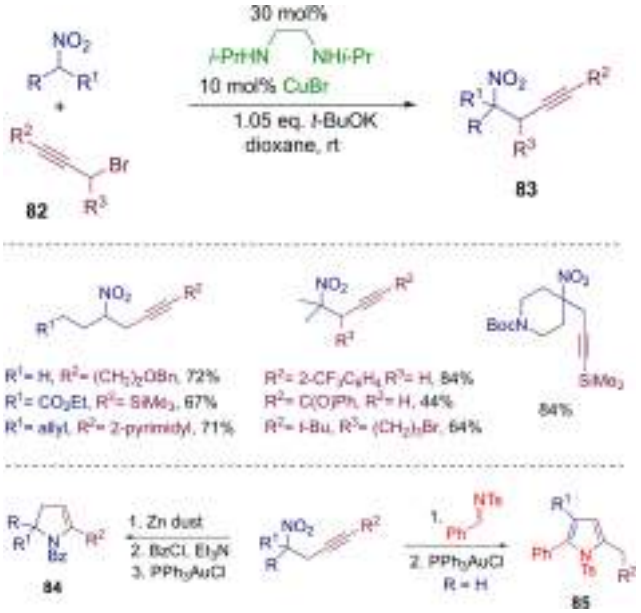
Scheme 25. Ir-catalyzed allylation of nitroalkanes.

with a notable number of functionalized substrates. Products **81** have been converted into the corresponding primary amines in almost quantitative yield using zinc metal and ammonium chloride in ethanol-water.

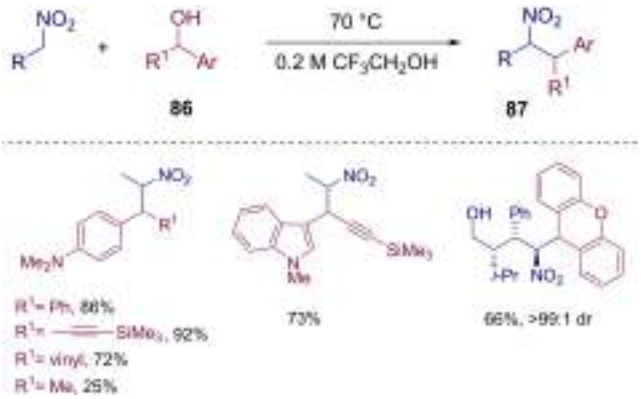
3.3. Copper-Catalyzed Reactions

Direct propargylation of unactivated nitroalkanes using functionalized propargyl bromides **82** can be efficiently pursued under copper catalysis in the presence of a

1,2-diamine ligand (Scheme 26).[48] To the best of our knowledge, this is the only synthetic protocol for the preparation of homopropargylic nitro derivatives **83** embedding a notable number of functional groups working on primary and secondary substituted reactants. The synthetic value of the obtained products **83** has been demonstrated by their conversion to pyrrolines **84** by preliminary nitro reduction followed by gold catalyzed cyclization. Alternatively, pyrroles **85** can be prepared through an initial nitro-Mannich reaction and a subsequent gold catalyzed cyclization also entailing a loss of nitrous acid to generate the heteroaromatic system.



Scheme 26. Synthesis of homopropargylic nitro derivatives by Cu-catalyzed coupling of nitroalkanes with bromides **82**.



Scheme 27. Reaction of nitroalkanes with activated alcohols *via* carbenium ion intermediates.

4. S_N1-Type Reactions with Activated Alcohols

Activated secondary alcohols are known to provide stabilized carbenium ions under acid catalyzed conditions or in highly ionizing solvents.[49]

In a study directed to evaluate the nucleophilicity of nitroalkanes, stable benzhydrylium tetrafluoroborates have been made to react with nitronate anions in water-acetonitrile mixtures leading to the corresponding adducts.[50,51] A more practical and efficient method starting from secondary alcohols **86** allows the S_N1-type reaction with nitroalkanes using 2,2,2-trifluoroethanol as a solvent (Scheme 27).[52]

Formation of adducts **87** is due to the enhanced electrophilic character of the carbenium ion generated upon dehydration of the alcohol associated with the solvent effect also enabling a sensible nitro to *aci* tautomeric shift. A notable number of doubly activated secondary alcohols **86** bearing aryl, vinyl and alkynyl substituents have been exploited in this process. Simple benzylic alcohols such as 1-phenylethan-1-ol are not enough activated for the efficient carbenium ion formation and thus provide unsatisfactory results. The diastereoselectivity achievable using enantioenriched nitroalkanes is usually excellent evidencing a strong preference for the *anti* stereoisomer.

5. Radical Induced Alkylations

5.1. Early Studies

During the middle of the last century, some studies have emphasized the different outcome observed in the reaction of aryl-substituted benzyl halides with the anion of 2-nitropropane (Scheme 28).[53] Expectedly, the reaction of 4-methylbenzyl bromide with the 2-

Scheme 28. S_N2 *vs* $S_{RN}1$ processes in the reaction of benzyl bromides with the anion of 2-nitropropane.

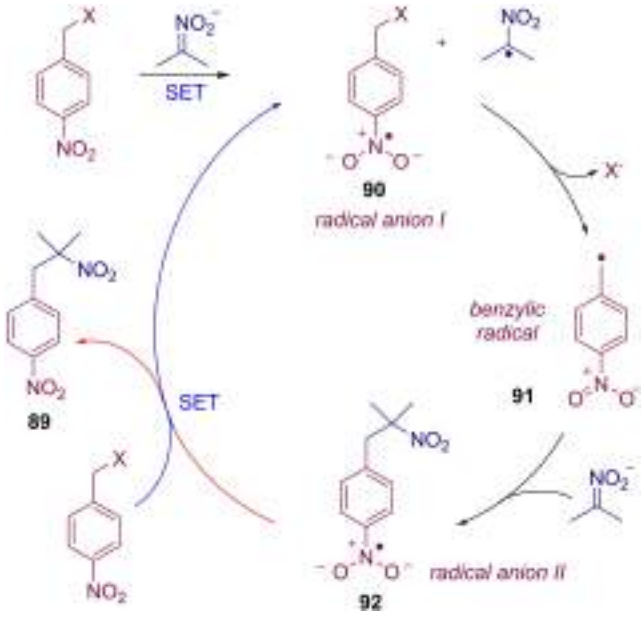
nitropropyl anion occurs through a S_N2 process favoring the *O*-alkylated intermediate **88** which rapidly decomposes to 4-methylbenzaldehyde and acetone oxime. This behavior is common to many other substituted benzyl halides resulting in a transformation also known as the Hass-Bender oxidation.[54] Conversely, the same reaction carried out on 4-nitrobenzyl bromide affords the corresponding *C*-alkylated product **89** in 83% yield with the presence of only 1% of the corresponding 4-nitrobenzaldehyde.

The well-known aptitude of nitro derivatives to be involved in single electron transfer (SET) processes is due to a low-energy π* (LUMO) molecular orbital which allows the formation of a relatively stable radical-anion. This behavior has been mainly evidenced in the reaction of nitro compounds with several nucleophiles.[55] The reaction of 4-nitrobenzyl halides with the anion of 2-nitropropane is actually a monomolecular radical chain process ($S_{RN}1$) in which a radical anion **90** is initially generated by a SET between the reactants (Scheme 29).[56] Elimination of the halide anion generates a stabilized benzylic radical **91** which upon addition with the nitronate anion affords a second radical anion **92**. The chain propagation is closed by the interaction of **92** with the 4-nitrobenzyl halide leading to the target product **89** and the formation of radical anion **90**.

The general mechanism portrayed in Scheme 29 can in principle be valid for any SET process in which a stabilized anion X^- can be eliminated from the intermediate radical anion. In this context, it should be observed that nitrite and arylsulfinate anions are enough stable to be involved in such process. This reaction pathway has been also observed in the reaction of other 4-substituted benzyl halides embedding the cyano group. Representative examples of possible transformations are collected in Scheme 30.[57,58]

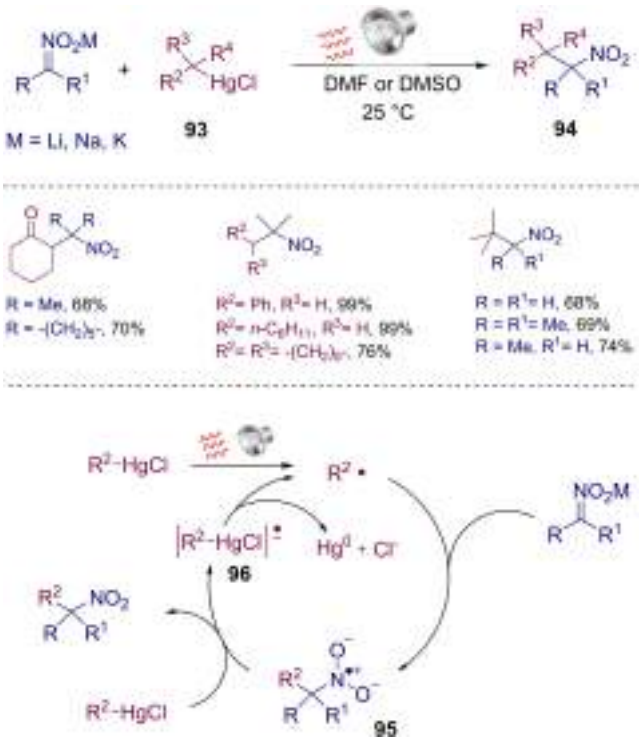
Although quite efficient, these $S_{RN}1$ processes are limited in scope since are mostly tailored for secondary nitroalkanes. Scattered examples of related reactions involving activated nitroalkanes (*e.g.*,2-nitroesters), phenylnitromethane or nitromethane are available, but their synthetic significance is rather limited.[56] A valuable feature of this approach stems in the possibility of generating highly branched functionalized derivatives since contrary to S_N2 reactions, the actual $S_{RN}1$ pathway is rather insensitive to the steric hindrance. The homolytic cleavage of carbon-mercury bonds promoted by sunlamp irradiation has been also employed for the generation of alkyl radicals. These species can add to nitronate anions through the $S_{RN}1$ mechanism leading to alkylated nitroalkanes **94** (Scheme 31).[59] Various alkylmercury compounds **93** have been exploited in the reaction with nitronate anions obtained from nitromethane, primary and secondary nitrocompounds.[60] The alkyl radical generated in the initiation step adds to the nitronate anion leading to nitrogen-centered radical anion **95**. The SET from this radical anion to the organomercury derivative release the target alkylated nitrocompound and generates a new radical anion **96.** Decomposition of this reactive intermediate affords the alkyl radical and metallic mercury.

Although rather versatile, this synthetic protocols is affected by evident sustainability problems because of the inherent toxicity of organomercury compounds. Visible light irradiation was also used to generate radicals from alkyl cobaloximes $RCo(III)(dmgH)_2py$ (dmgH = dimethylglyoxime monoanion).[61] The feasibility of this method has been tested on a very narrow number of examples and requires a fourfold excess of the nitronate anions. The whole process does not entail a radical chain reaction and therefore the alkyl radical

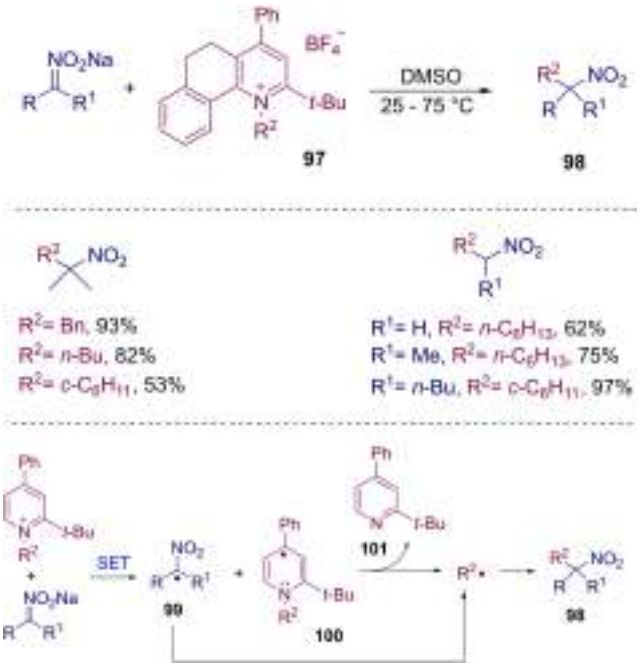


Scheme 29. Radical chain mechanism of the $S_{RN}1$ reaction of benzyl halides with the anion of 2-nitropropane.

Scheme 30. $S_{RN}1$ reaction of the 2-nitropropyl anion with various benzylic derivatives.



Scheme 31. Organomercury compounds in the $S_{RN}1$ reactions with nitronate anions.



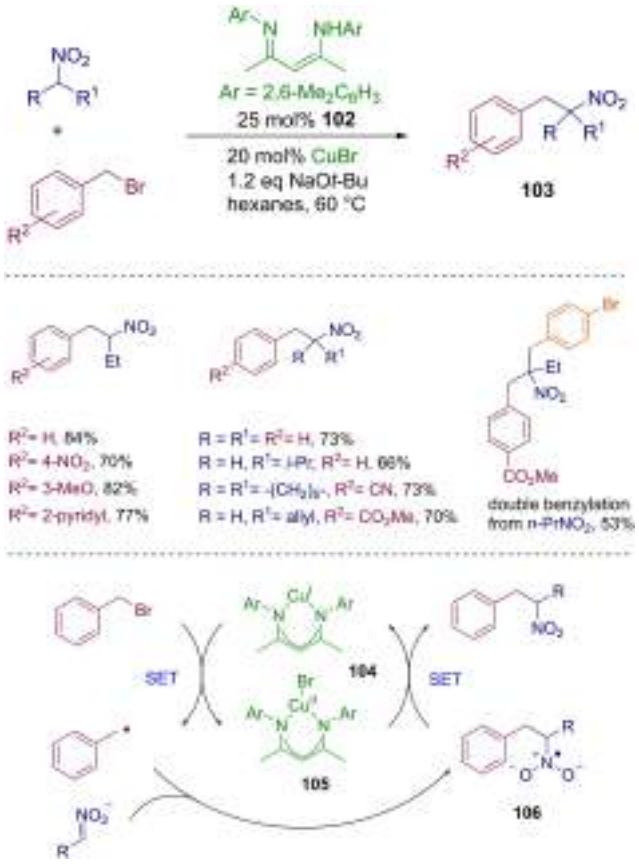
Scheme 32. Reaction of nitronate anions with dihydrobenzoquinolinium cations.

must be steadily generated by photochemical irradiation. Finally, alkylation of nitroalkanes can be also achieved by reaction of sodium nitronates with 2,4-disubstituted 1-alkyl-5,6-dihydrobenzo[*h*] quinolinium salts **97** (Scheme 32).[62] This reaction has been intitially set up using 2,4-disubstituted 1-alkylpyridinium salts which however are less effective than their quinolinium analogues.[63,64] Compounds **97** are available by amination of the corresponding pyrilium ions and can be used with a large variety of nitronate anions ranging from nitromethane to secondary nitroalkanes. The harsh reaction conditions usually required for S_N2-type alkylations with reagents **97** led to the conclusion that in the nitroalkane reaction a different mechanism is probably operative. Detailed mechanistic studies have demonstrated that reaction of pyridinium salts with nitronate anions provides a couple of radicals **99** and **100** by a SET process.[65] Homolytic cleavage of the carbon-nitrogen bond in radical **100** affords stable pyridine **101** and an alkyl radical which, by coupling with the α-nitro radical **99**, finally leads to the target alkylated nitrocompound **98**. The overall process does not entail a radical chain mechanism as observed in $S_{RN}1$ reactions. The relative complexity of the alkylating salts **97** has strongly limited the practical impact of this method which, to the best of our knwledge, has not found any application in synthesis.

5.2. Metal-Catalyzed Radical Processes

The turning point in the radical induced *C*-alkylation of unactivated nitroalkanes with alkyl halides was dictated just over ten years ago by Watson and coworkers who introduced a different paradigm for the SET process.[66,67] A copper(I) complex obtained using enamino imine ligand **102** has been used to promote the generation of benzyl radicals amenable to be coupled with nitronate anions (Scheme 33).

The devised protocol has a truly large field of application since is open to a wide array of functionalized benzyl bromides including simple (bromomethyl)benzene. More importantly, the nitroalkane usage has practically no restrictions spanning from nitromethane to secondary functionalized nitro compounds. This feature also allows a further reiteration of this procedure enabling the preparation of unsymmetrical bisbenzylated nitro derivatives **103**. In the proposed mechanism, which does not entail a radical chain process, the efficient generation of the benzylic radical is obtained by interaction of the benzyl bromide with Cu(I)-complex **104** which is oxidized to Cu(II)-complex **105**. A fast coupling of the benzylic radical with the nitronate anion affords radical anion intermediate **106** which is oxidized by complex **105** to the final product **103** restoring the complex **104** and thus closing the catalytic cycle. This procedure was initially limited to the use of benzyl groups but has hereafter been extended to other systems amenable of generating stabilized radical intermediates. The utilization of α-



Scheme 33. Cu-catalyzed radical induced benzylation of nitroalkanes.

bromocarbonyl derivatives **107** in the reaction with nitroalkanes under reaction conditions similar to those previously applied for benzyl bromides leads to the corresponding β-nitrocarbonyl compounds **108** (Scheme 34).[68] Esters, amides and other carbonyl substrates can be applied to this process working even with largely branched reactants although with reduced efficiency compared to less hindered combinations.

Scheme 34. Cu-catalyzed coupling of α-bromocarbonyls with secondary nitroalkanes.

The mechanism probably parallels that depicted in Scheme 33 and formation of stabilized α-carbonyl radical intermediates is very likely under these reaction conditions.

Following the same trend, α-bromonitriles **109** can be efficiently converted into 2-cyanonitroalkanes **110** (Scheme 35).[69] The scope of the reaction is similar to that previously disclosed with α-bromocarbonyls **107** allowing the utilization of a wide array of differently substituted reactants. The synthetic usefulness of the obtained adducts **110** is nicely demonstrated by their conversion into conjugated cyanoalkenes **111** by basic induced elimination of nitrous acid. Alternatively, 5-aminoisoxazoles **112** can be prepared exploiting a nitro to oxime conversion (Nef reaction),[70] followed by ring closure onto the cyano group. A common feature of these formerly released procedures is the need of resonance stabilized radical intermediates for the interaction with nitronate anions.

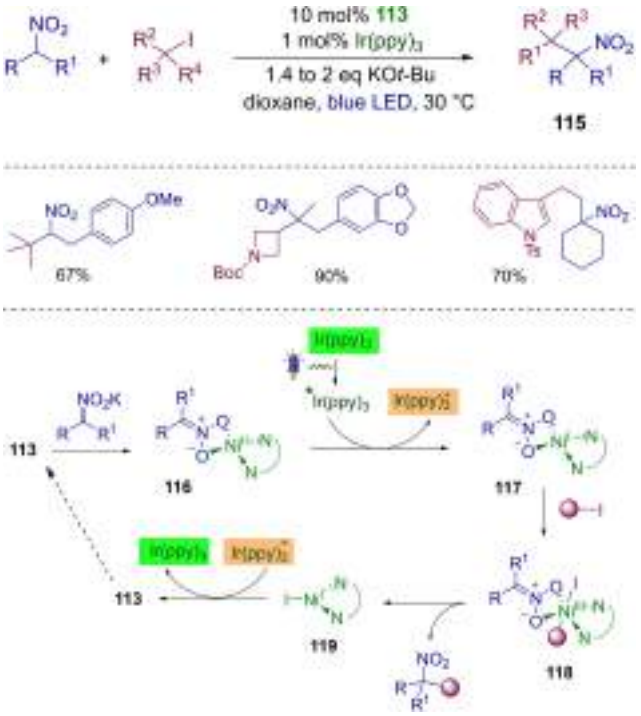
This limitation is no longer present using the nickel(II)-complex **113** which enables the utilization of primary to tertiary alkyl iodides in the reaction with primary nitroalkanes (Scheme 36).[71] Alkyl iodides as well as nitroalkanes can embed various functional groups in remote position of the molecule leading to the corresponding adducts **114** in satisfactory yield. Interestingly, 5-chloro and 5-bromo iodopentanes react chemoselectively at the iodo-bearing carbon enabling the incorporation of halide atoms in the target nitro derivative. The formation of radical intermediates in this process has been probed using iodomethylcyclopropane and 6-iodohex-1-ene as substrates which in a complementary process afford the corresponding 4-butenyl and the cyclopentylmethyl derivatives **114**. Furthermore, the reaction carried out in the presence of TEMPO was totally ineffective in generating the expected adducts.

Scheme 35. Cu-catalyzed coupling of α-bromonitriles with nitroalkanes and synthetic application of products **110**.

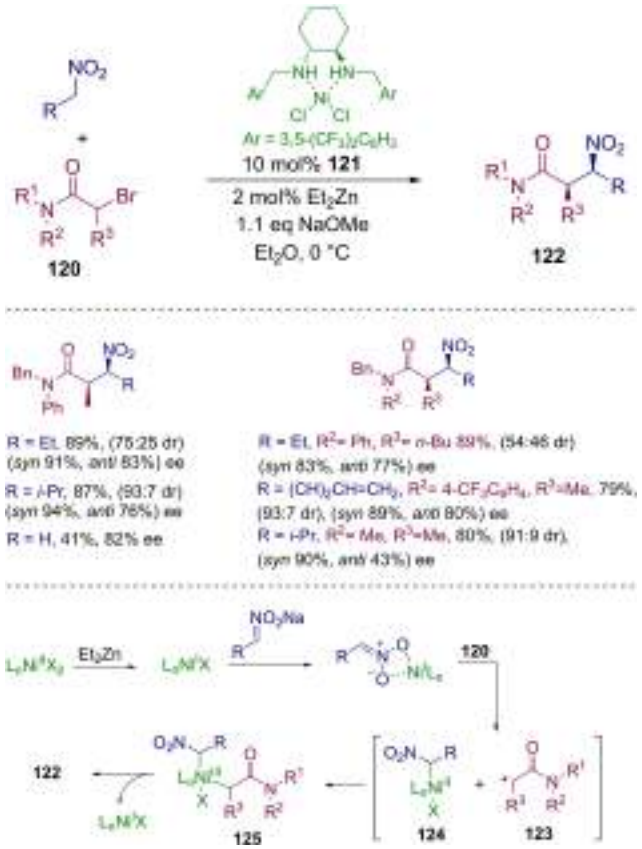
Scheme 36. Ni-catalyzed coupling of alkyl iodides with nitroalkanes.

The efficiency of this process can be notably increased allowing a photoredox reactivation of the catalyst **113** using tris(2-phenylpyridine)iridium(III) [$Ir(ppy)_3$] under blue LED irradiation (Scheme 37).[72] This improved protocol avoids the utilization of diethylzinc as activator and enables the utilization of a wide arrays of functionalized nitro derivatives ranging from nitromethane to secondary nitroalkanes. Reduction of the Ni(II) nitronate **116** is provided by the excited state of the photocatalyst $Ir(ppy)_3$ obtained by blue LED irradiation. Ni(I)-Complex **117** reacts with the alkyl iodide *via* a radical intermediate leading to a Ni(III) nitronate **118** which by reductive elimination affords the alkylated nitroalkane and Ni(I)-complex **119**. The latter intermediate is reoxidized to the actual catalyst **113** by the cation $Ir(ppy)_3^+$ released from the initial photoinduced process. The feasibility of these organometallic catalyzed processes has paved the way for the first asymmetric alkylation of nitroalkanes by α-bromoamides **120** using chiral Ni(II)-complex **121** (Scheme 38).[73] The observed diastereoselectivity in the formation of adducts **122** is not particularly remarkable, apart from some examples arising from hindered nitroalkanes, but is constantly in favor of the *syn* stereoisomer. Interestingly, a matching interaction of the reactants with the chiral catalyst enables a higher enantioselectivity of the *syn* adduct over the *anti* one.

The application of this synthetic protocol to nitromethane gives moderate results in term of chemical yield and enantioselectivity. Formation of radical intermediates in this process has been secured by various trials and a plausible mechanistic portrait would involve an initial formation of a Ni(I)-complex by reaction of **121** with diethylzinc. Although sodium nitronate is scarcely soluble in diethyl ether, the



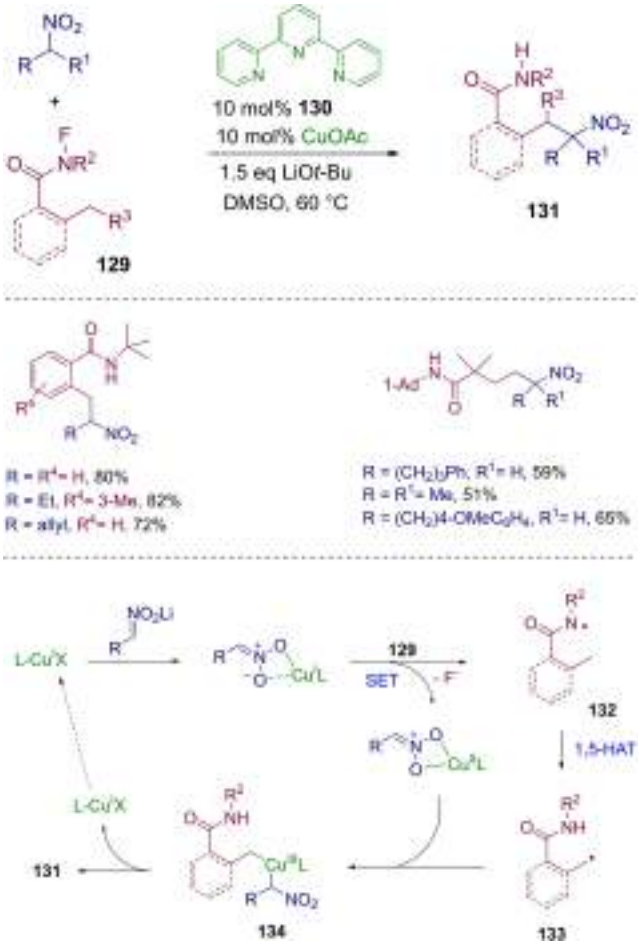
Scheme 37. Coupling of alkyl iodides with nitroalkanes with phodoredox catalyzed activation of the organometallic catalyst.



Scheme 38. Ni-catalyzed coupling of α-bromoamides with nitroalkanes.

nickel(I) nitronate has probably an increased solubility allowing a proper interaction with amide **120**. The electronic exchange between these reactants generates radical **123** and Ni(II) complex **124** which by recombination affords intermediate **125**. The final reductive elimination on **125** leads to the alkylated product **122** and regenerates the active Ni(I) catalyst. The obtained products **122** are amenable of further synthetic manipulations as demonstrated, among others, by the allylation of derivative **126** using allyl *t*-butyl carbonate under palladium-catalyzed conditions (Scheme 39). Compound **127** is formed with excellent stereoselectivity and can be subsequently transformed into β-amino acid derivative **128** by reduction of the nitro group and tosylation of the resulting amine. Reaction of 2-alkyl-*N*-fluoro-*N*-alkylbenzamides **129** with nitronate anions under Cu(I) catalyzed conditions affords nitro derivatives **131** arising from a formal alkylation of the 2-alkyl side chain (Scheme 40).[74] This versatile procedure is effective on differently substituted nitroalkanes and can be also extended to aliphatic *N*-fluoroamides providing that no enolizable hydrogen atoms are present in the substrate **129**. The process follows an established protocol involving the formation of a Cu(I) nitronate which by a SET reaction with the fluoroamide **129** generates the aminyl radical intermediate **132**. This radical species undergoes a 1,5-hydrogen atom transfer (1,5-HAT) leading to a benzyl or alkyl radical **133** which reacts with the previously released Cu(II) nitronate giving the Cu(III) derivative **134**. Finally, the usual reductive elimination of the Cu(I) complex affords the target compound **131** enabling the regeneration of the active catalyst.

Scheme 39. Synthesis of optically active β-amino amide **128**.



Scheme 40. Cu-catalyzed coupling of *N*-fluoroamides with nitroalkanes *via* 1,5-HAT process.

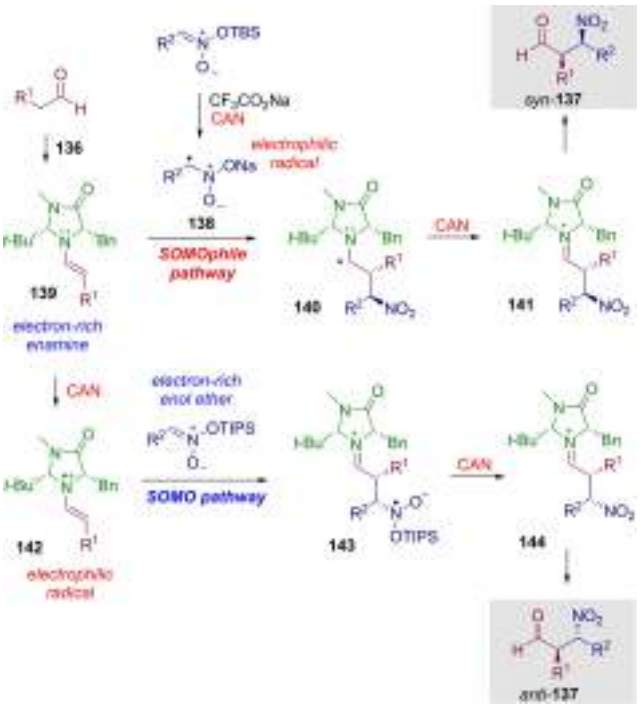
In this context, it should be observed that the reaction of *N*-fluoroamides bearing primary or secondary *N*-alkyl groups follows a totally different route. In these substrates the base-promoted hydrofluoric acid elimination generates a *N*-acylimine intermediate R-(CO)N=CHR[4] that undergoes a nitro-Mannich process with the nitroalkane.[75]

5.3. Organocatalyzed Radical Processes

Conversion of sodium nitronates into α-nitroalkyl radicals and their addition to electron-rich olefins has been reported about thirty years ago.[76,77] The radical formation was obtained by nitronate oxidation using cerium(IV) ammonium nitrate (CAN) and its addition to silyl enol ethers was successfully achieved. However, because of the instability towards purification of the resulting β-nitro ketones, the synthetic protocol was driven to the preparation of α,β-unsaturated ketones by nitrous acid elimination. Later on, the same approach was developed for the asymmetric organocatalyzed synthesis of β-nitro aldehydes **137** using the same oxidant (Scheme 41).[78] The diastereodivergent synthesis of compounds **137** has been carried out using aldehydes and silyl nitronates **135** as reactants under enamine catalysis by chiral pyrrolidine **136**. Through a complementary mechanistic pathway, triisopropylsilyl (TIPS) nitronates mainly lead to *anti*-**137** while *t*-butyldimethylsilyl (TBS) nitronates predominantly give *syn*-**137**.

R^1	R^2	SiR_3	yield (%)	anti:syn	ee (%)
$(CH_2)_3Ph$	Et	TIPS	86	4:1	86
$(CH_2)_3Ph$	Et	TBS	76	1:5	94
$(CH_2)_4OBz$	$(CH_2)_2CO_2Me$	TIPS	79	6:1	91
$(CH_2)_4OBz$	$(CH_2)_2CO_2Me$	TBS	68	1:8	91
$(CH_2)_4OBz$	$(CH_2)_2CH{=}CH_2$	TIPS	73	2:1	80
$(CH_2)_4OBn$	$(CH_2)_2CH{=}CH_2$	TBS	91	1:5	96

Scheme 41. Diastereodivergent organocatalyzed asymmetric synthesis of β-nitro aldehydes.



Scheme 42. Mechanistic course for the diastereodivergent asymmetric synthesis of β-nitro aldehydes **137**.

The key point in the adopted strategy stems from the different stabilty of silyl nitronates **135** under the different reaction conditions. Since TBS nitronates are easily cleaved by sodium trifluoroacetate, the resulting sodium nitronate having a low redox potential is readily oxidized to the low energy SOMO electrophilic radical **138** (Scheme 42). This radical species reacts with electron-rich enamine **139** through a SOMOphile pathways leading to radical **140**. Further oxidation of **140** by CAN gives iminium ion **141** which is finally hydrolyzed to *syn*-**137**. In the alternative SOMO pathway, the TIPS nitronates are stable in the devised reaction conditions. Therefore the oxidation only involves enamine **139** which is converted into the low energy SOMO electrophilic radical **142**. Addition of this radical to the TIPS nitronate generates a nitrogen-centered radical **143** which is oxidized to iminium ion **144** and finally hydrolyzed to *anti*-**137**.

5.4. Photoenzymatic Catalyzed Processes

The new frontier for the assembling of molecular frameworks entails the utilization of photobiocatalytic strategies.[79] The first asymmetric photoenzymatic catalyzed procedure for the reaction of nitroalkanes with α-chloroamides has been realized very recently using a flavin-dependent 'ene'-reductase (ERED) jointly with cyan LED irradiation.[80] The alkylation was successfully carried out but the nitro group was contextually eliminated as nitrite anion leading to the formation of enantioenriched alkylated amides. Later on, a modified version of the same process was proved effective in leading the nitroalkylated compounds **146** from α-chlorocarbonyls **145** (Scheme 43).[81]

The engineered ERED enzyme GkOYE-G7 was successfully employed in this process under cyan LED irradiation especially using α-chloro-*N,N*-dimethylacetamides and 2-nitropropylaryl derivatives.

Using this reactants combination, satisfactory yields and excellent levels of enantioselectivity have been obtained. However, chain elongation or chain shortage

Scheme 43. Asymmetric photoenzymatic coupling of nitroalkanes with α-chlorocarbonyl derivatives.

of the nitro derivative resulted in the formation of racemic mixtures or poor yield of products. Similarly, no enantioselectivity was observed moving from α-chloroamides to the corresponding ester or ketone derivatives. The whole transformation is conceivably assisted by a flavin residue of the enzyme which by proton exchange initially favors the formation of the nitronate anion. Upon irradiation, a charge transfer complex is activated resulting in a SET process generating the α-amido radical required for the interaction with the nitronate anion following the classical mechanism. Interestingly, introducing in the reaction mixture a NADPH turnover system, this protocol enables the utilization of nitroalkenes as substrates. Nitroalkenes are preliminarily reduced into the corresponding nitroalkanes which are then involved in the alkylation process.

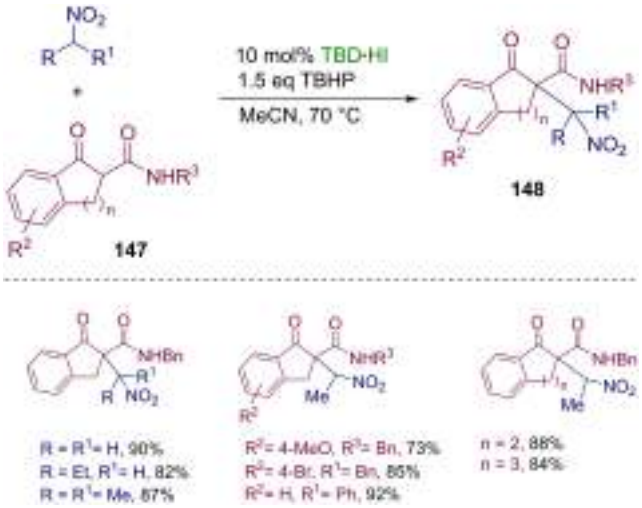
5.5. Other Radical Processes

Alkylation of nitroalkanes by β-ketoamides **147** can be obtained under oxidative condition using *t*-butyl hydroperoxide (TBHP) in the presence of triazabicyclodecene hydroiodide (TBD·HI) (Scheme 44).[82]

This procedure is viable for a series of differently sized cyclic β-ketoamides as well as various nitroalkanes. The reported transformation probably involves the oxidative iodination of the methylene active carbon atom followed by the generation of a stabilized radical by carbon-iodine homolytic cleavage. The interaction of this radical with the nitronate anion would lead to the target adducts **148** according to the established mechanism. The actual formation of radical intermediates in this process has been demonstrated by the failure of any reaction using TEMPO as radical scavenger. α-Trifluoromethylation of α-nitroesters can be carried out using the Togni's reagent,[83] but the same process on unactivated nitroalkanes has been only recently implemented. The reaction is based on the utilization of the commercially available Utimoto's reagent **149** and is effective on secondary nitroalkanes (Scheme 45).[84] Various functionalized nitroalkanes have been tested for this purpose with satisfactory results although the recorded diastereoselectivity, when applicable, is generally modest except with nitrocycloalkanes as substrates. Under basic conditions, the formed nitronate anion is supposed to form a tightly associated ion pair with the sulfonium ion **149** favoring a slow electron transfer process which generates the trifluoromethyl and the α-nitro radicals. A fast coupling of these radicals affords the target trifluoromethylated nitro compounds **150**. The known aptitude of the nitro group to undergo elimination of nitrous acid has been exploited to stereoselectively prepare trifluoromethylated alkenes.

6. Conclusion and Outlook

The easy and fast enolization of nitroalkanes has dictated their widespread utilization as stabilized carbanions in the formation of carbon-carbon bonds by reaction with different electrophiles. However, the limited nucleophilicity of the nitronate anions obtained from unactivated nitroalkanes has mostly privileged the development of synthetic protocols related to the use of sp^2 carbon electrophiles such those involved in nitroaldol (Henry) and conjugate additions. The bidentate character of the nitronate anion makes troublesome its involvement in nucleophilic substitution reactions (S_N2) with sp^3 hybridized carbon electrophiles because of the strongly competitive *O*-alkylation. An increase



Scheme 44. Organocatalyzed reaction of nitroalkanes with β-ketoamides.

Scheme 45. Trifluoromethylation of nitroalkanes by the Utimoto's reagent **149**.

of the nucleophilic power of the nitronate anion exploiting the formation of dianions offers only a partial solution to this drawback. Thus, metal catalyzed allylations soon appeared as a viable solution ensuring the formation of functionalized homoallylic nitro derivatives amenable of further synthetic manipulations at the terminal double bond. A different strategy envisages the utilization of coupling reactions involving the formation of radical intermediates surmounting the sluggish reactivity inherent in totally ionic processes. The old fashioned $S_{RN}1$ processes, involving the reaction of nitronates with electron-poor benzylic halides through a SET mechanism, have been used as a model for the recent development of organometallic-catalyzed reactions entailing outstanding levels of selectivity and efficiency. These are actually the most reliable synthetic protocols for the direct alkylation of unactivated nitroalkanes using simple and functionalized alkyl halides. Trends in these alkylative processes are represented by the very recently born photobiocatalytic strategies which ensure exciting prospects for future developments in this field.

Acknowledgements

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