

cine- and *tele-*Substitution reactions: review of work from 2002-2016

Jerzy W. Suwiński

Centre of Polymer and Carbon Materials, Polish Academy of Sciences,

M. Skłodowskiej-Curie 34, Zabrze 41-819

E-mail: jsuwinski@cmpw-pan.edu.pl

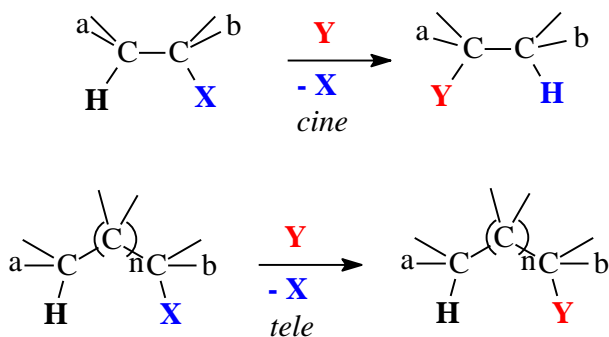
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Abstract

This report brings new facts and achievements on the *cine-* and *tele-*substitutions reactions published in the last fifteen years. The reactions occurred primarily in such systems as nitroarenes, metal homoarene complexes, and five- or six-membered heteroarenes. Sometimes similar reactions were also observed in other systems, including non-aromatic. *cine-* and *tele-*Substitution reactions are presented here independently of their mechanisms.



Keywords: Substitution, cine, tele, arene, complex

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1. Introduction

In 1998, F. Rose-Munch et al. summarized¹ the achievements on indirect nucleophilic substitution in arenetricarbonylchromium and cationic arenetricarbonylmanganese complexes presenting several examples of *cine*- and *tele*-substitutions, as well the first example of *cine*- and *tele*-substitution in neutral cyclohexadienyltricarboxylmanganese complex (119 references). A long review, titled “*Transition-Metal-Mediated Dearomatization Reactions*”², that appeared two years later only briefly mentioned *cine*- and *tele*-substitutions in arenetricarbonylchromium complexes, noting that both reactions probably involved the following sequence of reactions: nucleophilic addition, protonation, isomerization and elimination to reconstruct aromatic system (4 references). In 2001, we published the first general review article³ on the *cine*- and *tele*-substitutions describing these types of reactions in homoarenes, heteroarenes and aliphatic systems, regardless of nucleophilic, electrophilic or radical mechanisms of the reactions (210 references). One year later, Rose-Munch and Rose published a microreview on *cine* and *tele* nucleophilic substitutions describing newer achievements for the reactions of (arene)tricarbonyl-chromium and tricarbonyl(η 5-cyclohexadienyl)manganese complexes (over 50 references).⁴ The same authors and Didier Astru reviewed *ipso*-, *cine*- and *tele*- nucleophilic aromatic substitution of arenetricarbonylchromium complexes in a book chapter published in 2002 that became available online in 2004.⁵ A paper reviewing the progress in the radical reactions of arene metal complexes published in 2003⁶ reported no example of *cine*- or *tele*-substitutions. In their review of nucleophilic substitution of hydrogen in heterocyclic chemistry, Makosza and Wojciechowski⁷ devoted one short sub-chapter to *cine*- and *tele*-substitutions in heteroarenes (5 references). In their microreview, Peng and Li⁸ focused on the *cine*-substitution in Stille cross-coupling reactions which often occurred with sterically hindered vinyltin components (over 50 references). Much later Kaur et al. in a review⁹ on carbastannatranes as mediators in Stille coupling also gave an example of *cine*-substitution. Ni-catalyzed Suzuki-Miyaura, Fe-catalyzed Kumada cross-coupling reactions of phenol-based electrophiles and other reactions of unconventional phenol derivatives including *cine*-substituted products were reviewed by Mesganaw and Garg (5 references).¹⁰ In a review of the chemistry of nitroquinolones, Nishiwaki¹¹ described the unusual reactivity of 1-methyl-3,6,8-trinitroquinolone resulting in *cine*-substitution of 3-nitro group (52 references). In 2011, Tishler¹² presented a very comprehensive and interesting review of nucleophilic *tele*-

substitution in various heteroaromatic systems (37 references). With the exception of a review by us³, none of these reviews tried to cover more or less the whole field of *cine*- and *tele*-reactions. The present paper is a continuation of the work³ published fifteen years ago. According to the IUPAC Gold Book definition¹³, *cine*-substitution is a “substitution reaction (generally aromatic) in which the entering group takes up a position adjacent to that occupied by the leaving group”. Similarly, the IUPAC Gold Book defined¹³ *tele*-substitution as a “substitution reaction in which the entering group takes up a position more than one atom away from the atom to which the leaving group was attached”. Such terms as *cine*-addition, *cine*-cyclization, *cine*-elimination or *cine*-rearrangement, which also appear in the chemical literature, are not defined in the IUPAC Gold Book. *cine*- and *tele*-Substitutions probably are quite widespread but often they are not main processes and the terms *cine* or *tele* are not even mentioned in papers dealing with reactions of these types. Some authors consider such reactions as *abnormal* courses. In *Web of Science*, the term *cine*-substitution appeared in 63 papers published within the last fifteen years (Fig. 1) and 177 times since its introduction in 1968.

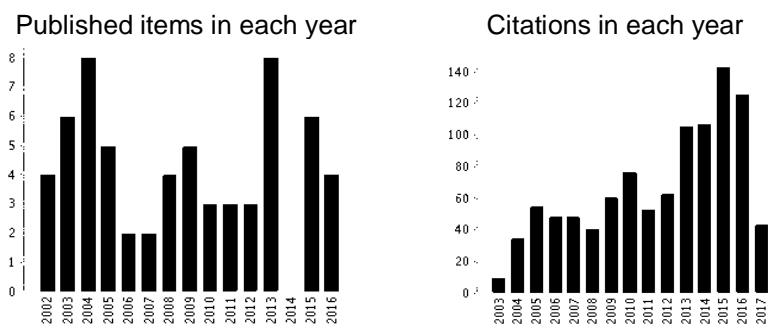


Figure 1. Number of papers using the term “*cine*-substitution” in the last fifteen years.

Often, these papers did not describe new *cine*-substitution reactions but merely cited the older papers. Most studies published within the recent fifteen years have been decidedly concentrated on the nucleophilic *cine*-substitution in conjugated systems such as homoarene complexes with metals or in heteroarenes. Most likely, only one paper dealt strictly with radical aromatic *cine*-substitution. Examples of *cine*- or *tele*-substitutions in aliphatic systems were reported very rarely as well. Studies of *tele*-substitution appears to be even less common recently (26 papers, Fig. 2) and have been mainly concerned with the reactions of heterocycles.

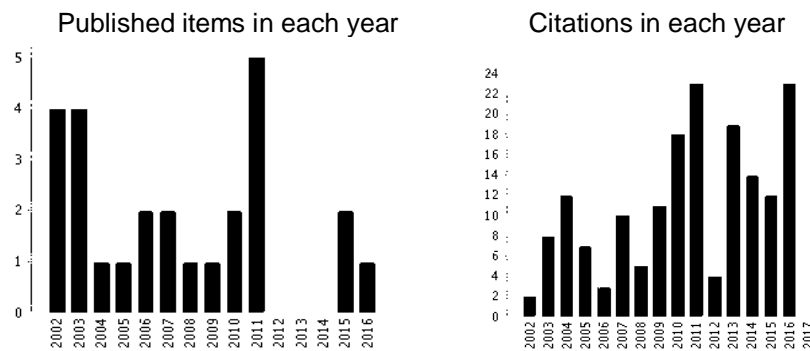


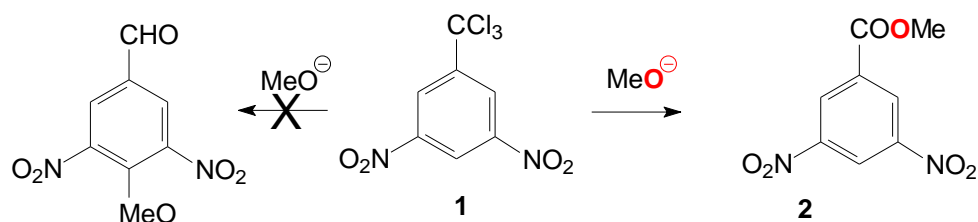
Figure 2. Number of papers using the term “*tele*-substitution” in the last fifteen years
Data taken from Web on Science on April 20, 2017.

The term “*tele*-substitution” was introduced in 1977 by Tishler¹⁴ and, until 2016, was used in 68 papers reported by Web of Science.

2. *cine*- and *tele*-Substitution of Homoarene Derivatives

2.1. Nitrohomoarenes

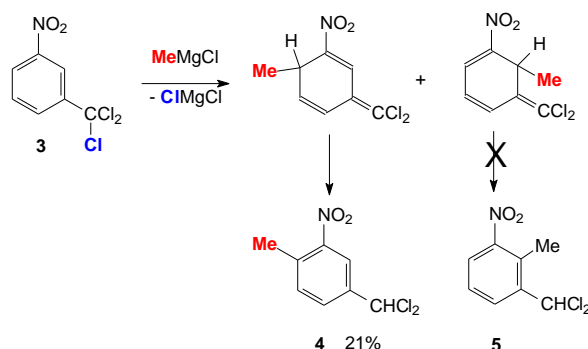
In 2000, Giannopoulos et al.¹⁵ reported *tele* nucleophilic aromatic substitution of 1,3-dinitro-5-trichloromethylbenzene with sodium methoxide with the formation of 4-methoxy-3,5-dinitrobenzaldehyde (55%). Later, Garner et al.¹⁶ corrected that finding proving that 1,3-dinitro-5-trichloromethylbenzene (**1**) treated with sodium methoxide affords methyl 3,5-dinitrobenzoate (**2**, Scheme 1) and not 4-methoxy-3,5-dinitrobenzaldehyde as was postulated earlier.¹⁵



Conditions: THF, -70 °C, (ratio of arene to MeMgCl, 1:1), then NH₃(liq.), -70 °C to room temp.

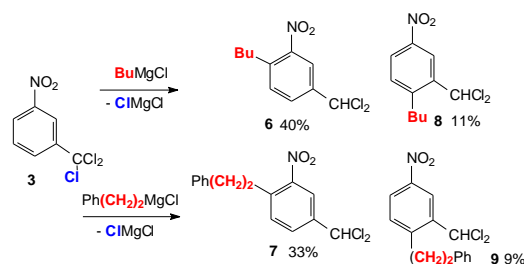
Scheme 1. Reaction of 1,3-dinitro-5-trichloromethylbenzene with sodium methoxide.

Mąkosza et al. investigated oxidative aromatic nucleophilic substitution of hydrogen atom by Grignard reagents in nitrobenzenes containing chlorinated methyl group in the *meta* position.¹⁷ Grignard reagents attacked nitroarenes in *ortho* or *para* positions to form σ^H -complexes. In the absence of easy leaving groups, the complexes could then be oxidized to produce respective alkyl nitroarenes. No oxidizing reagent was necessary for the rearomatization of σ^H -complexes forming from 1-(chloro-, dichloro-, trichloromethyl)-3-nitrobenzene with Grignard reagents. When 1-nitro-3-(trichloromethyl)benzene (**3**) was treated in tetrahydrofuran with methylmagnesium chloride at -70 °C followed by the addition of liquid ammonia, a nucleophilic *tele*-substitution of chlorine atom by methyl group was observed, resulting in the formation of 3-(dichloromethyl)-1-nitro-6-methylbenzene (**4**) in 21% yield. *cine*-Substitution of compound **3** leading to product **5** was not observed (Scheme 2).



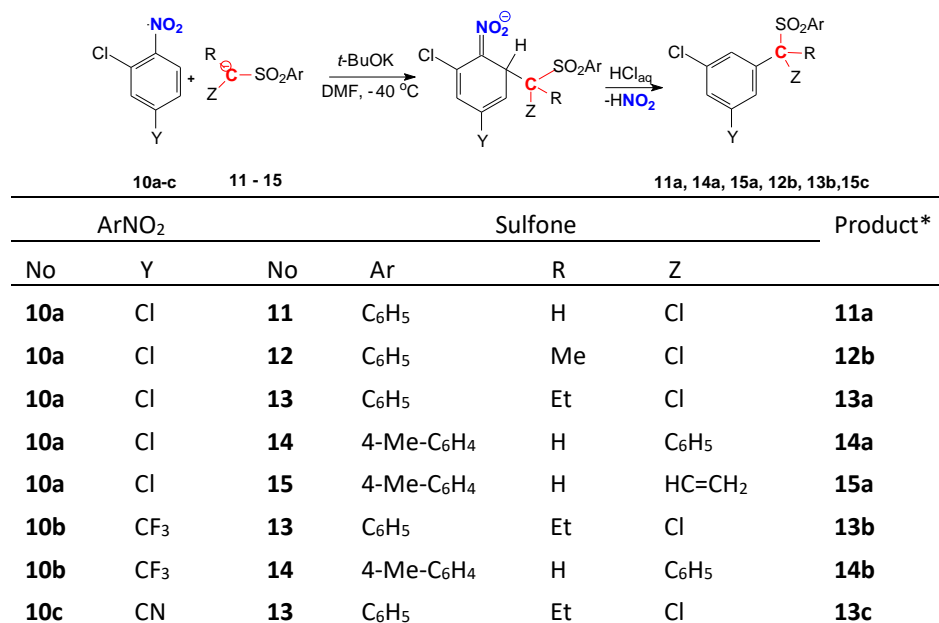
Scheme 2. *tele*-Substitution of 1-nitro-3-(trichloromethyl)benzene (**3**) with methylmagnesium chloride.

Butylmagnesium chloride and 2-phenylethylchloride reacted with 1-nitro-3-(trichloromethyl)benzene (**3**) under similar conditions to give products of both substitution types: *tele* **6**, **7** and *cine* **8**, **9** (Scheme 3).



Scheme 3. *cine*- and *tele*-Substitution of compound **3** with butylmagnesium and benzylmagnesium chlorides.

1-Chloromethyl-3-nitrobenzene and 1-(dichloromethyl)-3-nitrobenzene treated with Grignard reagents according to the same procedure as compound **3** also afforded their respective *tele*-substituted products in moderate yields. In the course of the search for the reaction mechanism, it was found that alkylmagnesium chlorides used in equimolar amount added to the *ortho* or *para* positions with respect to the nitro group of nitrobenzene derivative substituted in position 3 with the chlorinated methyl group and formed their respective σ^H adducts. The adducts released the chlorine anion from the chlorinated methyl group to give a cyclohexadiene intermediate which could be stabilized by 1,3- or 1,5-hydrogen shift following the addition of liquid ammonia to the reaction mixture. Nucleophilic *tele*-substitution was then observed. Liquid ammonia probably facilitated rearomatization. Cyclohexadiene intermediate in the presence of an excess of Grignard reagent reacted with a second molecule of the reagent to produce stable cyclohexene derivative.

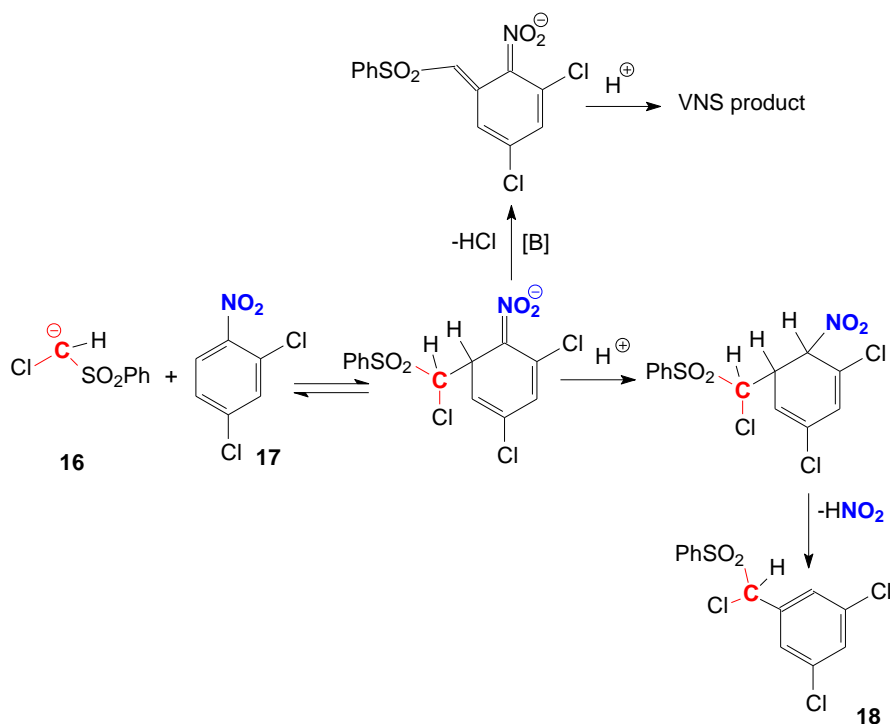


*General reaction conditions: sulfone and nitroarene (1:1) in DMF is added at -40 °C to a stirred t-BuOK (20% excess to sulfone) solution in DMF and THF (12:1). After certain time the reaction is quenched with hydrochloric acid, the resulting mixture is diluted with water, extracted with dichloromethane and the extract is analysed chromatographically.

Scheme 4. *cine*-Substitution of 2,4-disubstituted nitrobenzenes **10a-c** with aryl alkyl sulfone carbanions **11-15**.

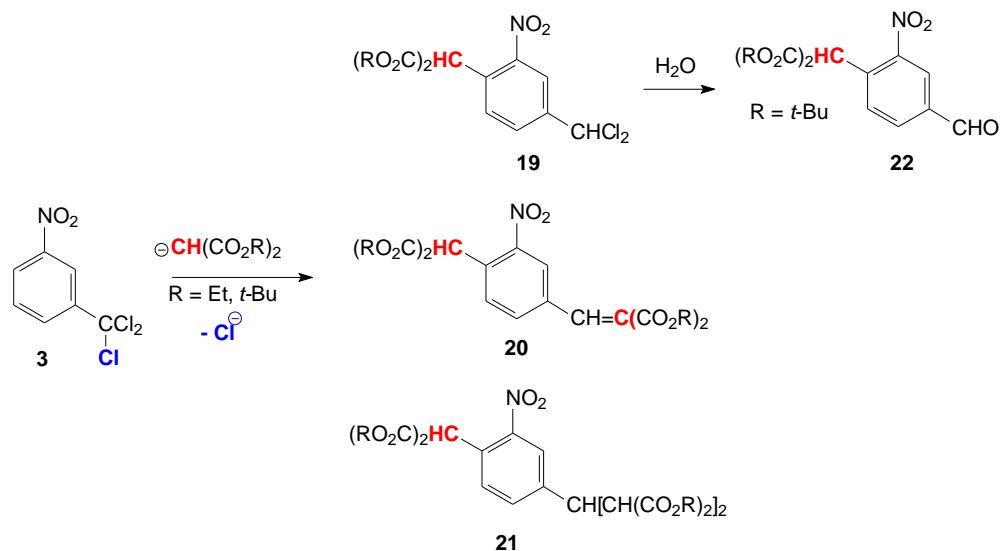
An *ipso* nucleophilic substitution of the chlorine atom in the chlorinated methyl group by a Grignard reagent was not observed. Makosza et al.¹⁸ also studied the behavior of 2,4-disubstituted nitroarenes with respect to the carbanions generated from alkyl aryl sulfones. Most important details concerning this new *cine*-substitution reaction are shown in Scheme 4 with the accompanying table.

It was observed that the carbanions were added to the nitroarenes in the *ortho* position to the nitro group to form short lived σ^H adducts. Protonation of the adducts led to the elimination of nitrous acid and formation of 1,3,5-trisubstituted benzenes as the products of a nucleophilic *cine*-substitution of the nitro group. Małosza et al.¹⁹ performed kinetic experiments for vicarious nucleophilic substitution of 2-chloronitrobenzene, 4-chloro-nitrobenzene, 2,4-dichloronitrobenzene, 2,4,6-trichloronitrobenzene, 2-bromonitrobenzene and 4-bromonitrobenzene by treating these compounds with chloromethyl phenyl sulfone in dimethylformamide in the presence of an excess of potassium *t*-butoxide at -40 °C. They measured the relative rates of formation of σ adducts obtained by nucleophilic addition of carbanions to nitroarenes. In an experiment with 2,4-dichloronitrobenzene, the authors observed the formation of an unexpected product identified as chloro(3,5-dichlorophenyl)methyl phenyl sulfone (**17**), which is therefore a product of a new aromatic *cine* nucleophilic substitution (Scheme 5).



Scheme 5. Substitution of 2,4-dichloronitrobenzene (**17**) with chloromethyl phenyl sulfone carbanion (**16**) to produce *cine*-product **18**.

In their conclusions, the authors stated that chlorine atoms activated nitroarene to attack the nucleophiles protecting the same positions that they occupied. In cooperation with Varounis,²⁰ Małosza showed that the reaction of dialkyl malonates with 1-nitro-3-(trichloromethyl)benzene (**3**) led to mixtures of products **19-22** with the proportions depending mainly on the stoichiometry of the reactants. Then, they extended their former investigations of the *tele*-substitution in 1-nitro-3-(trichloromethyl)benzene (**3**) with Grignard reagents on 1-chloro-4-nitro-2-(trichloromethyl)benzene (**23**) and on carbanions derived from dialkyl malonates, 2-phenylacetonitrile and 2-phenylacetate (Scheme 6).

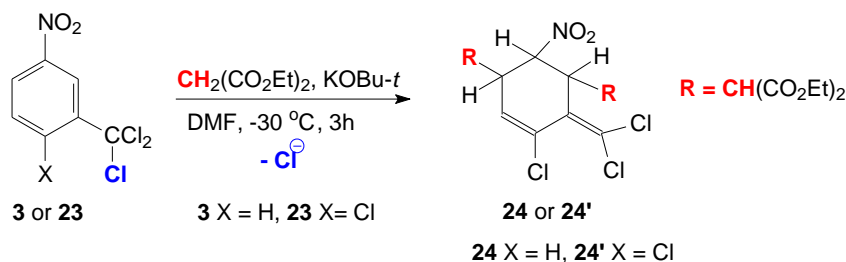


R	Proportions of reactants 3/t-BuOK/malonate	Products - yields [%]		
Et	1/2.5/1.5	19 - 23	20 - 17	21 - 22
Et	1/4.0/3.0	19 - 0	20 - 0	21 - 54
t-Bu	1/2.5/1.5	19 - 0; 22* - 26	20 - 18	21 - 20
t-Bu	1/4.0/3.0	19 - 0; 22* - 0	20 - 0	21 - 48

*) Compound **22** is a product of **19** hydrolysis

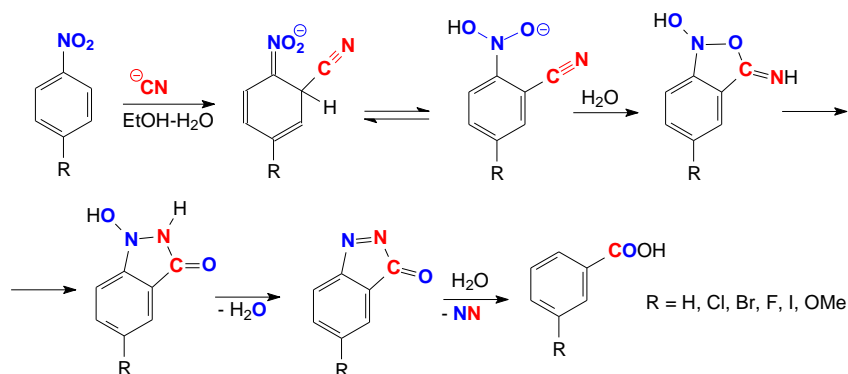
Scheme 6. Typical products of the *tele*-nucleophilic substitution of 1-nitro-3-(trichloromethyl)benzene (**3**) with dialkyl malonates.

A mechanism for the formation of compounds **19**, **20** and **21** was postulated. The course of the reaction depended not only on the stoichiometry of reactants but also on the temperature of the reaction. Compound **3** or 1-chloro-4-nitro-2-(trichloromethyl)benzene (**23**) treated with diethyl malonate at $-30\text{ }^{\circ}\text{C}$ afforded products **24** or **24'** that were different than those obtained from the reaction at $0\text{ }^{\circ}\text{C}$ (Scheme 7).



Scheme 7. Reaction of 1-nitro-3-(trichloromethyl)benzene (**3**) and 1-chloro-4-nitro-2-(trichloromethyl)benzene (**23**) with diethylmalonate at $-30\text{ }^{\circ}\text{C}$.

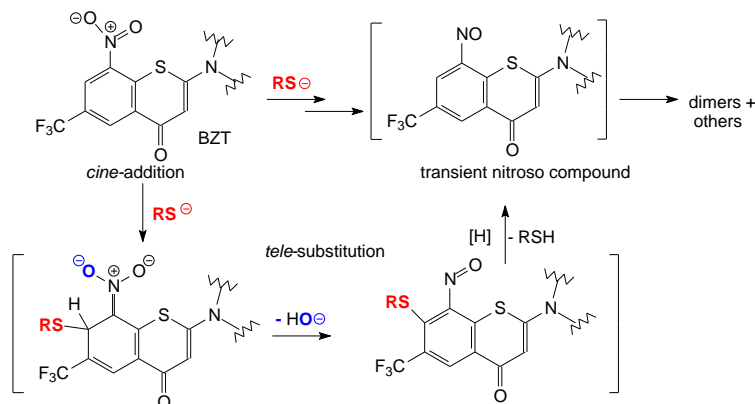
Conversion of substituted nitrobenzenes into benzoic acids under the action of an excess of potassium cyanide in aqueous ethanol is known as the von Richter reaction. It is an example of an aromatic nucleophilic *cine*-substitution.³ In the reaction, the carboxylic group replaces the hydrogen atom in the *ortho*-position to the leaving nitro group. The postulated²¹ mechanism of the von Richter reaction is shown in Scheme 8.



Scheme 8. Postulated mechanism of the von Richter reaction.

Makhova et al.²¹ presented their results on the investigations of the first examples of ionic liquid-promoted von Richter reaction. They studied the conversion of electron-deficient *para*-substituted nitroarenes to the corresponding *meta*-substituted benzoic acids²¹ and found that the von Richter reaction of the investigated nitroarenes in the presence of ionic liquids (usually biimidazolium tetrafluoroborate) led to high yields of products including such compounds as 3-fluoro- or 3-methoxybenzoic acids which were practically not achievable under common reaction conditions. The authors also found that the von Richter reaction was slowed by electron-donating substituents in nitrobenzenes. The use of ionic liquids as solvents allowed to avoid or diminish the formation of tars in the reaction.

Miller et al. have recently published a paper²² in which they used the term “*cine* addition” for the chemical reduction of nitro to nitroso group in an aromatic compound (BZT) by the action of the thiolate anion (Scheme 9).

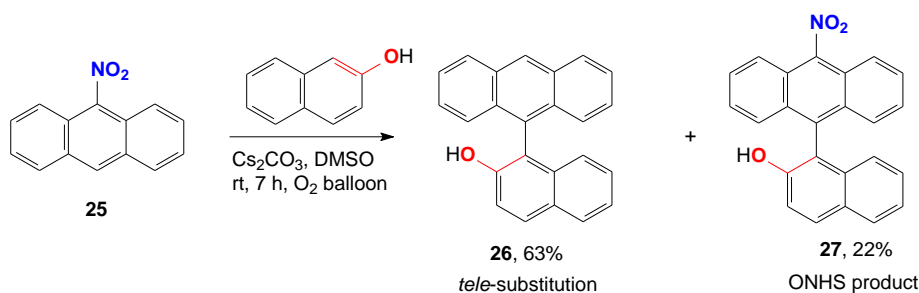


Scheme 9. Chemical activation (*cine*-addition of thiolate anion) of nitro group in BZT.

The term *cine* was used to indicate the location of an attack of the thiolate anion on the *ortho* position to the reduced nitro group in BZT. In light of the definitions of the terms *cine* and *tele*, we are of the opinion that a part of the reaction may also be treated as *tele*-substitution.

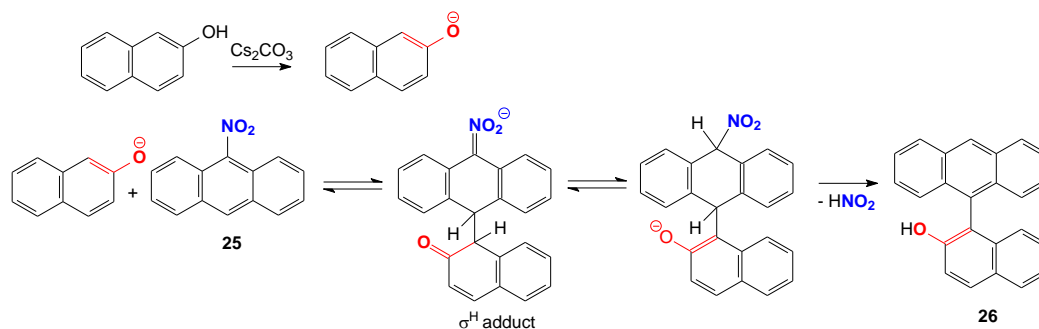
Kim et al.²³ investigated oxidative nucleophilic substitution of hydrogen (ONSH) in 9-nitroanthracene (**25**) under the action of 2-naphthols and phloroglucinol. When compound **25** was treated with 2-naphthol in dimethylsulfoxide in the presence of 50% excess of cesium carbonate for seven hours at room temperature, the main unexpected product, namely, 1-(anthracen-9-yl)-2-naphthol (**26**, 63%), was formed as the result of

tele substitution of the nitro group while the typical ONSH product 1-(10-nitroanthracen-9-yl)-2-naphthol (**27**) was obtained in 22% yield only (Scheme 10).



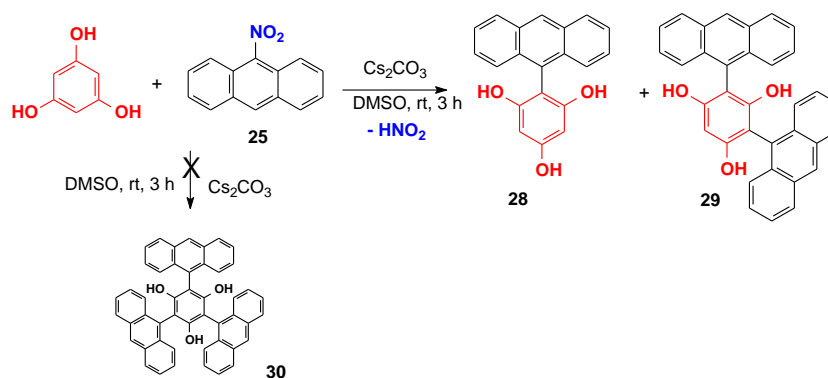
Scheme 10. *tele*-Substitution of 9-nitroanthracene (**25**) with 2-naphthol.

Other 2-naphthols, namely, 2,7-dihydroxy-, 2-hydroxy-7-methoxy-, 2-hydroxy-8-methoxy- and 2-hydroxy-3-methoxynaphthalene reacted in a similar way (Scheme 11).



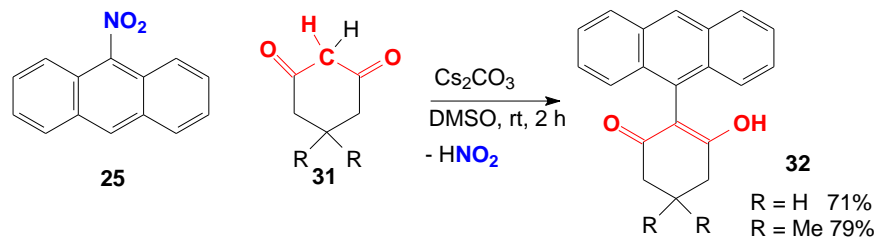
Scheme 11. Proposed mechanism of *tele*-substitution of 9-nitroanthracene (**25**) with 2-naphthol.

The yields of the *tele* substitution products exceeded the yields of the ONSH products for all naphthols. A mechanism of the reaction was postulated. Nitroarene **25** under the action of the more nucleophilic phloroglucinol gave two *tele*-substitution products (Scheme 12).



Scheme 12. *tele*-Substitution of 9-nitroanthracene (**25**) with phloroglucinol.

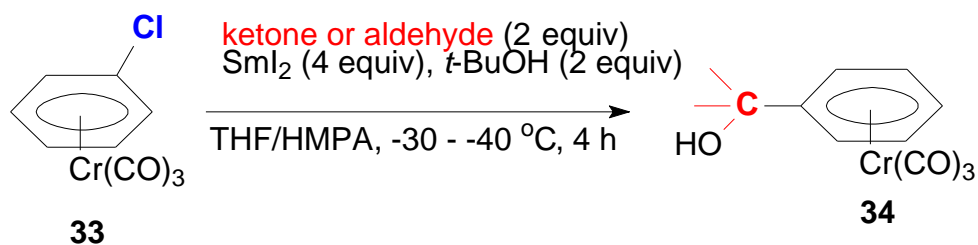
The previously formed *tele*-product 2-(anthracen-9-yl)phloroglucinol (**28**) reacted with the second molecule of compound **25** to give 2,4-di(anthracen-9-yl)phloroglucinol (**29**). The proportions of these two products depended mainly on the proportions of the reactants. Formation of 2,4,6-tri(anthracen-9-yl)phloroglucinol (**30**) was not observed. A nucleophilic aromatic predominating *tele*-substitution was also typical for the reaction of nitroarene **25** with 1,3-cyclohexanediones **31** (Scheme 13).



Scheme 13. Reaction of 9-nitroanthracene (**25**) with 1,3-cyclohexanediones **31**; the formation of *tele*-substitution products **32**.

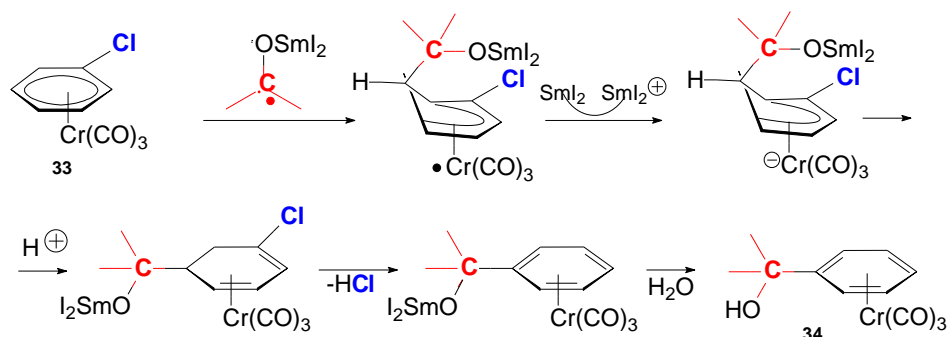
2.2. Complexes of homoarenes with metals

As mentioned in the introduction, three reviews have dealt with *cine*-substitution of homoarene complexes with metals, but nevertheless some new papers should be presented here. A review of radical aromatic substitution of arenetricarbonylchromium complexes published in 2003⁶ did not even mention the terms *cine* or *tele* even though one year earlier Li et al.²⁴ presented the results of their investigations of radical aromatic substitution of (η^6 -chloroarene)tricarbonylchromium complexes **33**. When complexes **33** were treated with acetone and samarium iodide in a tetrahydrofuran/hexamethylphosphoramide solution containing *t*-butanol as the proton source, *cine*- and *tele*-substitution products were formed. Other ketones and aldehydes e.g., cyclopentanone, cyclohexanone, propanal or butanal reacted accordingly (Scheme 14).



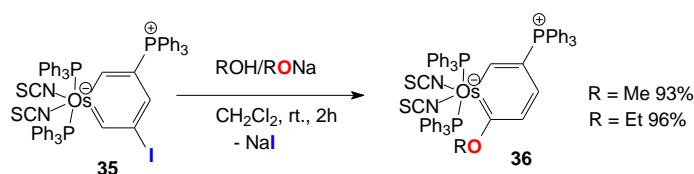
Scheme 14. Substitution of chlorine atom by a carbonyl compound in (η^6 -chloroarene)tricarbonylchromium complex (**33**) in the presence of samarium iodide.

Yields of both *cine* and *tele*-substitution products **34** were 66-89%. Complex **33** containing a methyl group in the *ortho*- or *para*-position to chlorine atom gave both *cine*- and *tele*-substitution products of type **34**, while no *ipso* substitution products were found. The experiment with the deuterated complex indicated that the reaction occurred according to the radical aromatic *meta-tele*-substitution mechanism as shown in Scheme 15.



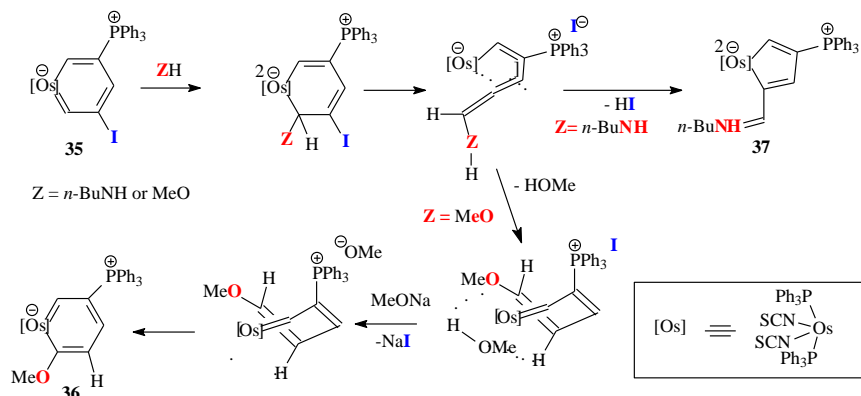
Scheme 15. Proposed mechanism of *meta-tele*-substitution of chlorine atom by a carbonyl compound in (η^6 -chloroarene)tricarbonylchromium complex (**33**) in the presence of samarium iodide.

Xia et al.²⁵ investigated the *cine*-substitution of metallabenzene both experimentally and by density functional theory (DFT) quantum mechanical calculations. The authors presented the first examples of the *cine*-substitution reactions of metalla-aromatic compounds showing that alkali-resistant osmabenzene complex **35** reacted with alcohols in the presence of sodium alkoxides to afford exclusively *cine*-substituted products **36** (Scheme 16).



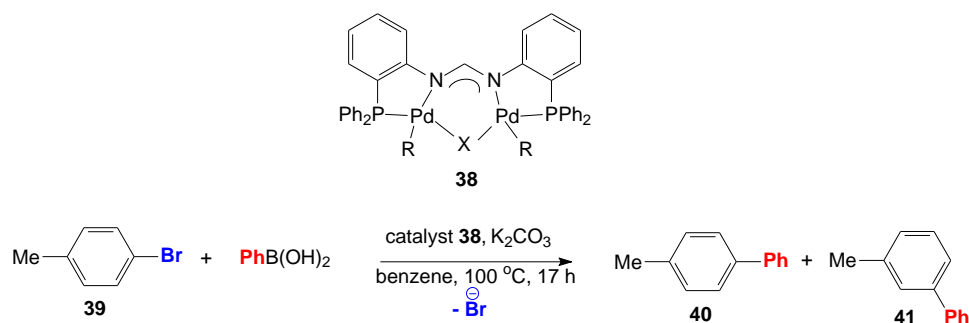
Scheme 16. *cine*-Substitution of iodine atom by alkoxy group in osmabenzene complex **35**.

In contrast to that, complex **35** treated with amines in the presence of e.g., sodium methoxide gave five-membered ring compounds **37** with *cine*-substitution as a side reaction only. The authors assumed that strong alkalis did not take part in the reaction with amines. A mechanism of the reactions of osmabenzene complex **35** with nucleophiles was postulated. DFT calculations supported the experimental findings concerning the course of the reactions. Conclusions of NMR *in situ* and from labeled compounds also appeared to support the proposal that the studied *cine*-substitution reactions occurred in three following key steps: addition of a nucleophile-ring opening-ring closure, therefore according to an *ANRORC* mechanism (Scheme 17).



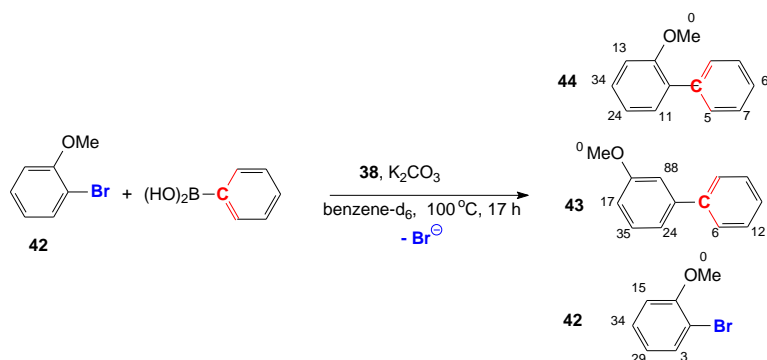
Scheme 17. Postulated mechanism of reactions of osmabenzene complex **35** with nucleophiles (alkoxides or amines).

cine-Substitution accompanied by the formation of *ipso*-substitution (**40**) of aryl bromides (**39**) in Suzuki-Miyaura coupling reaction catalyzed by dinuclear Pd complexes (**38**) was reported (Scheme 18, product **41**).²⁶



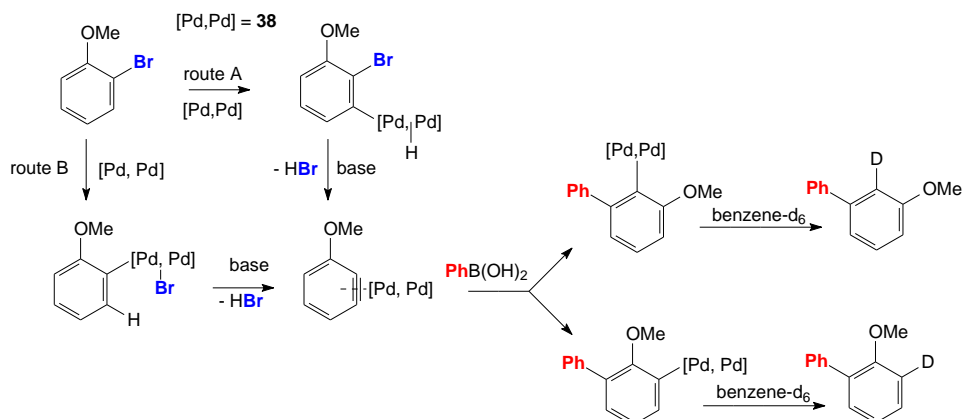
Scheme 18. *ipso*- (**40**) and *cine*-Substituted (**41**) products from *p*-bromotoluene (**39**) in Suzuki-Miyaura cross-coupling catalyzed by dinuclear palladium complex **38** where: R = *p*-MeC₆H₄, *p*-ClC₆H₄ or Me and X = OH, Br, Cl or I.

The highest proportion (ca. 30%) of *cine*-substituted **41** to *ipso*-substituted product **40** was obtained with the use of complex **38** in which R was *p*-MeC₆H₄ and X was I. In addition to compound **39**, various other mono-substituted bromobenzenes were treated with phenylboronic acid in the presence of catalyst **38**. In most of the reactions, the yields of *cine*-substituted compounds did not exceed 25% and bromoarenes were still present in the post-reaction mixtures. Ratios of *cine*- to *ipso*-substituted products did not depend on *para* or *meta* position of substituents and their electronic properties. *tele*-Substituted (*ortho*) products were not observed at all. By contrast, the yields of *cine*-substituted products varied with the types of the *ortho*-substituents in the case of starting *ortho*-substituted bromobenzenes. The effect of the solvent on the ratios of *cine*- to *ipso*-substitution was also studied, showing that benzene strongly (ca. 4 : 1) favored *ipso*-substitution. When the reaction was performed in *per*-deuterated benzene, the *ipso*-position in the *cine*-substituted product was also deuterated to a great extent. The deuteration did not occur in the reaction catalyzed by a mononuclear palladium complex e.g., [Pd(PPh₃)₄]. A dinuclear Pd complex appeared to be necessary also for *cine*-substitution because mononuclear Pd complex was proved not to be active in this case. The mechanism of the reaction is still not fully clear. As shown in Scheme 19, the *ipso*-position of *meta*-methoxybiphenyl (**43**) was highly deuterated.



Scheme 19. Distribution of deuterium in products of reaction of *ortho*-bromoanisole (**42**) in benzene-d₆; the smaller numbers close to structural formulas indicate the percentage of deuteration in a given position.

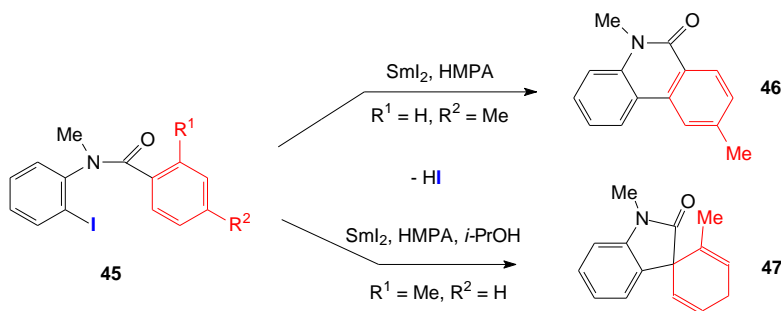
The *ipso*-H-atom was most likely derived from the solvent. Unexpectedly, H/D exchange reactions occurred in various positions of the benzene rings in *meta*- (**43**) and *ortho*-methoxybiphenyl (**44**) as well as in recovered *ortho*-bromoanisole (**42**). The reaction with benzene- d_6 may indicate a mechanism of the reaction *via* the respective aryne as is depicted in Scheme 20.



Scheme 20. The proposed mechanism of Suzuki-Miyaura cross-coupling of *ortho*-bromoanisole with phenylboronic acid in the presence of dinuclear palladium complex in perdeuterated benzene.

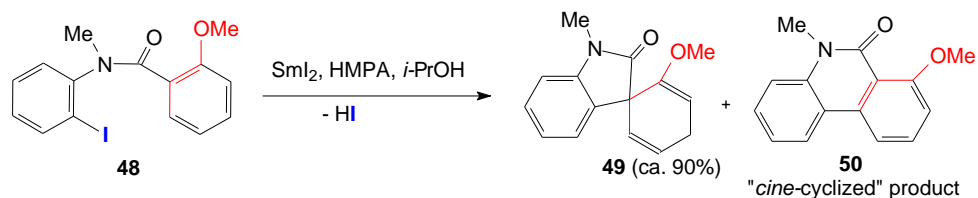
2.3. Other homoarene derivatives

Ohno et al.^{27, 28} studied the behavior of *N*-(2-iodophenyl)-*N*-methylbenzamides toward samarium(II) iodide. Compound **45** ($R^1 = \text{H}$, $R^2 = \text{Me}$) treated with samarium(II) iodide in the absence of the proton donor gave dimethylphenanthridone **46** as the predominant product. By contrast, benzanilide derivative **45** ($R^1 = \text{Me}$, $R^2 = \text{H}$) treated also with samarium(II) iodide but in the presence of isopropanol as a proton source underwent spirocyclisation to afford diene **47** in an excellent yield (Scheme 21).



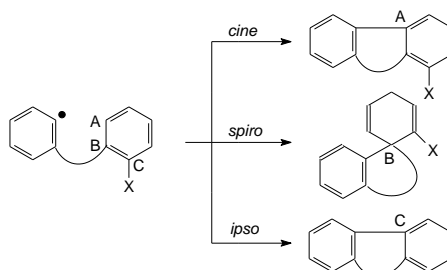
Scheme 21. Cyclization of *ortho*-iodobenzanilides **45** treated with samarium(II) iodide.

Product **46** was possibly formed *via* the rearrangement of the spirocyclohexadienyl radical. The best yields of spiroproducts were obtained from *ortho*-substituted benzanilide derivatives e.g., from compound **48**. The *ortho*-substituents hindered the rearrangement and the intermediate radicals become sufficiently stable to be reduced and then protonated to afford spiroproduct **49** in high yield while the *cine*-cyclized phenanthridone derivative **50** can be a by-product only (Scheme 22).



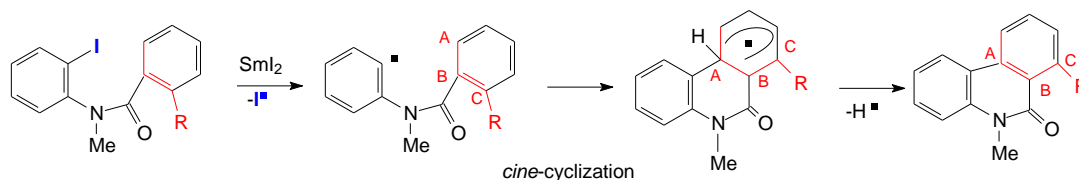
Scheme 22. Effect of *ortho*-methoxy group in iodobenzamide **48** on the ratio of spirocyclized **49** and "cine-cyclized" **50** product.

Therefore, the studies showed that intramolecular arylation of aryl radicals mediated by SmI_2/HMPA in the presence of *i*-PrOH led to spirocycles and to reduced "cine-cyclized compounds". The spirocyclization proceeded *via* a cyclohexadienyl anion intermediate and 1,4-reduction of the cyclohexadiene intermediate. In most cases, spirocyclization was difficult and *cine*-cyclized products were formed in considerable amounts. Reactions of indole derivatives were an exception to this rule. Three possible mechanisms of cyclization of a radical derived from e.g., *ortho*-iodoanilides in the presence of samarium(II) iodide are shown in Scheme 23.



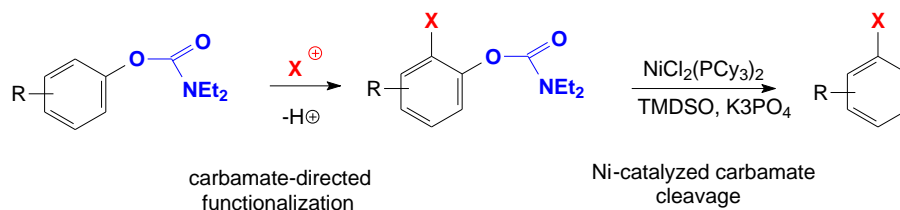
Scheme 23. Three possible ways of cyclization of a radical derived from e.g. *ortho*-iodoanilides in the presence of samarium(II) iodide.

A postulated mechanism of *cine*-cyclization of *ortho*-iodobenzamide mediated by samarium(II) iodide is depicted in Scheme 24.



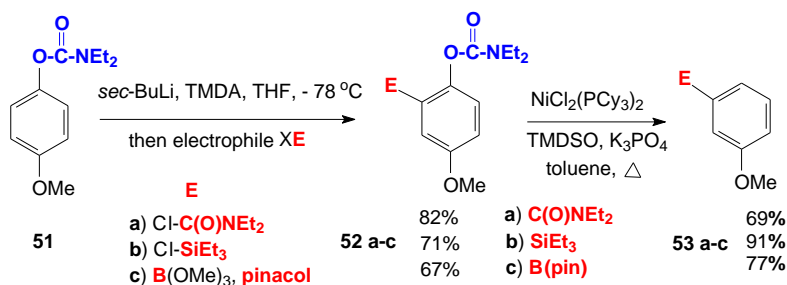
Scheme 24. Radical mechanism of *cine*-cyclization of iodobenzamide derivatives to phenanthridones.

Mesganaw et al.²⁹ elaborated and reported an efficient method of *cine*-substitution of various arenes with the methodology based on the use of aryl *O*-carbamates as an easily removable directing group. The idea of *cine*-substitution of arenes *via* aryl *O*-carbamates is presented in Scheme 25.

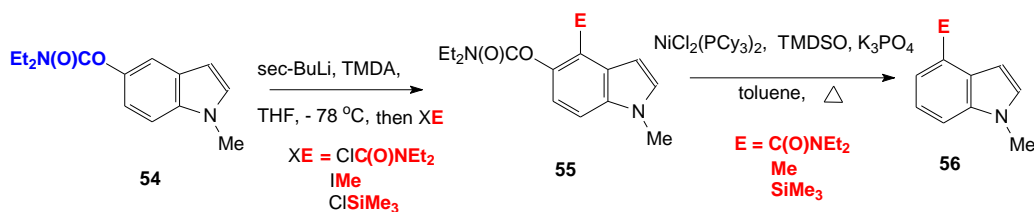


Scheme 25. An idea of *cine*-substitution of aryl *O*-carbamates with Ni-catalyzed carbamate cleavage.

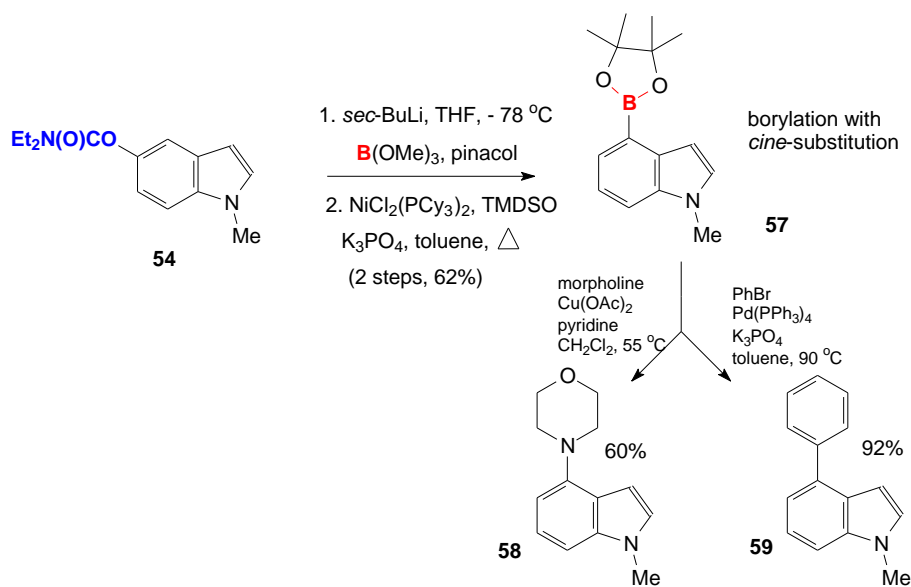
Very recently Tobisu and Chatani in a review³⁰ on nickel-catalyzed cross-coupling reactions have cited work by Mesganaw giving an example of the *cine*-substitution. *cine*-Substitution based on the use of aryl *O*-carbamates as readily removable directing groups for arene functionalization provided a new tool for the preparation of some important arene and heteroarene derivatives. A key part of this tool is the reductive cleavage of aryl carbamates. The cleavage proceeded well under the following reaction conditions: homo- or heteroaryl carbamate (1 equiv), NiCl₂(PCy₃)₂ (5-20 mol %), TMDSO (2.5 equiv), K₃PO₄ (4.5 equiv), toluene (0.27 M), 115-125 °C for 15 h. Examples of Mesganaw's method applications are depicted in schemes 26, 27 and 28.



Scheme 26. Examples of *cine*-substitution of aryl *O*-carbamates.

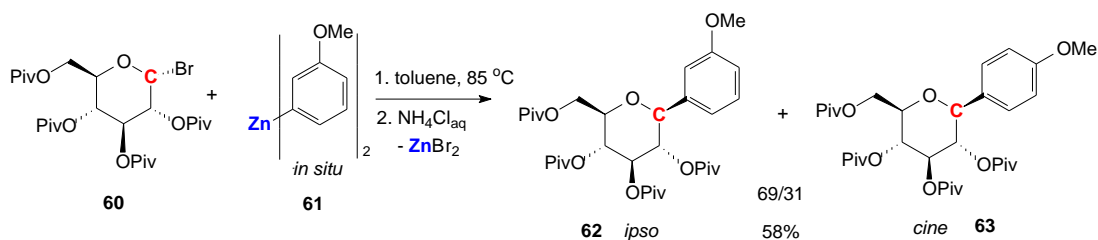


Scheme 27. Examples of *cine*-substitution of indolylcarbamate **54**.



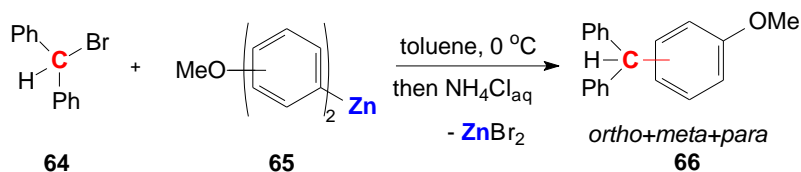
Scheme 28. Examples of cross-coupling approaches to *cine*-substituted products from *N*-methylindolylcarbamate **54**.

Very recently, a paper has been published³¹ proving that arylzinc reagents bearing electron-donating substituents were able to undergo *cine*-substitution with certain electrophiles such as perpivaloylated glucoside bromide or benzohydril bromide under the conditions where stereoelectronic factors promoted *cine*- versus *ipso*-substitution (Scheme 29).



Scheme 29. Substitution (*ipso* versus *cine*) of *meta*-anisylzinc reagent with perpivaloylated glucoside.

A mechanism of the substitution was studied and proposed. It was established that *cine*- and *tele*-substitutions occurred according to the Friedel–Crafts type mechanism consisting of two competing intramolecular pathways. In one of the pathways, the carbon-zinc bond remained untouched. An example of *cine*- and *tele*-substitution reactions of benzhydryl bromide using arylzinc reagents is shown in Scheme 30.



Distribution of product **66**

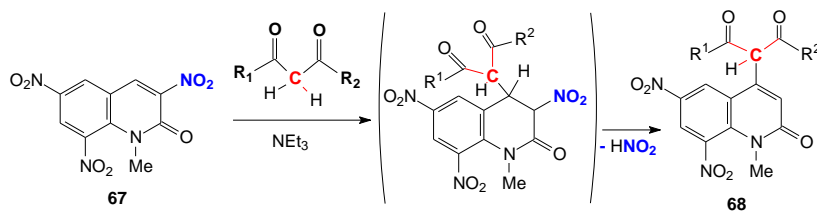
diarylzinc 65	<i>ortho</i>	<i>meta</i>	<i>para</i>
<i>ortho</i>	<i>ipso</i> 38%	<i>cine</i> 0%	<i>tele</i> 62%
<i>meta</i>	<i>cine</i> 9%	<i>ipso</i> 6%	<i>cine</i> 85%
<i>para</i>	<i>tele</i> 8%	<i>cine</i> 0%	<i>ipso</i> 92%

Scheme 30. Substitution (*cine*, *tele*, *ipso*) of benzhydryl bromide **64** with anisylzinc reagents **65**.

3. Nucleophilic *cine*- and *tele*-Substitution of Heteroarene Derivatives

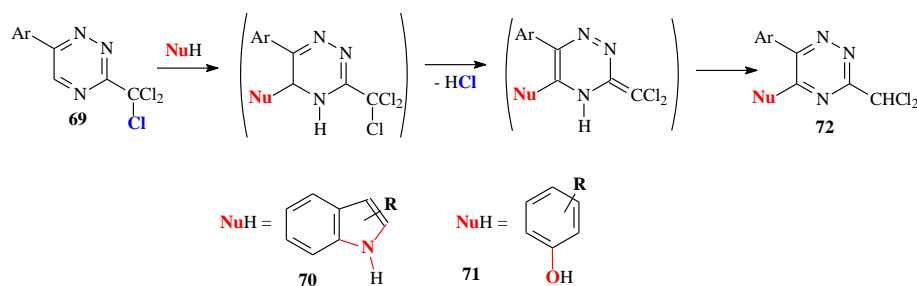
3.1. Six-membered heterocycles with a leaving group at a carbon atom

Nishiwaki et al.³² proposed a new method for the functionalization of quinolones. When 1-methyl-3,6,8-trinitro-2-quinolone **67** was reacted with 1,3-dicarbonyl compounds in the presence of trimethylamine, a regioselective reaction occurred to afford *cine*-substitution product **68** forming according to the typical addition-elimination mechanism (Scheme 31).



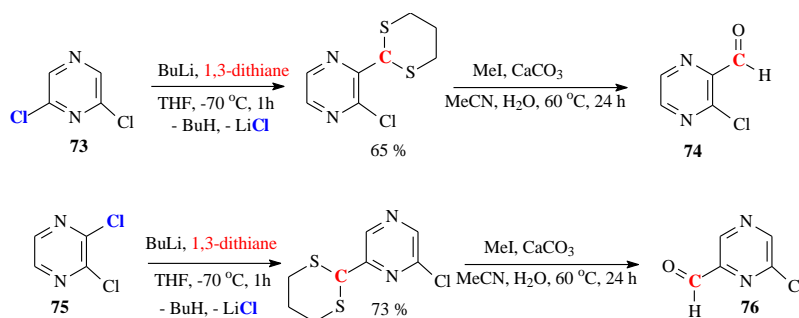
Scheme 31. *cine*-Substitution of trinitroquinolone **67** with carbanion derived from a 1,3-dicarbonyl compound.

Based on this finding, the authors elaborated a method for a simple preparation of 1-methyl-6,8-dinitro-2-quinolone by treating compound **67** with tertiary or quaternary amines which contained at least two long alkyl chains. Chupakhin et al.³³ elaborated a new procedure for the synthesis of some 1,2,4-triazine derivatives with chlorinated methyl groups at the position 3. One type of such derivatives, namely, 6-aryl-3-trichloromethyl-1,2,4-triazines (**69**) reacting with indoles (**70**) or phenols (**71**) afforded *tele*-substituted products 6-aryl-5-indolyl- or 6-aryl-5-hydroxyphenyl-3-dichloromethyl-1,2,4-triazines (**72**), respectively (Scheme 32). This example of *tele*-substitution was mentioned in a review by Kovalev et al. on the nucleophilic substitution of hydrogen in arenes and hetarenes³⁴.



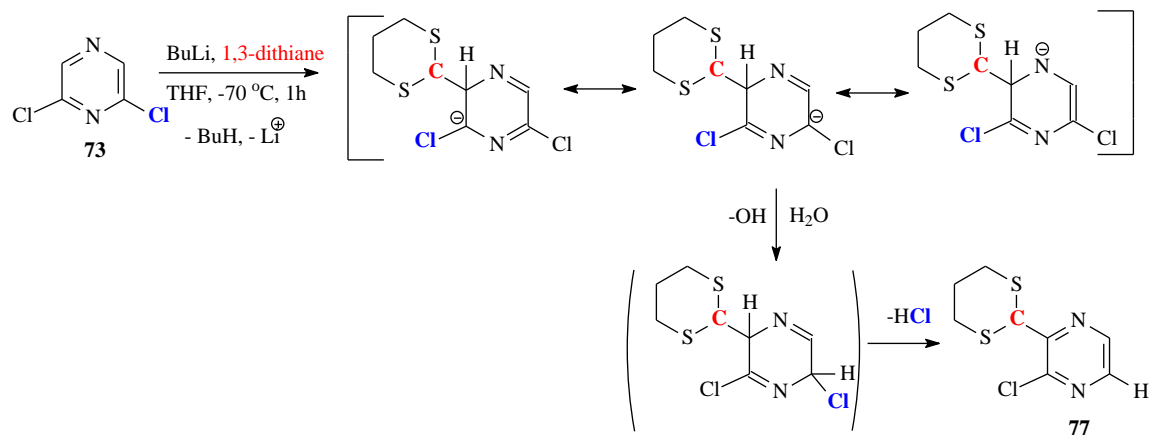
Scheme 32. *tele*-Substitution of triazines **69** with indols **70** or phenols **71** to afford new derivatives **72**.

Yields of *tele*-products (**72**) exceeded 50%. The reaction of dichloropyrazines **73** and **75** with a dithiane anion was described by Torr et al.³⁵ The reaction (after the decomposition of dithiane protecting group with methyl iodide) produced the expected isomeric formylated chloropyrazines **74** and **76** respectively (Scheme 33).



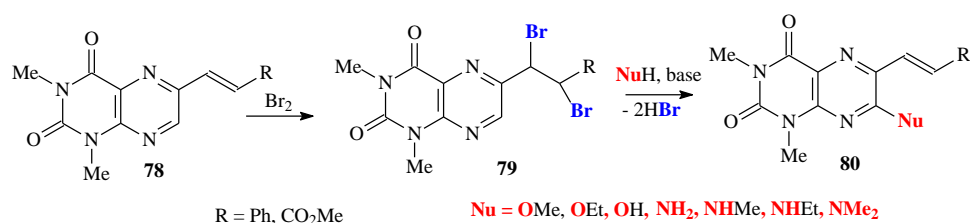
Scheme 33. Indirect *tele*-formylation of dichloropyrazines **73** and **75**.

A *tele*-substitution mechanism was studied using deuterium derivatives and was postulated by taking into considerations all the experimental observations (Scheme 34). A formation of *cine*-substitution product was not observed.



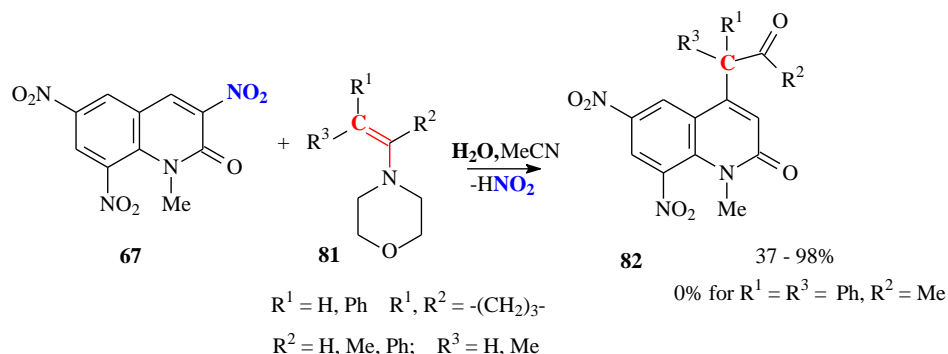
Scheme 34. A postulated mechanism of *tele*-substitution of dichloropyrazine **73** with lithiated dithiane to give compound **77**.

In contrast to the reaction with the dithiane anion, dichloropyrazines **73** and **75** were *ipso*-substituted with morpholine. Pfeleiderer et al.³⁶ treated 1,3-dimethylpteridine-7-styryl-2,4(1*H*,3*H*)-dione (**78a**) or 1,3-dimethylpteridine-7-[2-(methoxycarbonyl)ethenyl-2,4(1*H*,3*H*)-dione (**78b**) with bromine and then with nucleophiles to give *tele*-substituted products **80** (Scheme 35).



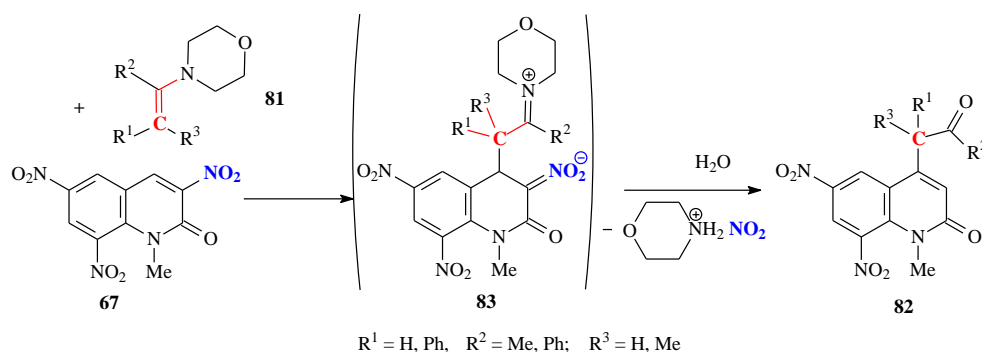
Scheme 35. Nucleophilic *tele*-substitution of product of bromine addition to pteridine derivatives **78**.

1,3-Dimethylpteridine-6-[2-(methoxycarbonyl)ethenyl-2,4(1*H*,3*H*)-dione under action of bromine and then a nucleophile behaved differently, not giving the *tele*-substituted products. Enamines **81** were added to synthetic 1-methyl-3,6,8-trinitro-2-quinolone (**67**) and products of the addition were then hydrolyzed to furnish 4-acylmethyl-1-methyl-6,8-dinitro-2-quinolones (**82**, Scheme 36).³⁷



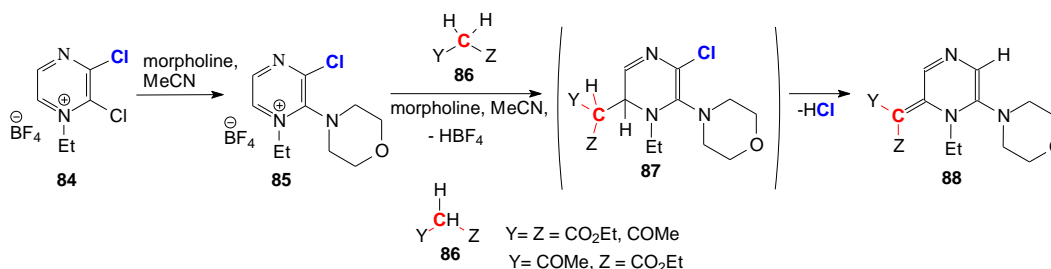
Scheme 36. *cine*-Substitution of trinitroquinolone **67** with enamines **81**.

Compounds **82** were also obtained in reaction of quinolone **67** with certain ketones in the presence of triethylamine. A plausible mechanism of *cine*-substitution of the nitro group in compound **67** by the acylmethyl group present in products **82** was formulated (Scheme 37).



Scheme 37. Mechanism of formation of acylmethyl dinitroquinolone **82** in reaction of trinitroquinolone **67** with enamines **81** followed by hydrolysis of an intermediate **83**.

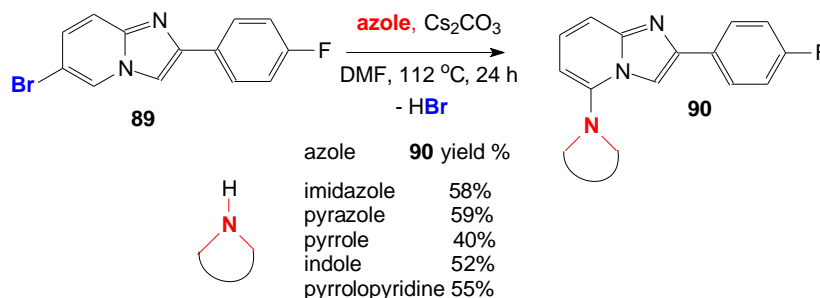
2,3-Dichloro-derivatives **84** and 3-chloro-2-morpholino-derivatives **85** of 1-ethyl-pyrazinium tetrafluoroborates reacting with the anions of active carbonyl compounds **86** produced *tele*-substituted products **88** *via* intermediates **87** (Scheme 38).³⁸



Scheme 38. *tele*-Nucleophilic substitution of dichloropyrazinium derivatives **84** and **85** with active methylene compounds **86**.

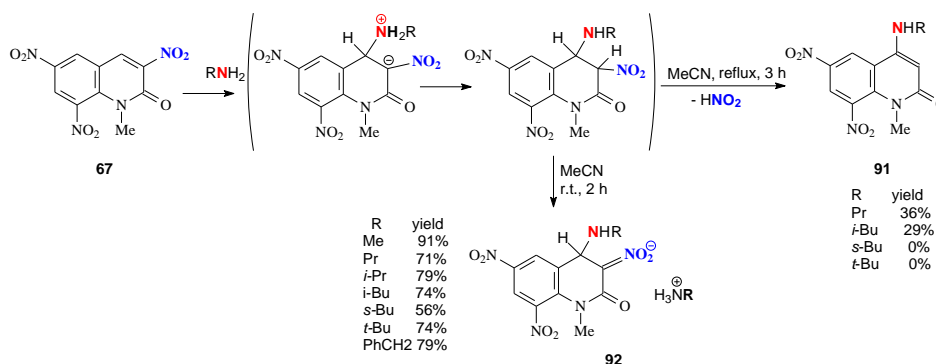
Other compounds of type **86** in which $\text{Y} = \text{Z} = \text{CN}$ or $\text{Y} = \text{COOEt}$, $\text{Z} = \text{CN}$ reacting with pyrazinium compounds **84** or **85** afforded predominantly or exclusively products of *ipso*-substitution of the chlorine atom.

Copper- and cesium-catalyzed couplings of haloimidazo[1,2-*a*]pyridines with azoles were studied by Gueiffier et al.³⁹ The authors found that the coupling performed in the presence of a copper catalyst led to *ipso*-substitution of the halogen while the reaction catalyzed by cesium carbonate afforded the *cine*-substituted product (Scheme 39).



Scheme 39. Cesium catalyzed *cine*-substitution of heterocycle **89** with 1*H*-azoles.

That was the first example of *cine*-substitution for imidazo[1,2-*a*]pyridines. Earlier in this review^{9,29,33} it was described that the 3-nitrogroup in trinitroquinolone **67** treated with some carbon nucleophiles such as carbanions from 1,3-dicarbonyls, methyl ketones or neutral enamines could undergo *cine*-substitution with C-C bond formation at the position 4. Later, Nishiwaki et al.⁴⁰ showed that treatment of compound **67** with an excess of aliphatic primary amines could be an effective approach for the formation of the C(4)-N bond with the formation of addition products in form of salts **92** (Scheme 40).

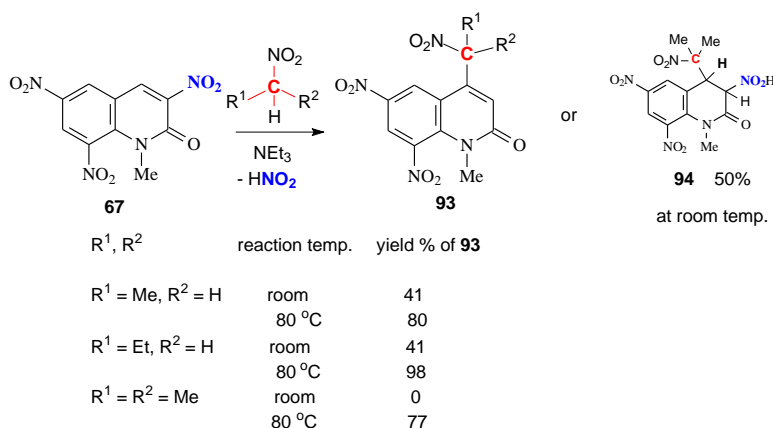


Scheme 40. Reactions of trinitroquinolone **67** with primary amines; the formation of nucleophilic *cine*-substitution **91** and addition **92** products.

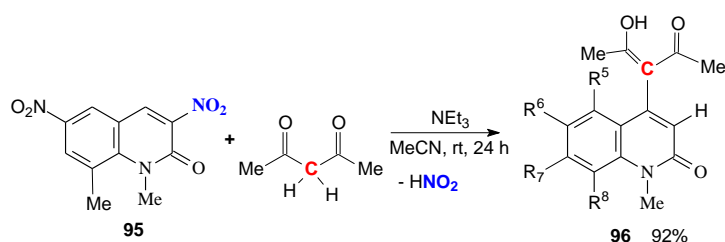
Unfortunately, *cine*-substitution of quinolone **67** to afford products **91** was possible only for sterically unhindered amines such as propylamine or isobutylamine. Nishiwaki et al.⁴¹ also described the reaction of trinitroquinolone **67** with nitroalkanes in the presence of triethylamine, demonstrating another new tool for regioselective C(4)-C bond formation on quinolone **67** skeleton. High yields of *cine*-substitution products **93** (Scheme 41) were observed for the reactions performed at 80 °C.

The reactions with nitroalkanes conducted at room temperature afforded *cine*-products **93** in much lower yields. Here, instead of *cine*-substitution, only addition-product **94** was formed in a moderate yield. Continuing their investigations of the reactions of di- and tri-nitro-1-methyl-2-quinolones with nucleophiles,

Nishiwaki et al.³⁸ found for the first time that dinitroquinolone derivative **95** reacted with a carbanion derived from acetylacetone in a similar way as trinitroquinolone **67** to give *cine*-substitution product **96** (Scheme 42).

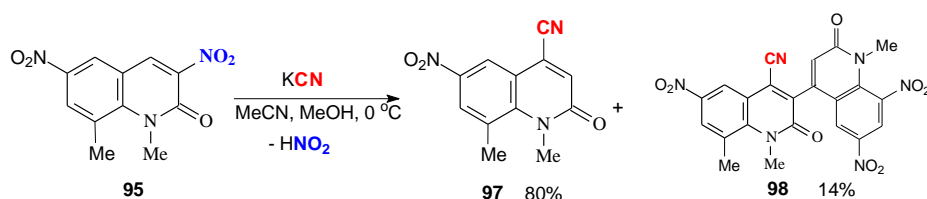


Scheme 41. Effect of the reaction temperature on *cine*-substitution of trinitroquinolone **67** with the formation of 1-methyl-4-nitroalkyl-6,8-dinitro-2-quinolones **93**.



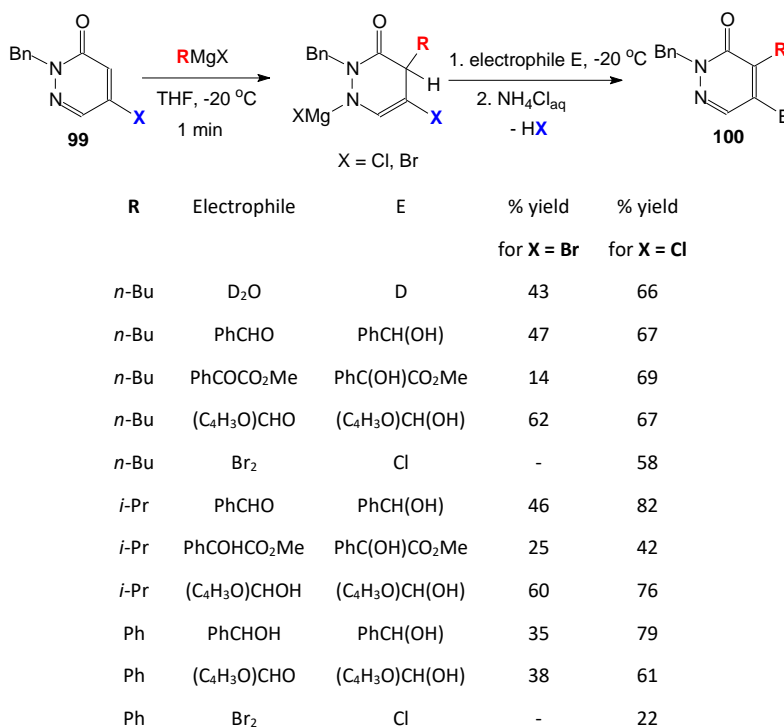
Scheme 42. *cine*-Substitution of 1,8-dimethyl-3,6-dinitro-2-quinolone **95** with carbanion derived from acetylacetone.

Other dinitroquinolones did not follow this reaction pattern. The authors assumed that the high reactivity of compound **95** was caused by steric interactions between the two methyl groups in positions 1 and 8 in the starting material. To check this assumption, they used a small nucleophile such as cyanide instead of a bulky acetylacetone anion in the reaction with quinolone **95**. The reaction with potassium cyanide in acetonitrile at 60 °C resulted in the formation of a complex mixture of compounds. Among others, the mixture contained *cine*-substitution product **97** and dimeric compound **98**. Under optimized reaction conditions, the total yield of compounds **97** and **98** was 94% while the yield of *cine*-product **97** reached 80% (Scheme 43).



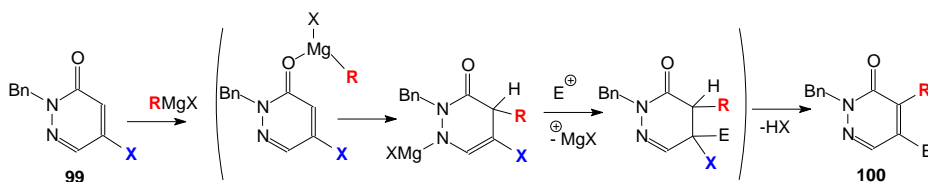
Scheme 43. The highest yields of *cine*-substituted **97** and dimerized **98** products in the reaction of dinitroquinolone **95** with cyanide.

When trimethylsilyl cyanide/cesium fluoride was used instead of potassium cyanide, the yield of *cine*-product **97** increased up to 90% while dimerized compound **98** was not present in the post-reaction mixture. Considering the results of the reactions of dinitroquinolone **95** with acetylacetonate anion and with cyanides, it appeared that the presence of a methyl substituent in position 8 was crucial for the occurrence of *cine*-substitution. Maes et al. described⁴³ a reaction of pyridazinones with Grignard reagents which led to the formation of anionic σ^H adducts. The adducts were then quickly quenched with electrophiles to avoid elimination and afforded *cine*-substitution products (Scheme 44).



Scheme 44. Examples of *cine*-substitution of 5-halopyridazin-3-ones **99**.

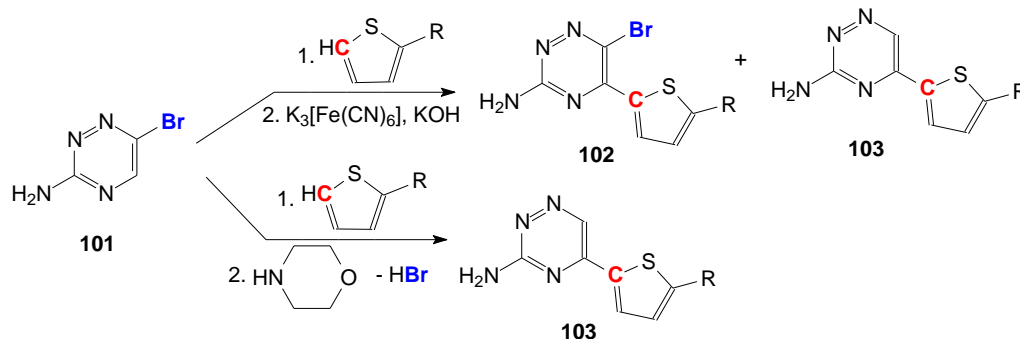
A mechanism of the reaction was proposed (Scheme 45).



Scheme 45. Plausible mechanism of compound **100** formation as the result of *cine*-substitution of pyridazine derivative **99**.

The authors performed an experiment in which pyridazine derivative **99** was treated with Grignard reagents and then with benzoyl chloride as an electrophile. With this electrophile, an elimination step leading to aromatization did not occur and the reaction stopped at the formation of an addition product. Berezin et al. reported⁴⁴ that a bromo derivative of triazine **101** reacting with thiophenes under acidic conditions and then oxidized with K₃[Fe(CN)₆]-KOH resulted in the formation of a mixture of OHVS **102** and *cine*-substitution **103**

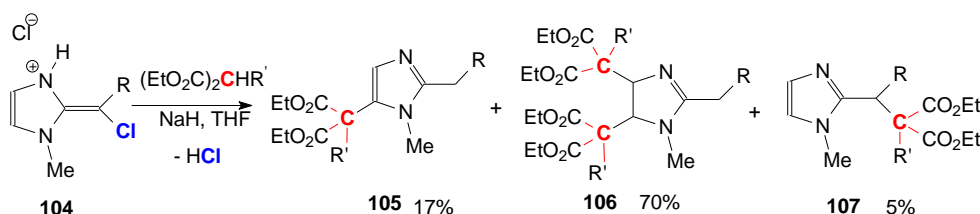
product. The use of morpholine instead of an oxidizing agent led to obtaining compound **103** as the only product (Scheme 46).



Scheme 46. Formation of *cine*-substitution products **103** from triazine derivative **101**.

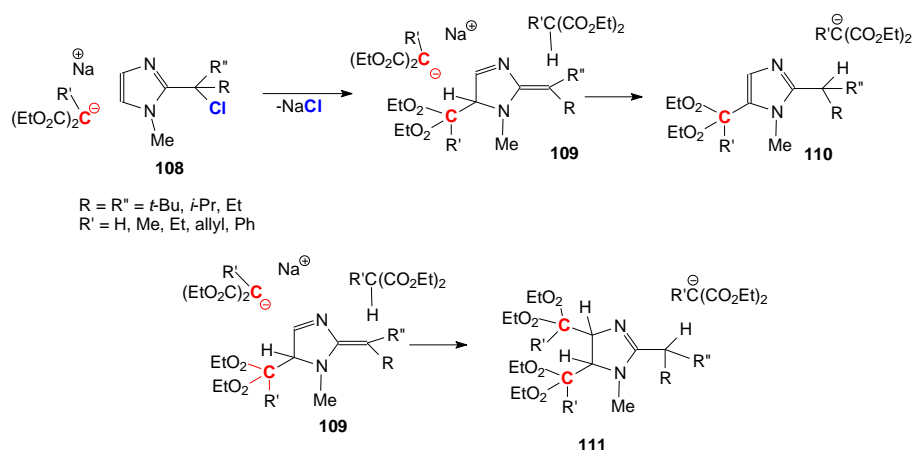
3. 2. Five-membered heterocycles with a leaving group at a carbon atom

Ohta et al.⁴⁵ studied the reaction of chloroalkyl imidazole derivative **104** with diethyl malonate. The reaction conducted in tetrahydrofuran in the presence of sodium hydride produced a mixture of two *tele*-substituted **105**, **106** and one *ipso*-substituted **107** products. The *tele*-products predominated in the mixture (Scheme 47).



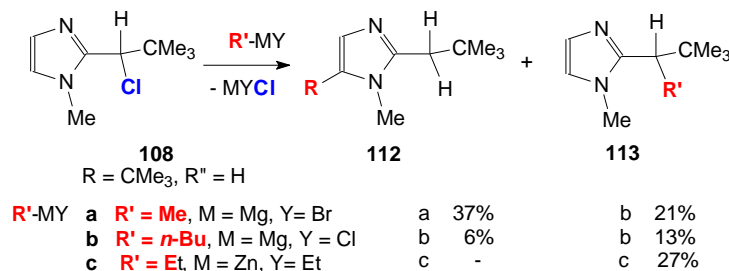
Scheme 47. *tele*- and *ipso*-Substitution of chloroalkylimidazole derivative **104**.

Several other 2-(1-chloroalkyl)-1-methylimidazoles reacted with malonates in a similar way as compound **104**. In all attempts, the yields of both *tele*-products (like **105** and **106**) were high and exceeded the yields of *ipso*-substituted compounds (like **107**). A mechanism of the *tele*-substitution was discussed and formulated (Scheme 48).



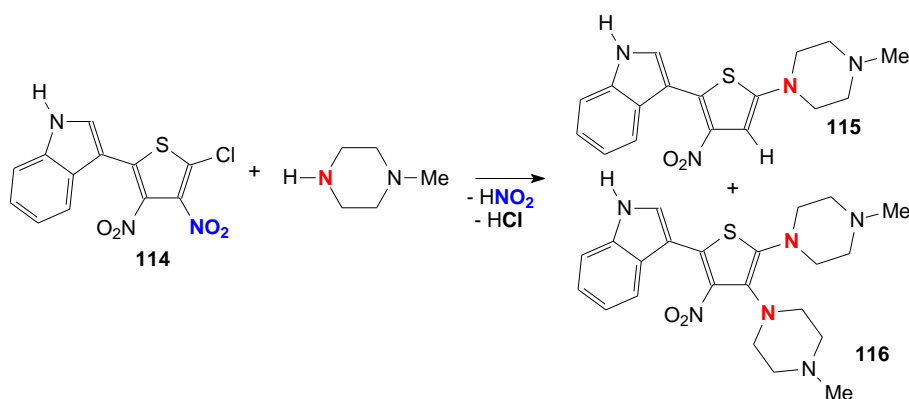
Scheme 48. Postulated mechanism of *tele*-substitution of chloroalkylimidazole derivatives **108** with sodium malonates.

Compound **108** also underwent a nucleophilic substitution with Grignard reagents and diethylzinc. With methylmagnesium bromide and with butylmagnesium chloride, the post-reaction mixtures contained *tele*- **112** and *ipso*-substituted **113** products while the reaction with diethylzinc afforded *ipso*-product only. Formation of compounds of type **106** (diadducts) was not observed in the reaction probably due to the absence of an acidic proton in the used reagents (Scheme 49).



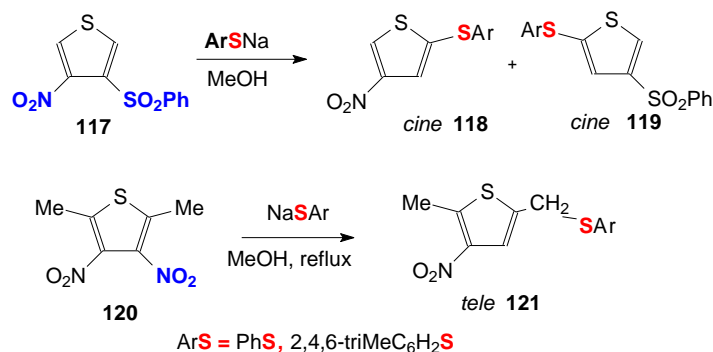
Scheme 49. Reaction of chloroalkylimidazole **108** with Grignard reagents and diethylzinc.

An anomalous course of the reaction similar to *cine*-substitution was observed by Fasfous et al.⁴⁶ when 3-[5-(4-methylpiperazin-1-yl)-3-nitrothien-2-yl]indole (**114**) was treated with *N*-methylpiperazine to give compound **115** together with the typical *ipso*-substitution product **116** (Scheme 50).



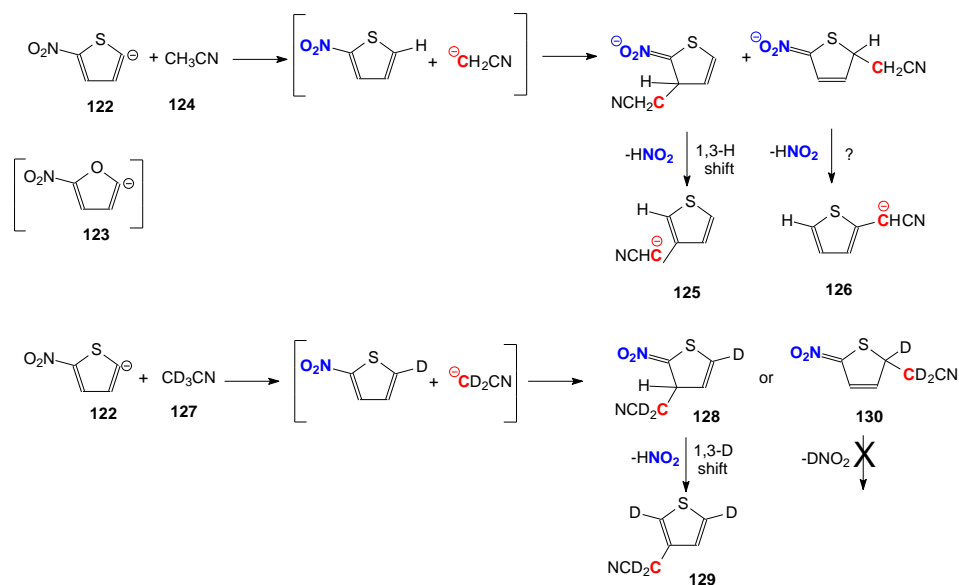
Scheme 50. An anomalous course of reaction of compound **114** with *N*-methylpiperazine.

Reactions of *cine*- and *tele*-substitution in thiophene derivatives were briefly discussed in sub-chapter 3.5 (*cine*- and *tele*-Substitution Chemistry p.p. 95-96) as a part of the chapter *Thiophene Substitution Chemistry* written by V. Ryabova and L. Ignatovich⁴⁷ and published on-line in 2014. Examples of *cine*- and *tele*-substitutions cited in this sub-chapter are shown in Scheme 51. In compound **117**, each of the substituents can play the role of the leaving group in the reaction with arylthiolate. *cine*-Substitution of compound **120** was not possible and therefore, *tele*-substitution of an active hydrogen in methyl group occurred.



Scheme 51. Nucleophilic *cine*- and *tele*-substitution of active thiophene derivatives.

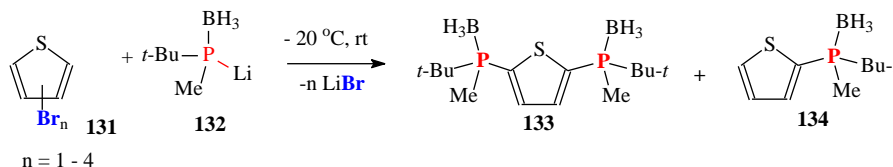
A very interesting first example of nucleophilic *cine*- and *tele*-substitutions in the gas-phase has recently been described by Danikiewicz and Zimnicka.⁴⁸ The authors performed reactions of derivatives of nitrothiophene and nitrofuran with some compounds able to form carbanions in an especially adapted mass spectrometer. The formation of σ -adducts and products of their transformations were observed in reactions characterized by moderate values of proton affinity difference between the C-H acid conjugate base and anions from 2-nitrothiophene (**122**) or nitrofuran (**123**). *cine*- and *tele*-substituted compounds were present among the products from nitrothiophene. Reaction pathways were proposed. Further experiments with deuterated acetonitrile (**127**) revealed that *tele*-substitution was possible but could not occur *via* the 1,5-H shift because the intermediate adducts **128** or **130** eliminated only HNO₂ as shown in Scheme 52. Elimination of DNO₂ was excluded in the experiment.



Scheme 52. Proposed pathways of formation of *cine*-substituted anionic products (**125**) in gas-phase reaction of 2-nitrothiophene carbanion **123** with acetonitrile (**124**).

Several mono- and oligo-bromothiophenes **131** reacted with lithium boranato(*tert*-butyl) methylphosphide (**132**) without a catalyst to afford mixtures of two products **133** and **134**. The mixtures were formed despite the differences in the number and positions of the bromine atoms in the starting bromothiophene.⁴⁹ It was shown that at least most of the reactions occurred according to *cine*- and/or *tele*-

substitution patterns. The lower yields of products **133** and **134** obtained from 2,5-dibromothiophene (**131d**) may be interpreted to mean that also in this case, the reaction did not proceed according to the conventional halogen exchange. A reaction of 2,3-dibromothiophene (**131 b**) with enantiopure (*S*)-**132** performed at -80 °C gave completely racemized product **134** while the reaction of 1,3-dibromobenzene with (*S*)-**132** delivered an almost enantiopure product. This finding can be interpreted to indicate that each of the latter reactions followed a different mechanistic pattern. The reaction of 1,3-dibromobenzene involved the formation of an intermediate benzyne derivative. In the case of reaction of 2,3-dibromothiophene, the authors suggested an initial single electron transfer followed by the formation of ions from 2-lithio- or 2,5-dilithiothiophenes and then their combination with a phosphorus reagent (Scheme 53).

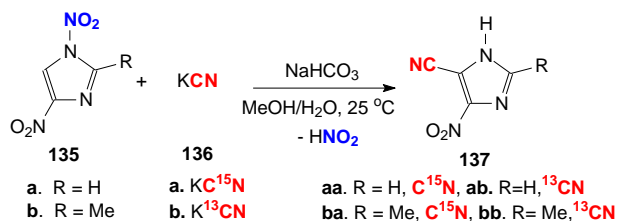


Starting compound	Products yield %	Products %	Starting compound	Products yield %	Products %
131	133	134	131	133	134
a 3,4-diBr	42	34	f 2-Br	6	15
b 2,3-diBr	46	34	g 3-Br	11	18
c 2,4-diBr	43	30	h 2,3,4-triBr	45	19
d 2,5-diBr	13	24	i 2,3,5-triBr	35	18
e mix a-d	38	29	j tetraBr	32	17

Scheme 53. Reactions of bromothiophenes **131 a-j** with lithium (± 1)-boranato(*tert*-butyl)methylphosphide (**132**).

3.3. Five-membered heterocycles with a leaving group at a nitrogen atom

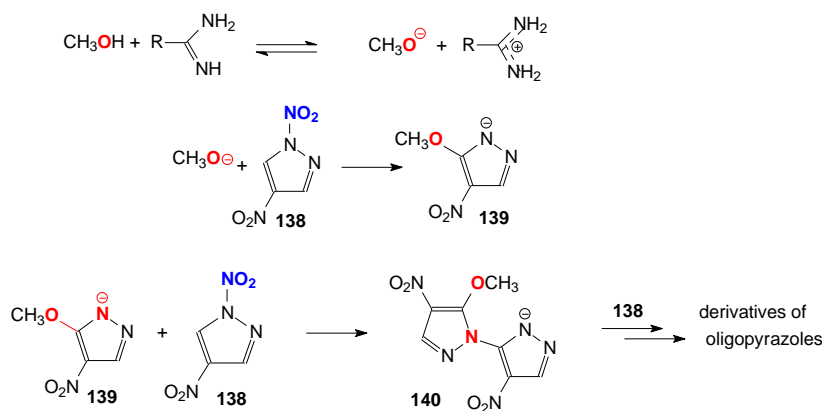
A nucleophilic *cine*-substitution reaction of 1,4-dinitroimidazole and 2-methyl derivative was applied in a synthesis of labelled 4(5)-nitro-1*H*-imidazole-5(4)-carbonitriles⁵⁰ The starting dinitroimidazoles **136a,b** were treated with $K^{15}N$ (**136a**) or $K^{13}CN$ (**136b**) potassium cyanides and gave the respectively labelled carbonitriles **137** (Scheme 54).



Scheme 54. *cine*-Substitution of dinitroimidazoles **135a,b** with nitrogen-15 (**136a**) or carbon-13 (**136b**) KCN.

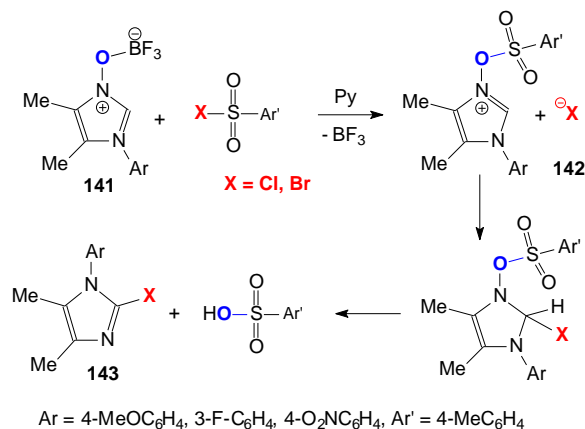
Detailed analysis of mass spectra confirmed the structures of the products and the labeling. Luo et al.⁵¹ followed the procedure used earlier by Suwinski and Swierczek⁵⁰ for the preparations of labeled 5-cyano-4-nitro-1*H*-imidazoles and obtained one new doubly isotopically modified compound: 5(4)-(^{15}N , ^{13}C)cyano-4(5)-

nitro-1*H*-imidazole, which was then used in the syntheses of the respectively substituted adenine and adenosine derivatives. It is well-known that 1,4-dinitropirazoles react easily with several nucleophiles to form 5-substituted 4-nitropirazoles. Suwinski et al.⁵² showed that the reaction of 1,4-dinitropyrazole (**138**) with amidines carried out in methanol gave essentially a mixture of oligomethoxynitropyrazoles together with small amounts of the expected respective 5-nitropyrimidines. Under these reaction conditions, methanol was deprotonated by strongly basic amidines and the forming anion then reacted with pyrazole **138** to afford 5-methoxy-4-nitropyrazole anion **139**. The latter anion then reacted with compound **138**, giving anion **140**. A cascade of similar *cine*-substitutions resulted in the formation of mixtures of oligomethoxynitropyrazoles (Scheme 55).



Scheme 55. Formation of oligomethoxynitropyrazoles in reaction of 1,4-dinitropyrazole (**138**) with methanol in the presence of amidines.

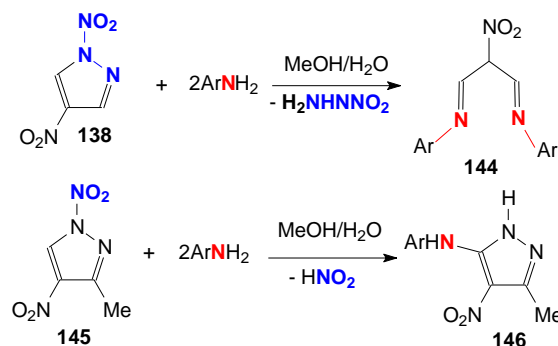
Mityanov et al.⁵³ investigated the nucleophilic halogenation of imidazole at carbon atom 2 treated 1-aryl-4,5-dimethylimidazole-1*H*-1-oxide fluoroborate complexes (**141**) with tosyl halogenides and obtained 1-aryl-2-halo-4,5-dimethyl-1*H*-imidazoles (**143**). A mechanism involving *cine*-substitution of intermediate cation **142** with halogen anion was formulated (Scheme 56).



Scheme 56. Nucleophilic halogenation of imidazole *N*-oxides involving *cine*-substitution.

The authors also proposed that the addition of the halogen anion to the atom C-2 of cation **142** was the rate-limiting step. In 2015, Suwinski⁵⁴ published a review on 1,4-dinitro-1*H*-imidazoles. A short sub-section

4.2 of the review was dedicated to nucleophilic *cine*-substitution of the dinitroimidazoles. Investigations of the reactions of 1,4-dinitropyrazoles with nucleophiles⁵² were continued later by Jędrzyśiak and Suwiński⁵⁵ who focused on reactions of 3-methyl derivative in this study. It was found that 1,4-dinitro-1*H*-pyrazole (**138**) with an excess of anilines afforded ring-opening compounds **144** while 3-methyl derivative **145** gave *cine*-substituted compounds **146** in high yield (Scheme 57).

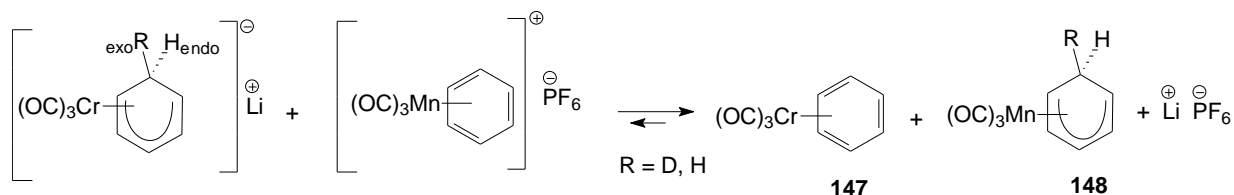


Scheme 57. Different courses of reactions of dinitropyrazoles **138** and **145** with anilines.

Shreeve et al.⁵⁶ looking for energetic compounds with good detonation performance and high thermal stability studied nucleophilic *cine*-substitution of 1,3-dinitro-1*H*-triazole with other 1*H*-azoles in the presence of bases and obtained four derivatives of 5-(azol-1'-yl)-3-nitro-1*H*-1,2,4-triazoles. The products were fully characterized by NMR and X-ray.

4. *cine*- and *tele*-Substitution in Nonaromatic Systems

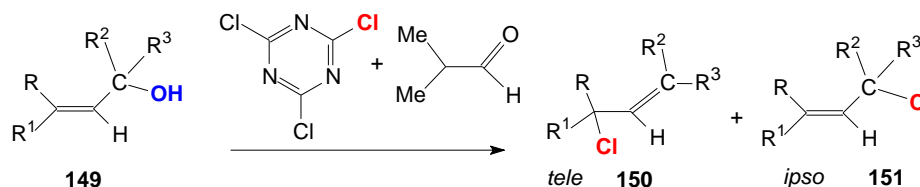
As mentioned earlier, *cine*- and *tele*-substitution in nonaromatic systems is rare. Furthermore, in certain cases, it is not easy to determine whether a paper addresses reactions occurring in aromatic or nonaromatic system. This characteristic primarily concerns the substitution of complexes of organic compounds with metals. A paper by Rose et al.⁵⁷ providing several references to former articles on *cine*- and *tele*-substitutions is a good example of this. Among other references, the paper cited nucleophilic substitutions of $[(\eta^5\text{-cyclohexadienyl})\text{Mn}(\text{CO})_3]$ complexes **148**. It was shown that the mechanisms of the reactions were very similar to those described for $[(\eta^6\text{-arene})\text{Cr}(\text{CO})_3]$ complexes **147**. The similarity can be easily understood by taking into account the reversible addition-elimination of hydride anion between the complexes (Scheme 58).



Scheme 58. Reversible addition-elimination of hydride anion between complexes.

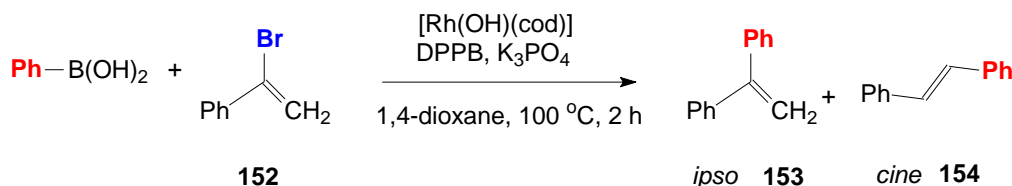
Due to the similarity of *cine*- and *tele*-substitution mechanisms of cyclohexadienylmanganese and arene chromium complexes, the reactions of cyclohexadienylmanganese complexes are treated here as the reactions of aromatic systems.

Sanjay et al.⁵⁸ described the synthesis of unsymmetrical allyl chlorides from allyl alcohols or β -aminoalcohols using cyanuric chloride in dimethylformamide. In some cases, *ipso*-substitution was accompanied by *tele*-substitution. Ratios of the *ipso*- to *tele*-substitution depended on the positions, and electronic and steric effects of substituents. Only the abstract of this article was available to the author of the present review. The overall picture of the reaction is given in Scheme 59.



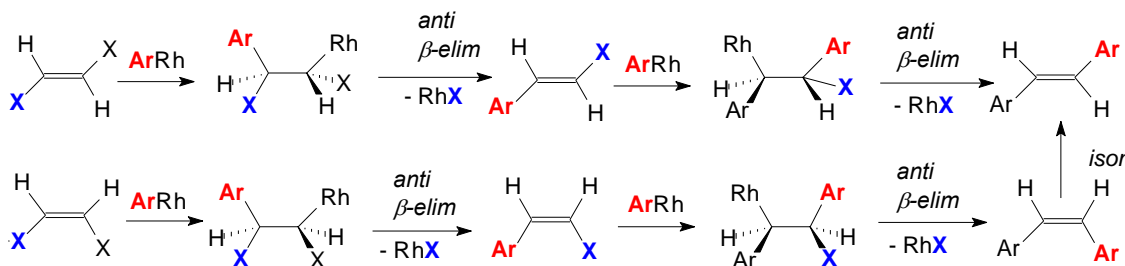
Scheme 59. Formation of allyl chlorides in *tele*- and *ipso*-substitution of allyl alcohols.

Matsuda et al.⁵⁹ studied rhodium-catalyzed cross-coupling of alkenyl halides with arylboron compounds. They observed mono- and double-arylation of 1,2-dichloroethene with arylboronic esters in the presence of rhodium(I) catalyst. To gain some more information on the course of the studied reaction, the authors coupled α -bromostyrene (**152**) with phenylboronic acid and obtained a mixture of 1,1-diphenylethene (**153**) and (*E*)-stilbene (**154**) in the ratio of 4:1 with combined yield of 46% (Scheme 60).



Scheme 60. Arylation of bromostyrene **152** with phenylboronic acid in the presence of rhodium catalyst.

The formation of product **154** could indicate the addition/ β -elimination mechanism of arylation (Scheme 61).



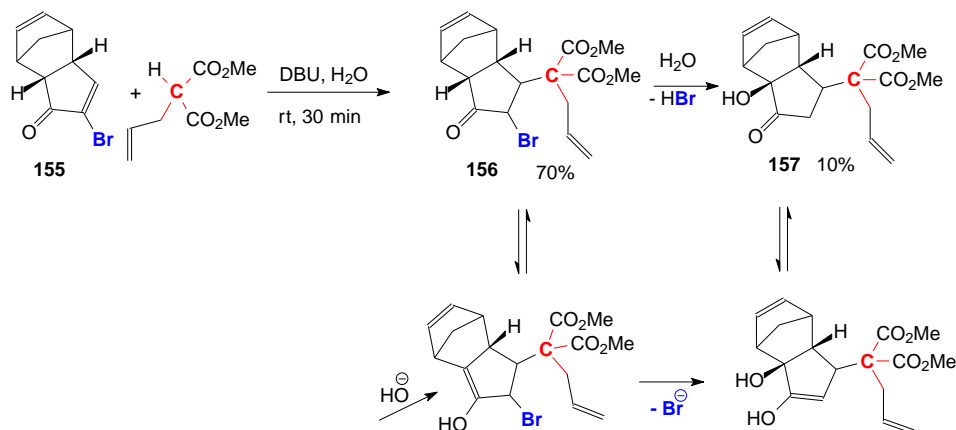
Scheme 61. Proposed mechanism for rhodium(I)-catalyzed arylation of 1,2-dihaloethenes.

Such mechanism was earlier proposed for the known rhodium-catalyzed *cine*-substitutions of alkenyl sulfones and alkenyl acetates.

Dinesh et al.⁶⁰ described a new original stereo-controlled synthesis of triquinane framework. In the course of the investigations, compound **155** underwent Michael addition with malonic ester to afford Michael adduct

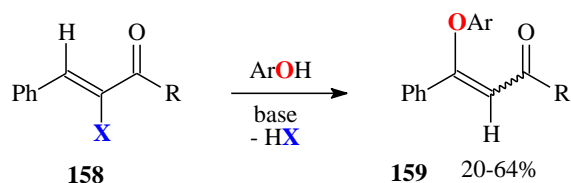
156 in 60-70% yield accompanied by compound **157** in 10-15% yield. According to the authors, product **157** was probably formed by *cine*-rearrangement of the enolic form of compound **156**.

Formally, the conversion of compound **156** into product **157** may also be called *tele*-substitution. In principle, the reaction does not seem to differ from highly well-known reactions denoted by S_N' (Scheme 62).



Scheme 62. *tele*-Substitution of bromine by hydroxyl in a triquinane synthesis.

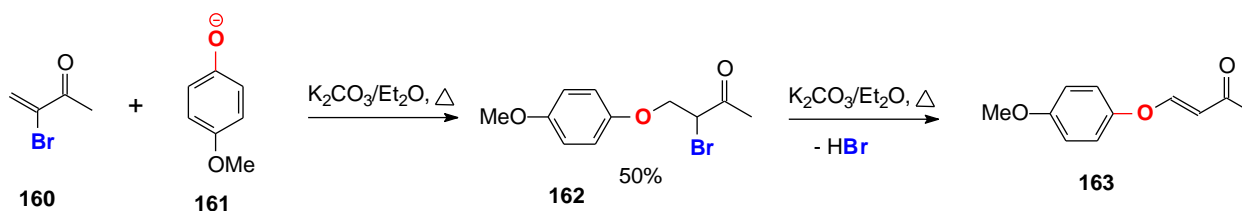
Rulev et al.⁶¹ elaborated a new method for the synthesis of push-pull aryloxyenones by nucleophilic *cine*-substitution of haloenones with phenolates. Yields of α -aryloxyenones depended on nucleophilicity of phenolates and decreased in the following order: 4- $\text{BrC}_6\text{H}_4\text{O}^-$, 4- $\text{MeO-C}_6\text{H}_4\text{O}^-$, 4- $\text{O}_2\text{NC}_6\text{H}_4\text{O}^-$. Products were obtained as mixtures of *E* and *Z* isomers. Two alternative pathways (*E*-Ad and Ad-*E* sequences) were considered for the *cine*-substitution and *E*-Ad mechanism was found less favorable (Scheme 63).



158 a: R = Me, Ar = Ph; **b:** R = Me, Ar = 4- BrC_6H_4 ,
c: R = Me, Ar = 4- MeOC_6H_4 , **d:** R = Me, Ar = 4- $\text{O}_2\text{NC}_6\text{H}_4$,
e: R = Ph, Ar = 4- MeOC_6H_4

Scheme 63. *cine*-Substitution of haloenones with phenolates.

A successful experiment with addition of 4-methoxyphenolate **161** to terminal bromoenone **160** led to isolation of β -4-methoxyphenoxy- α -bromo enone (**162**) in 50% yield which under action of a base eliminated hydrogen bromide to afford β -aryloxyenone **163**. This result pointed out to Ad-*E* pathway as the most probable mechanism in the studied synthesis of α -aryloxyenones (Scheme 64).



Scheme 64. Addition of 4-methoxyphenolate ion (**161**) to terminal bromoenone (**162**).

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Jerzy Wiktor Suwiński was born in 1939. His M.S. (1961), Ph.D. (1968), D.Sc. (1978) were earned at Silesian University of Technology, Gliwice, Poland where he was employed until 2012. Since 1990, he is a full professor. In 1973-74, he was a post-doc at the University of East Anglia with Prof. A. R. Katritzky. He has lectured several times in Italy, USA and Brazil as a contract or visiting professor. In 2012, he moved to the Centre of Polymer and Carbon Materials of the Polish Academy of Sciences, Zabrze, Poland. His scientific interests lie in the fields of organic synthesis, reaction mechanisms and nitrogen-containing heterocycles.