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Review

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Addition-elimination reactions of 2,2-disubstituted malononitriles and α-aryl nitriles. Subsequent transformations

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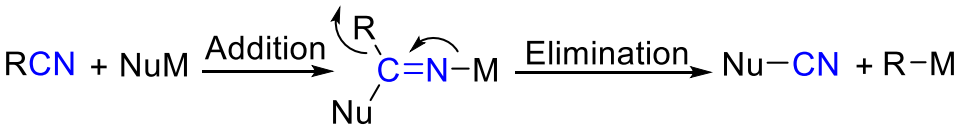
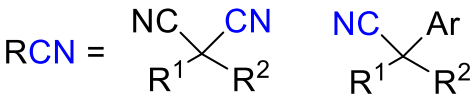
Abstract

This review focuses on addition-eliminations on the cyano group of 2,2-disubstituted malononitriles and α-aryl nitriles. Mechanistic insights and applications are provided. This mechanism operates in cyanations of organometallics and in various decyanations. Further reactions of the expelled anion offer new perspectives in organic synthesis.





NuM = organometallics, metal hydrides, KOH or NaOH

Keywords: Organometallics, anion, transnitrilation, decyanation, electrophile

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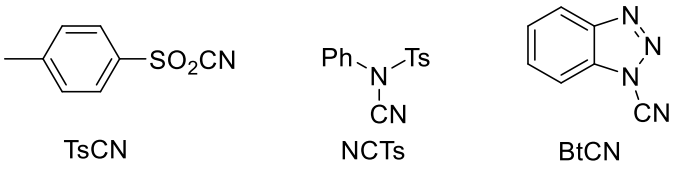
1. Introduction

Nitriles are important intermediates in organic synthesis, precursors of a large variety of other functional groups such as ketones, amides, carbamidines and different carbocyclic or heterocyclic compounds.[1-4] Many reviews illustrate the versatility of these building blocks.[5-11] On the other hand, the preparation of nitriles remains an attractive challenge. In recent years, efforts have been focused on safe cyanide sources and cyanating agents.[12] One of the strategies consists of electrophilic cyanation with reagents acting as formal "CN^+" cation donors (Figure 1).[12-16]

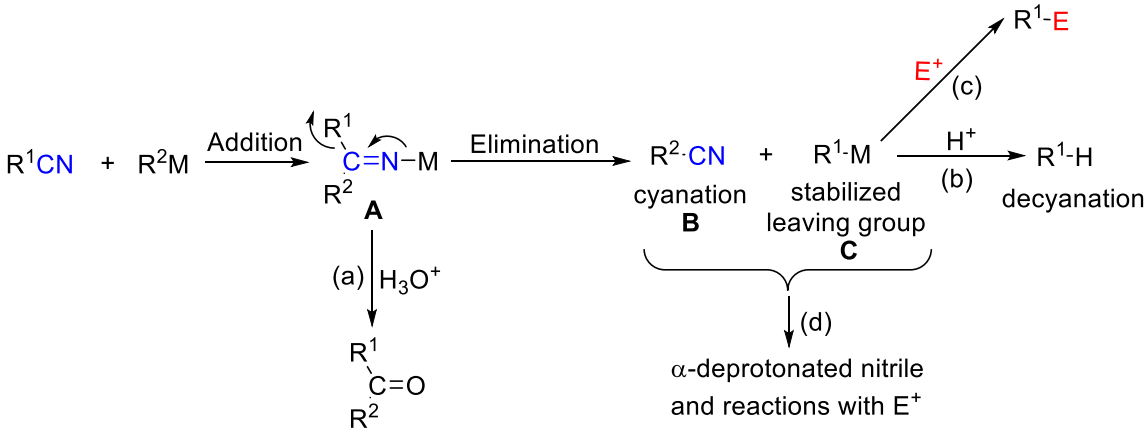


TsCN NCTs BtCN

Figure 1. Some important electrophilic "CN^+" transfer reagents: TsCN (*p*-toluenesulfonyl cyanide), NCTs (*N*-cyano-*N*-phenyl-*p*-toluenesulfonamide), BtCN (1-cyanobenzotriazole).

A plausible mechanism for such cyanation involves a nucleophilic addition to the nitrile group followed by an elimination (fragmentation) involving a carbon-heteroatom bond breaking.[17-21] If the expelled carbanion is stabilized, such a pathway can be applied to nitriles (Scheme 1). The nucleophile R^2M adds to the cyano group to give a metal imine adduct **A**, precursor of a carbonyl product in the classical way (path a). Alternatively, **A** can fragment into the cyanation product **B** and the stabilized leaving group **C**. While the strong C-CN bond usually needs activation to be cleaved,[9] this reaction proceeds under transition metal-free conditions. When **C** is protonated, the decyanation product is obtained (path b). Under aprotic conditions, the nucleophile

intermediate **C** is able to react with various electrophiles (path c). With an appropriate leaving group, nitriles **B** bearing an α-hydrogen can be deprotonated by **C** to yield a new nucleophile (path d). A previous computational approach to elimination step pointed out the roles of steric hindrance, pKa of the acid related to the leaving group and of the metal bound to the imine-type intermediate.[22]



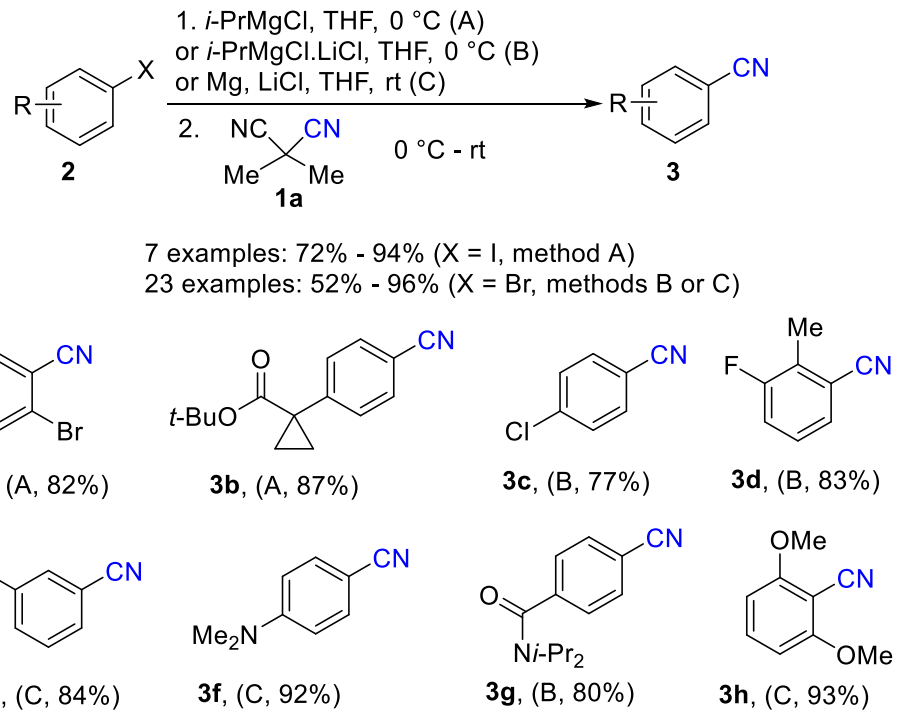
Scheme 1. Addition-elimination on nitriles and resulting pathways.

This work details the different pathways described in Scheme 1. The first part focuses on the transnitrilation reaction of disubstituted malononitriles, starting point of a series of applications in organic reactions. The second part is devoted to α-aryl nitriles.[23] Indeed, another way to stabilize the anionic leaving group in an addition-elimination process is to substitute the α position of the nitrile group with one (or more) aryl groups. Some transformations involving addition-eliminations on α-aryl nitriles were discovered by serendipity, however, more recent works bring a fresh view on this process. Mechanistic insights are proposed as well as selected examples describing the scope of these transformations. Unless otherwise specified, yields given refer to those of isolated products. Addition-elimination pathways proposed in transition metal-catalyzed reactions are not discussed here.[24-27]

2. Addition-eliminations to disubstituted malononitriles

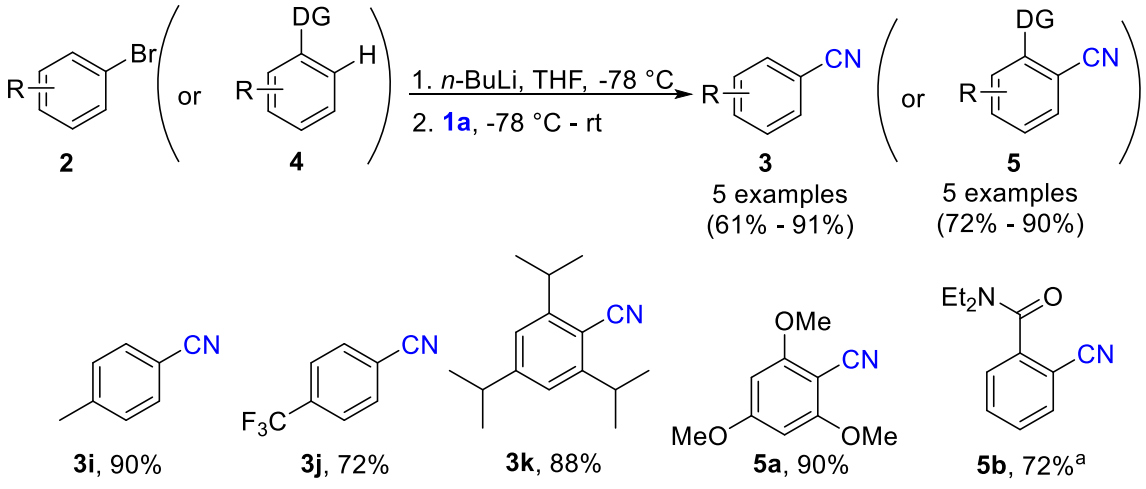
2.1 Transnitrilation of organometallics with DMMN

The cleavage of disubstituted malononitriles was first described in 1935,[28] but the transnitrilation of aryl Grignard and lithium reagents with dimethylmalononitrile **1a** (DMMN) and structural variants was extensively developed by Reeves and co-workers in 2015.[29] That study was the starting point of a series of works using transnitrilation with DMMN.[30-36] The scope of the reaction was first investigated with commercially available phenylmagnesium bromides substituted with methyl or methoxy groups (5 examples, 78% - 96%). A larger set of Grignard reagents was prepared *in situ*,[37] by iodine or bromine/magnesium exchange (methods A, B) as well as by magnesium insertion (method C) before the reaction with **1a** (Scheme 2). Various functional groups are tolerated such as halides (**3a**, **3c**, **3d**), ester (**3b**), thioether (**3e**), amine (**3f**), or amide (**3g**). This method was convenient for electron-rich and sterically hindered halides (**3f**, **3h**).



Scheme 2. Transnitrilation of aryl Grignard reagents prepared *in situ*. Method A applies for aryl iodides, methods B and C for aryl bromides.

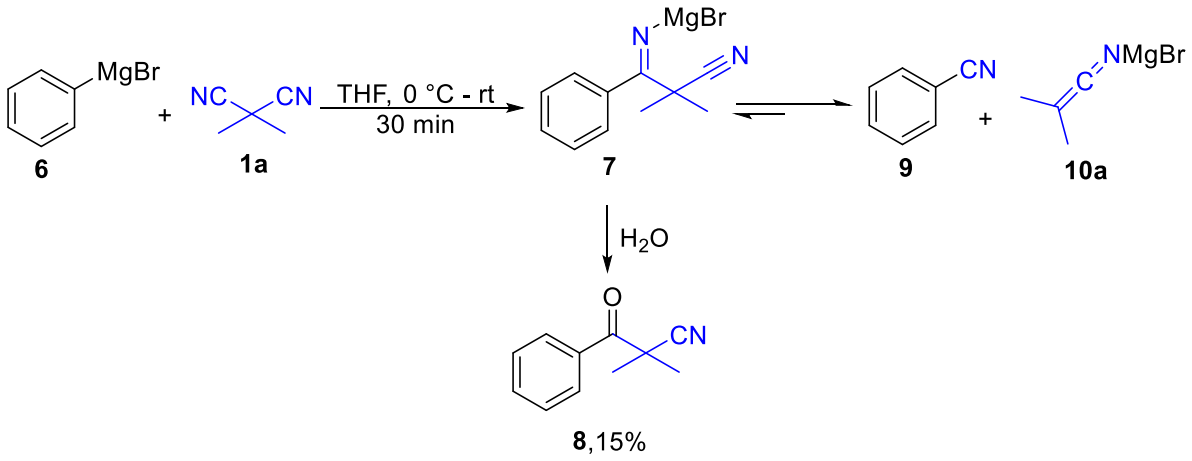
The use of aryllithium reagents was also successfully investigated (10 examples, 61% - 91%). Aryllithiums were generated *in situ* by bromine/lithium exchange using *n*-BuLi (**3i**-**3k**) or *via* directed *ortho*-lithiation by various organolithiums (**5a**, **5b**) (Scheme 3).



Scheme 3. Transnitrilation of aryllithiums prepared *in situ*. DG = directing group.[a] Lithiation with *s*-BuLi and TMEDA.

The addition-elimination pathway proposed is outlined in Scheme 4 in the case of PhMgBr (**6**). After the addition step, part of the imine adduct **7** was transformed into ketone **8** by quenching the reaction mixture after 30 minutes. The elimination step (retro-Thorpe fragmentation)[38] furnishes benzonitrile **9** (transnitrilation from **1a** to **6**) and isobutyronitrile anion **10a** (decyanation-metalation of **1a**). Infrared monitoring of the

reaction confirmed the formation of **7**, **9** and **10a**. The structure of **10a** was proposed according to the IR assignments and comparison with an authentic sample prepared from *i*-PrMgBr and isobutyronitrile.[39-40] Interestingly, "small amounts" of **8** were detected "even after extended reaction times" in agreement with a reversible step. However, the fragmentation is favored due to stabilization of the expelled anion, relief of steric strain and increased entropy. DFT calculations supported an energetically favorable fragmentation.

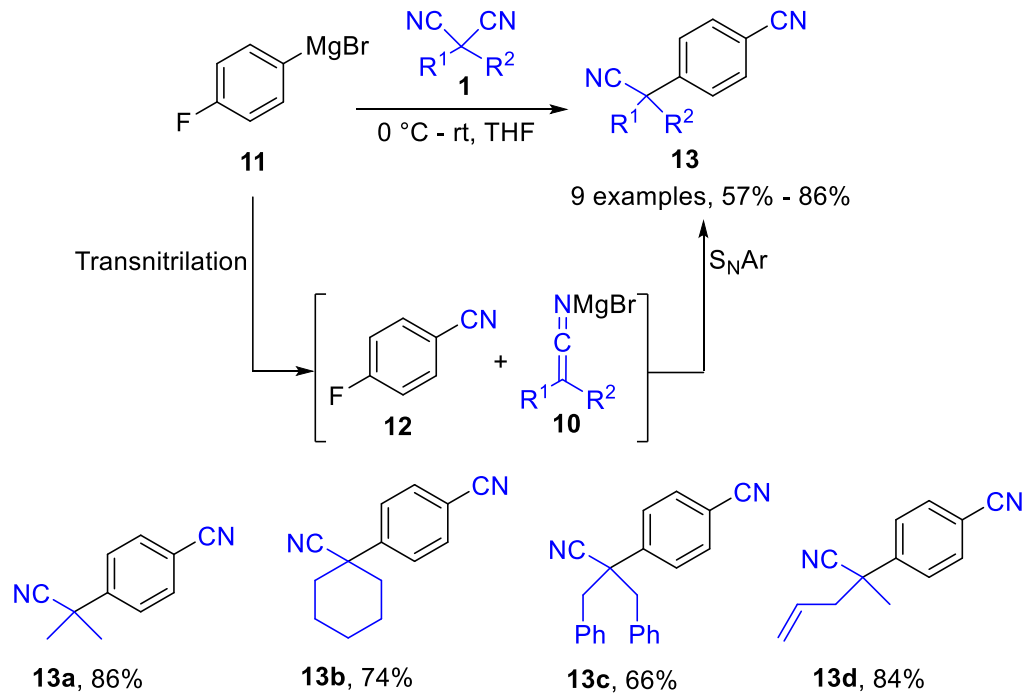


Scheme 4. Addition-elimination mechanism for the reaction of phenylmagnesium bromide **6** with **1a**.

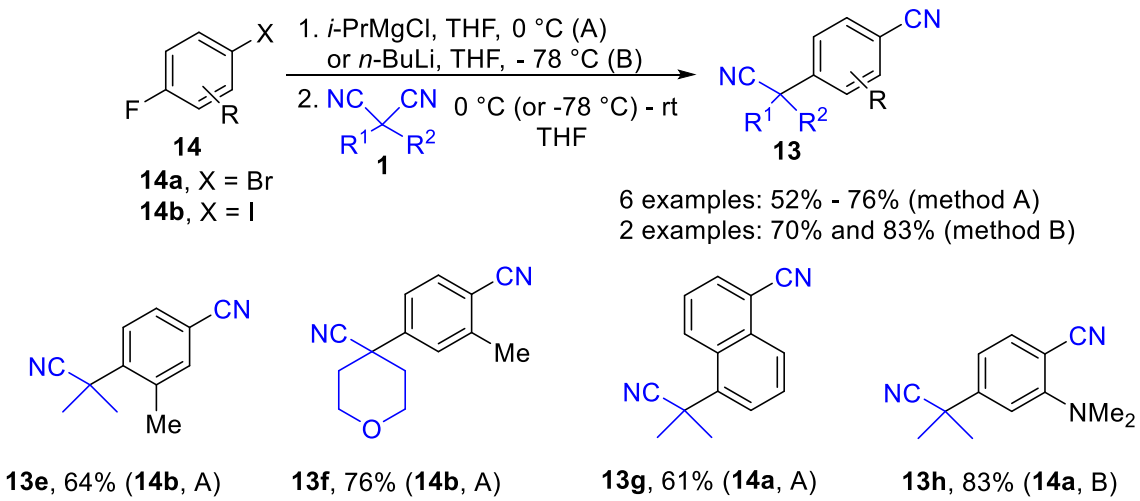
2.2 Transnitrilation-S_NAr reaction

Starting from 4-fluorophenylmagnesium bromide **11** and disubstituted malononitriles **1**, a tandem transnitrilation-S_NAr reaction takes place to give the 1,4-dicarbofunctionalized product **13**.[41] The scope of the reaction was first examined by varying the structure of disubstituted malononitriles **1** and, therefore, the nature of the anionic leaving group **10** acting as nucleophile in the S_NAr reaction (Scheme 5). The reaction can be achieved with cyclic malononitriles (**13b**), and malononitriles substituted with benzyl (**13c**) or allyl (**13d**) groups.

The scope of the 4-fluoroaryl organometallic reagents was then investigated (Scheme 6). Reagents were prepared *in situ* from halogen/magnesium (conditions A, **13e**-**13g**) or lithium (conditions B for electron-rich aryl bromides, **13h**) exchange reactions.[37] Fair to very good yields are obtained. The presence of a methyl group ortho to the fluorine was tolerated (**13e**) but two neighboring methyl groups preclude the S_NAr reaction, and the sequence failed for *o*-fluoro and *m*-fluoro Grignard reagents.

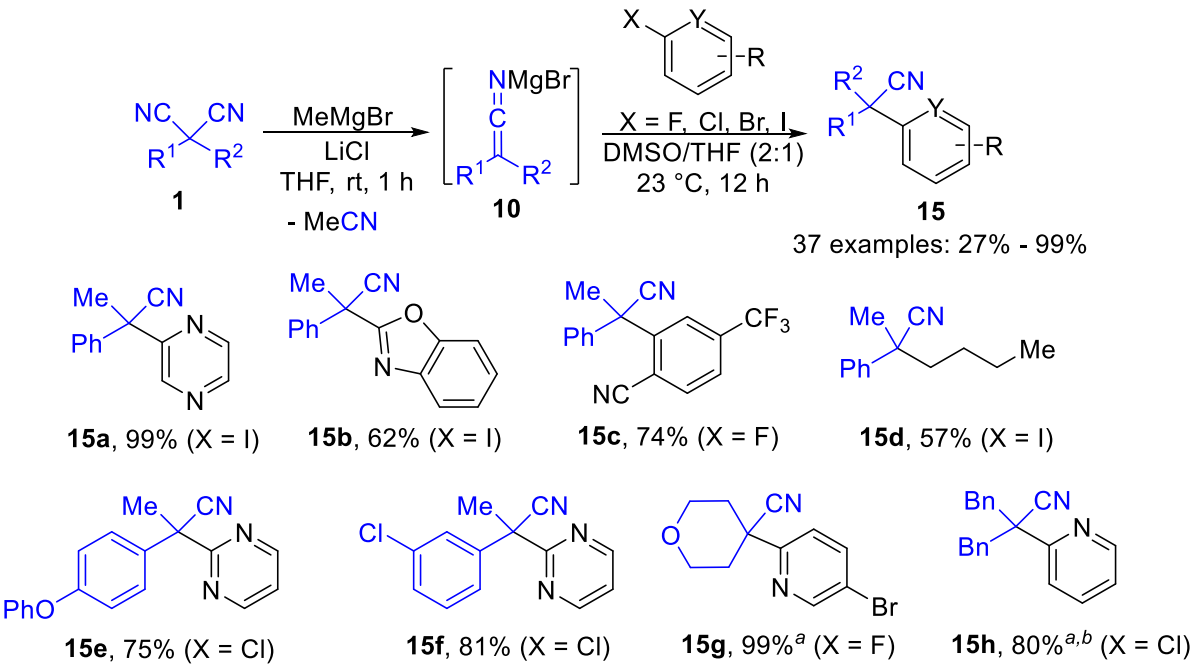


Scheme 5. One-pot transnitrilation-S_NAr reaction from **11** and various disubstituted malononitriles **1**.



Scheme 6. Transnitrilation-S_NAr reaction from various organometallics prepared *in situ*. The starting halide and the method used are shown in parentheses.

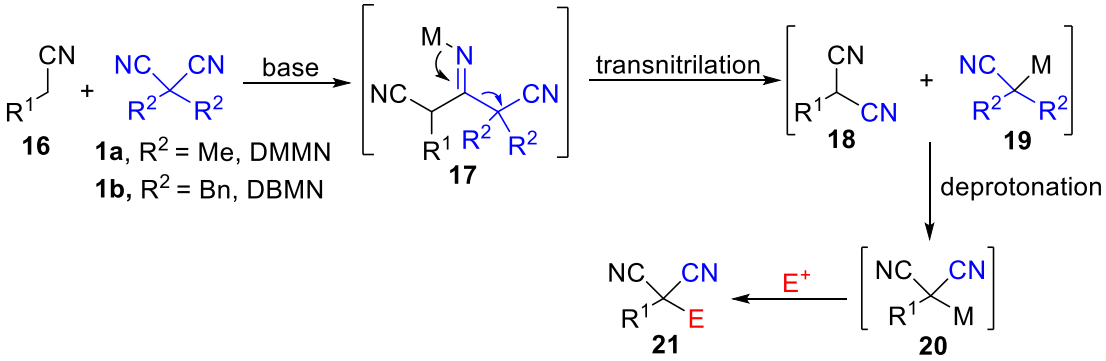
Rousseaux and co-workers used a similar strategy for the preparation of α-(hetero)aryl nitriles **15**.[42] The novelty of this work is that the expelled anion **10** reacts with an activated (hetero)aryl halide electrophile. After evaluation of reaction conditions, the decyanation-metalation of **1** was induced with MeMgBr in THF with LiCl to increase the solubility of the resulting anionic intermediate **10** (transnitrilation of MeMgBr). The latter was then reacted in a mixture of DMSO and THF with various electrophiles (Scheme 7). This one-pot method seems to be efficient with a large number of electrophiles and malononitriles **1**. Many heterocycles (**15a**, **15b**, **15e**-**15h**) and functional groups (**15c**, **15e**-**15g**) are compatible. This sequence is applicable to alkyl iodides as electrophiles (**15d**) and dialkyl malononitriles (**15g**, **15h**).



Scheme 7. One-pot decyanation-metalation and (hetero)arylation of malononitriles **1**. [a] In PhMe/THF (2:1) at 50 °C instead of DMSO/THF. [b] GC-MS yield.

2.3 The transnitrilation-deprotonation strategy: synthesis of disubstituted malononitriles

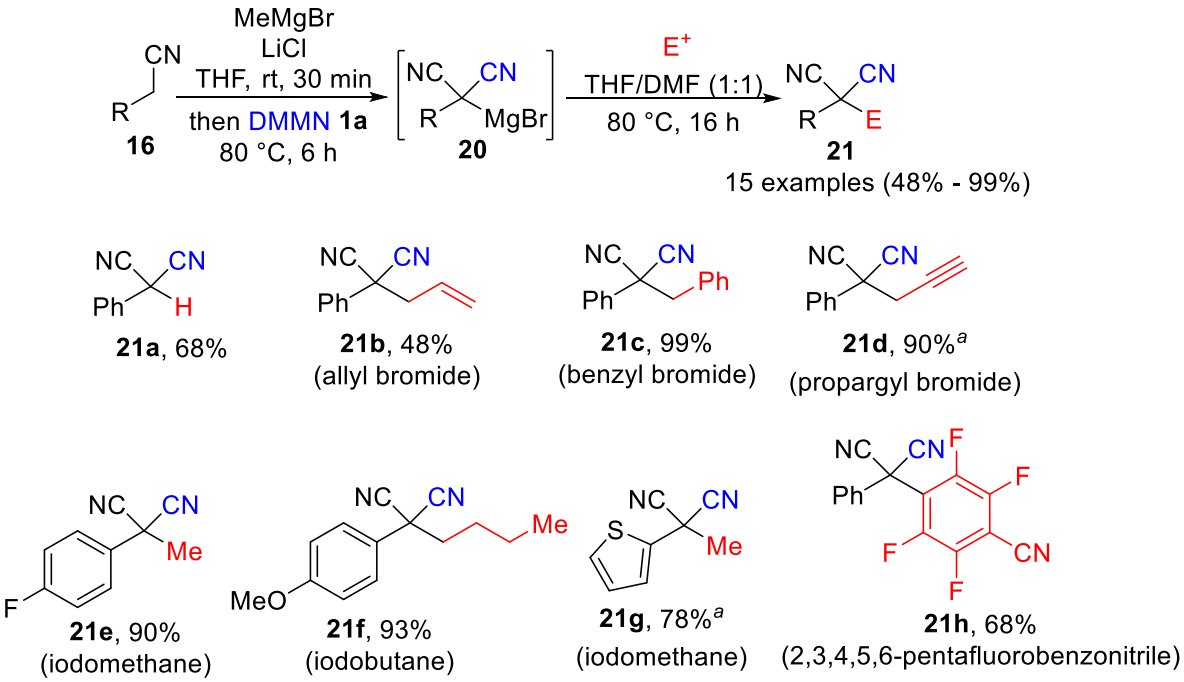
The strategy outlined in this section corresponds to path (d) in Scheme 1 and has been investigated by Rousseaux and Mills.[43] A primary nitrile **16** is deprotonated with a base and led to an addition-elimination process with DMMN or DBMN (dibenzylmalononitrile). Fragmentation of the metal imine intermediate **17** generates the α-anion **19**. The latter deprotonates the dinitrile **18** to produce the more stable carbanion **20**, which can be trapped with an electrophile (Scheme 8).



Scheme 8. Transnitrilation, deprotonation and electrophile trapping: general concept.

The authors successively optimized the conditions for transnitrilation and electrophilic functionalization. Primary nitriles are deprotonated with methylmagnesium bromide, in the presence of lithium chloride in THF. After 30 minutes at room temperature, DMMN (or DBMN) was added and the reaction was stirred at 80 °C for the transnitrilation step and generation of the α-anion intermediate **20**. Finally, DMF and the electrophile were added and the reaction mixture was stirred at 80 °C to yield the substitution product **21** (Scheme 9).

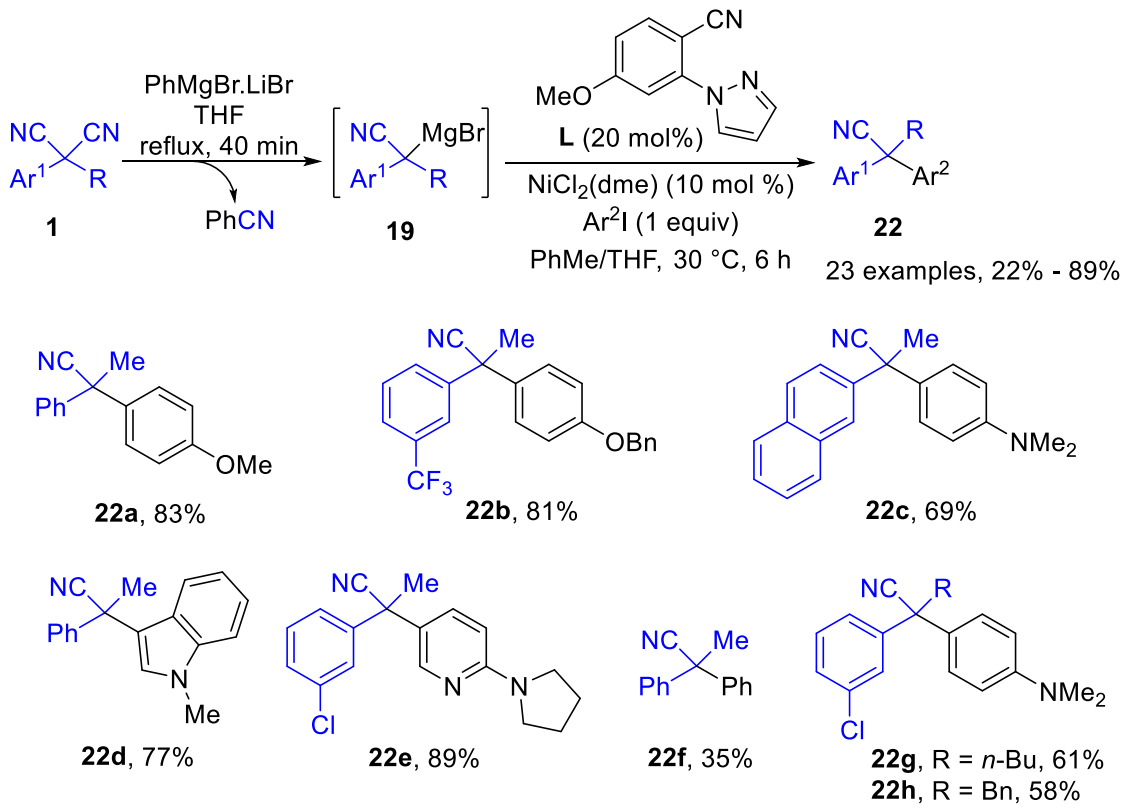
Primary benzylic nitriles **16** were used including electron-rich (**21f**), electron-deficient (**21e**) and heterocyclic (**21g**) derivatives. If the mixture was quenched after reaction with **1a**, the monosubstituted malononitrile **21a** was isolated. The reaction with electrophiles was successful for various primary alkyl halides (**21b**-**21g**). The S_NAr reaction was possible using the activated pentafluorobenzonitrile (**21h**). This method was applicable from primary alkyl nitriles using LDA as a base instead of MeMgBr (2 examples: 85% and 98%). The conversion of benzyl bromide into disubstituted malononitriles was also feasible *via* formation of the Grignard reagent, double transnitrilation with DBMN and electrophile trapping (3 examples 60% - 81%).



Scheme 9. One-pot transnitrilation, deprotonation and electrophile trapping: scope of the reaction. [a] With DBMN **1b** instead of DMMN **1a**. E^+ is shown in brackets.

2.4 The Ni-catalyzed cross coupling reaction

Rousseaux and co-workers developed a Ni-catalyst for cross coupling of the generated nucleophile with aryl iodides.[44] A screening of benzonitrile-containing ligands led them to design the optimal bidentate ligand **L**. The α-anion **19** resulting from the addition-elimination process was previously prepared in THF and added to a mixture of **L**, $NiCl_2$(dme) and aryl iodide (Ar^2I) in PhMe/THF (Scheme 10). The reaction was successfully performed with electron-rich aryl iodides (**22a**-**22c**, **22g**, **22h**) and (hetero)aryl iodides (**22d**, **22e**). Electron-neutral (**22f**) and especially electron-deficient aryl iodides (<5% yield) gave lower yields due to formation of a larger amount of the reduced product Ar^2H. Regarding the malononitrile, the method is convenient with electron-deficient (**22b**, **22e**, **22g**, **22h**) and electron-neutral (**22c**) aryl substituents. The substitution of **1** with some other alkyl substituents R instead of a methyl group is also described (**22g**, **22h**). However, α-anions resulting from electron-rich malononitriles gave only poor conversions in the coupling step. A set of experiments including a kinetic study and a Hammett analysis allowed to suggest a catalytic cycle and clarify the role of **L**.

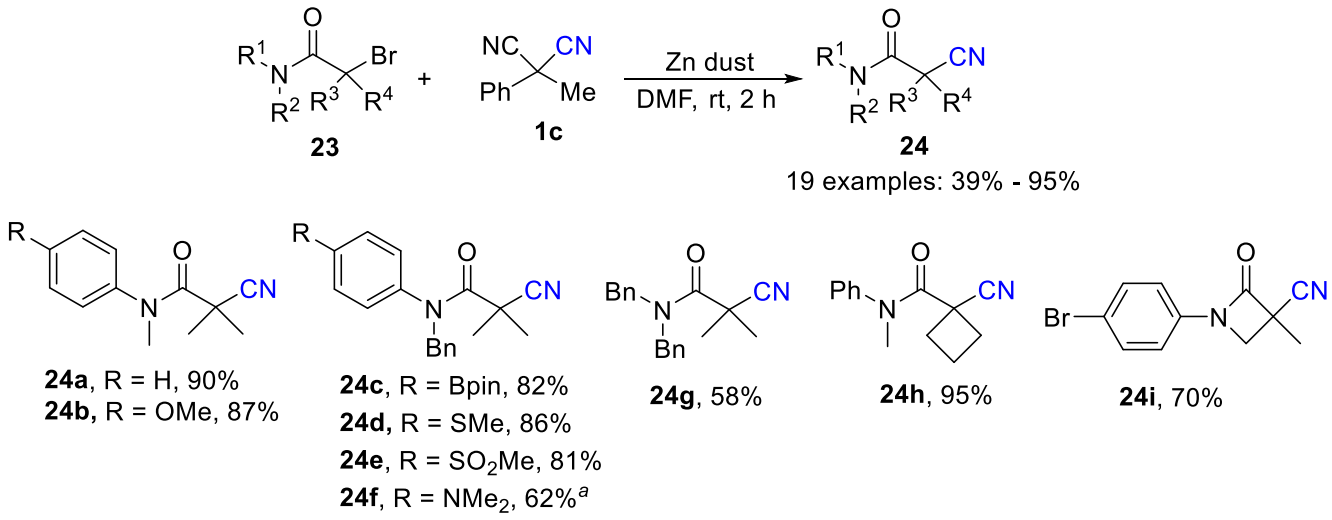


Scheme 10. Decyanation-metalation and arylation of **1**.

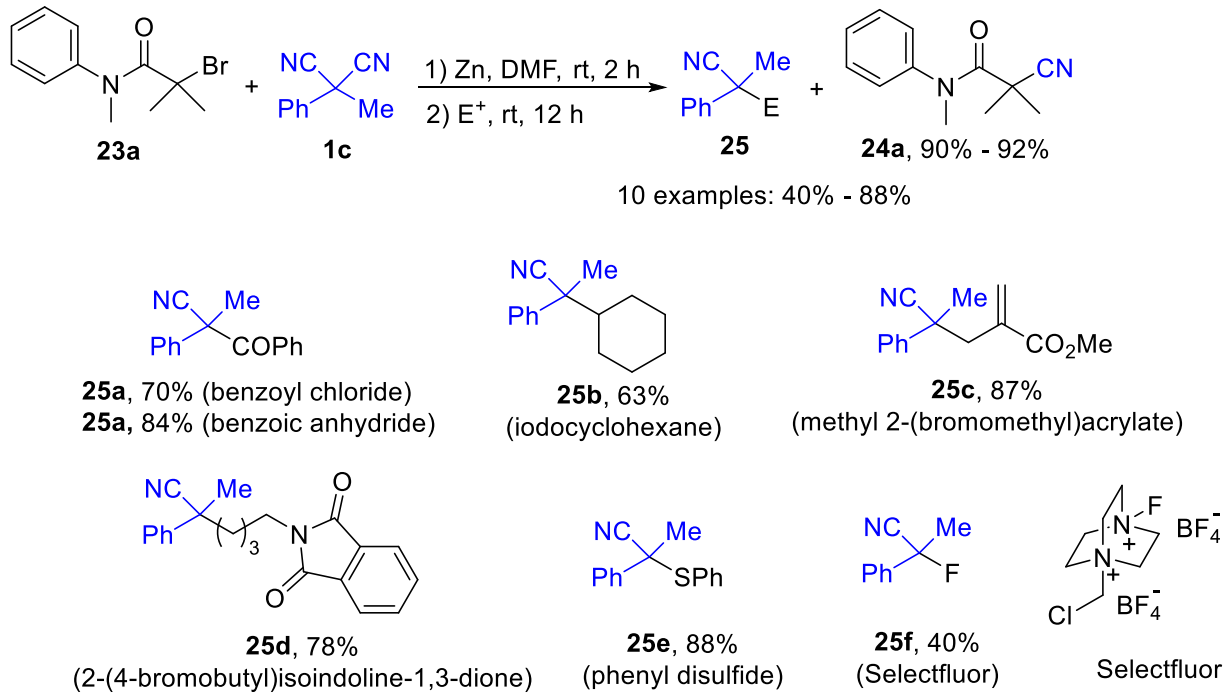
2.5 Preparation of α-cyano carboxamides by reductive cyanation

Dong and co-workers developed a route to α-cyano carbonyls bearing a quaternary carbon center by using an organozinc reagent as nucleophile in the addition-elimination process.[45] An α-bromo compound was reacted with zinc dust and NCTs or MPMN (**1c**, methylphenylmalononitrile) as cyanating reagents. Starting from α-bromo ketones and esters, NCTs was the more reactive reagent, while for the reductive cyanation of α-bromo carboxamides **23**, both reagents displayed a similar reactivity. Scheme 11 shows the reaction scope of synthesis of carboxamides **24** using MPMN **1c** as cyanating reagent. *α*-Cyano *N*-aryl and *N*-alkyl isobutyramides (**24a**-**24g**) are prepared usually in high yields as well as cyclobutanecarboxamide **24h**. Many functional groups are tolerated (**24b**-**24f**, **24i**) and the method can be applied to the cyanation of α-bromo-β-lactams (**24i**). DFT calculations supported the addition-elimination pathway and were in agreement with reactivity of cyanating reagents.

In an additional work, the authors introduced, after the transnitrilation step, electrophiles for the reaction with the expelled anionic leaving group. Thus, they formed, in a one pot manner, another type of nitriles bearing a quaternary center (Scheme 12).[46] The benzoyl group was successfully introduced from benzoyl chloride or benzoic anhydride (**25a**) and substitution reactions with various alkyl halides gave the expected nitriles **25b**-**25d**. The reaction with phenyl disulfide led to the hindered sulfide **25e** in a very good yield, while the fluorination can be performed with Selectfluor (**25f**). This sequence was also applied to other disubstituted malononitriles (8 examples, 60% - 90%) and allyl bromides were used as both precursors of the organozinc reagent and electrophiles, usually in fair yields (4 examples, 41% - 63%).



Scheme 11. Reductive cyanation of α-bromo carboxamides **23**. [a] The reaction temperature was 80 °C.

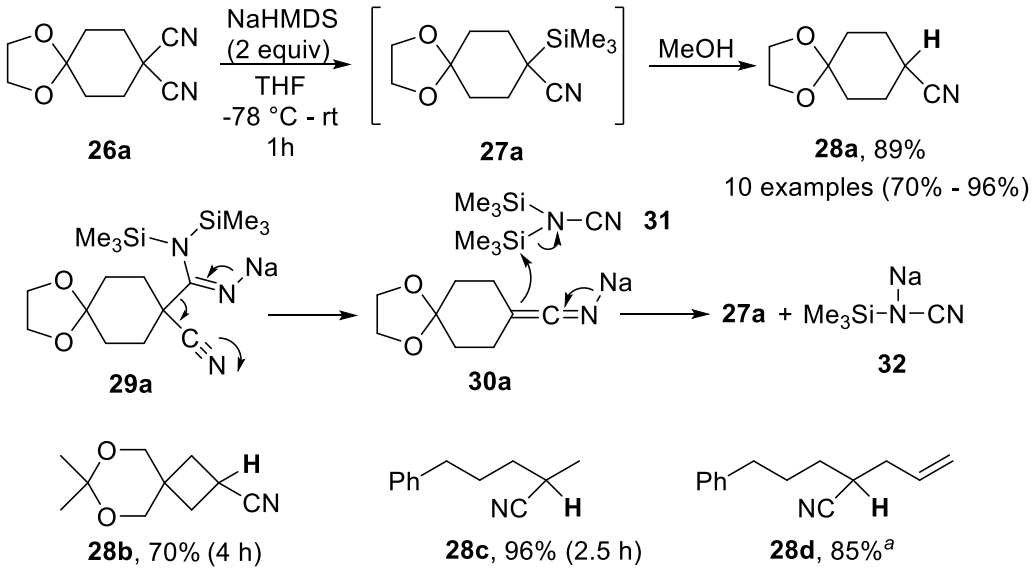


Scheme 12. One-pot reductive cyanation of α-bromo carboxamide **23a** and electrophile trapping. E^+ is shown in brackets.

2.6 Decyanation of disubstituted malononitriles promoted by NaHMDS

Tanino et al. have developed a procedure for the decyanation of disubstituted malononitriles without reducing agents (Scheme 13).[47] When they attempted to induce the decyanation of **26a** in an addition-elimination process using *n*-BuLi, they observed side reactions involving the anionic leaving group. They solved this drawback by using NaHMDS (sodium bis(trimethylsilyl)amide) as a nucleophile. In this case, the α-trimethylsilyl nitrile **27a** is formed and treated with methanol to yield the decyanation product **28a**. After the addition-elimination process, the leaving group **30a** is rapidly silylated with bis(trimethylsilyl)cyanamide **31** to

give **27a** and the less reactive anion **32** thus avoiding side reactions. This method appears convenient for cyclic (**28a**, **28b**) and acyclic (**28c**, **28d**) malononitriles.



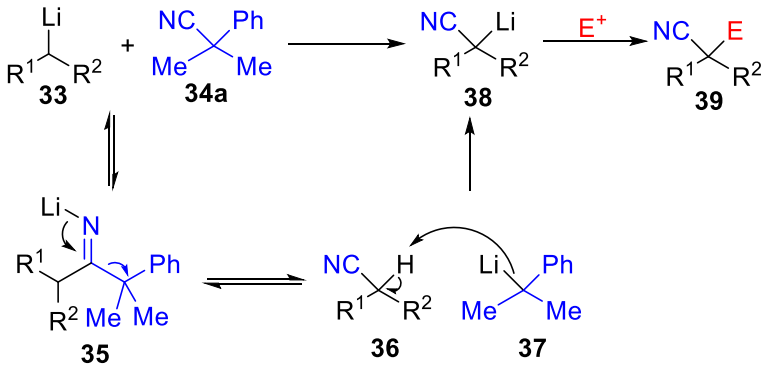
Scheme 13. Mechanism and examples of decyanation of disubstituted malononitiles with NaHMDS. The reaction time before treatment with MeOH is shown in brackets. [a] Reaction in a mixture Et_2O/toluene, -78 °C - rt, 3 h.

3. Addition-eliminations to α-aryl nitriles

3.1 Reaction with organolithiums: the transnitrilation-deprotonation strategy from α-aryl nitriles

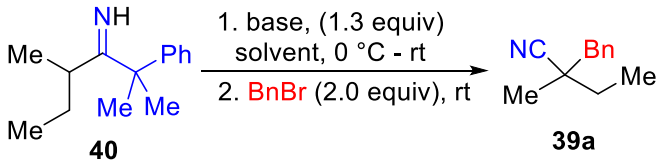
The reductive decyanation of α-diaryl substituted nitriles induced by Grignard reagents was particularly described in the 1950s.[48-51] Later, Kulp and Romanelli observed similar decyanation reactions with organolithium nucleophiles.[52] Rousseaux and co-workers investigated a strategy comparable to section 2.3 to obtain nitriles containing quaternary centers (Scheme 14). After the addition-elimination process involving **33** and **34a**, the tertiary organolithium leaving group **37** acts as a base for deprotonation of **36** in an "equilibrium driven transnitrilation and anion-relay strategy".[53] The basicity of **37** appears essential to drive the equilibrium towards the transnitrilated organolithium intermediate **38**, which can react with various electrophiles E^+.

Before the evaluation of the scope of the reaction, the authors examined the transnitrilation of *s*-BuLi **33a** with several electrophilic "CN^+" sources (namely structure of the leaving group **37**) and trapping with benzyl bromide. They found that 2-methyl-2-phenylpropanenitrile **34a** was the reagent of choice. Then, they optimized the reaction conditions for the imine fragmentation by deprotonation of imine **40**, prepared by the reaction between *s*-BuLi **33a** and **34a**. Key results are given in Table 1. When the nitrogen atom is bound to Li, the fragmentation is favored in THF compared to Et_2O (Entries 1-2). The dissociative power and Lewis base strenght of THF compared to Et_2O could favor the fragmentation by complexation with the lithium cation. A similar solvent effect was observed for the decyanation reaction induced by $LiAlH_4$ (see Section 3-4). When the nitrogen atom is bonded to MgBr, the metal imine intermediate does not undergo fragmentation (Entry 3).[22] This trend could be related to the higher electronegativity of the MgBr group compared to Li.[54-55]



Scheme 14. Functionalization of alkyllithiums by transnitrilation, deprotonation (anion-relay) and electrophile trapping.

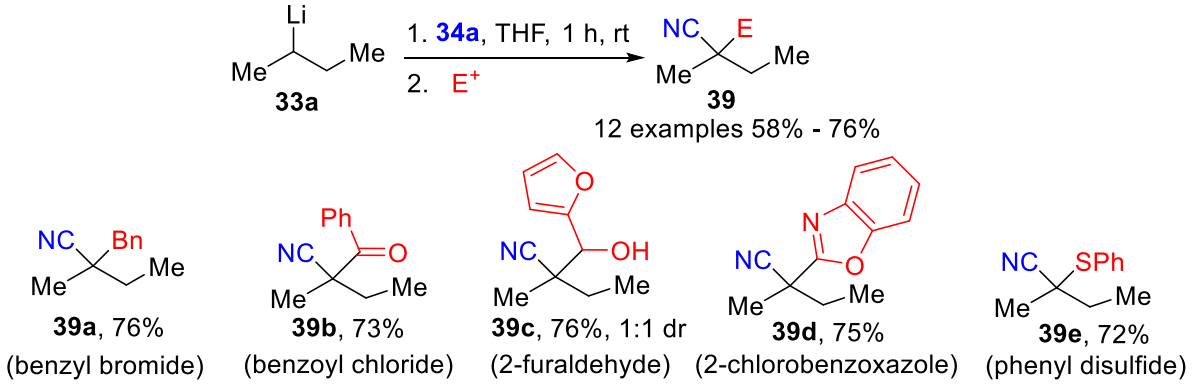
Table 1. Effects of solvent and base on imine fragmentation



Entry	Base	Solvent	Yield[a]
1	*n*-BuLi	THF	69
2	*n*-BuLi	Et_2O	0
3	MeMgBr	THF	0

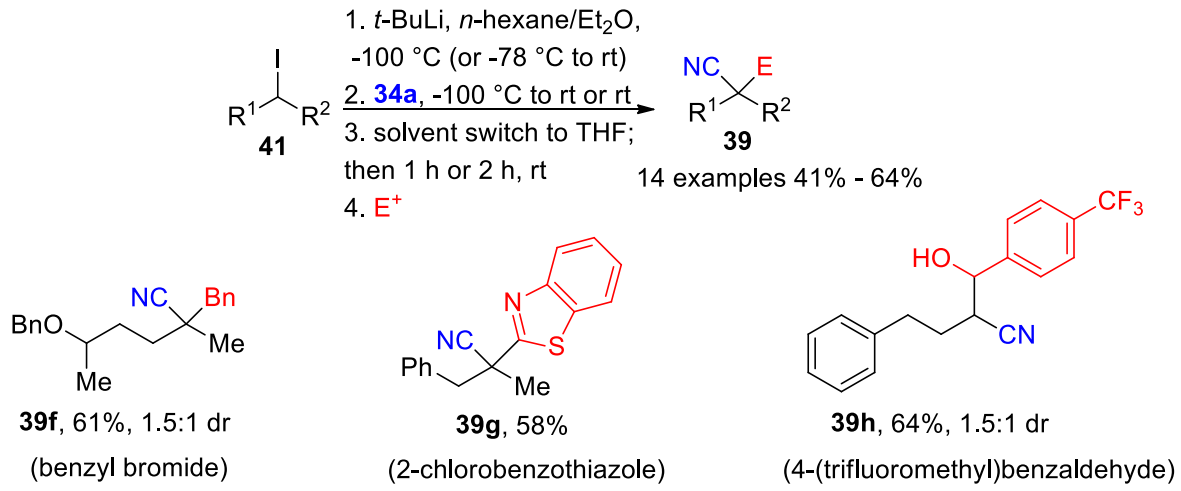
[a] Determined by NMR.

The authors explored the reaction of *s*-BuLi **33a** with **34a** in THF. Alkyl halides (**39a**), carbonyl-based compounds (**39b**, **39c**), aromatic halides (**39d**) and phenyl disulfide (**39e**) appeared as efficient electrophiles for trapping (Scheme 15).



Scheme 15. Reaction scope of the one-pot transnitrilation and anion-relay functionalization of *s*-BuLi **33a**. E^+ is shown in brackets.

The authors examined the reaction scope by varying the alkyllithium reagents **33** prepared by a lithium-halogen exchange from alkyl iodides **41**. This procedure needs a solvent switch to THF to trigger the fragmentation, and therefore, the anion-relay process (Scheme 16). This method was convenient starting from secondary and primary alkyl lithium reagents to respectively yield nitriles bearing quaternary (**39f**, **39g**) and tertiary centers (**39h**).



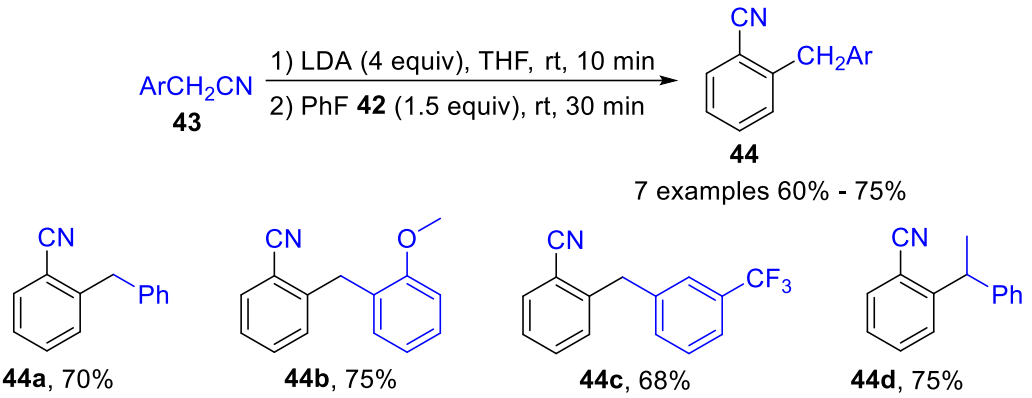
Scheme 16. Reaction scope of one-pot transnitrilation and anion-relay functionalization of alkyllithiums. E^+ is shown in brackets.

α-Aryl nitriles **39** can be prepared using the carbolithiation of styrene with alkyllithiums to get the starting α-aryllithium reagent **33** (3 examples, 69% - 83%). Another protocol involves the deprotonation of toluene derivatives with the superbase *t*-BuOK/*t*-BuLi in THF; switch to THF was not necessary in this case (5 examples, 46% - 77%).

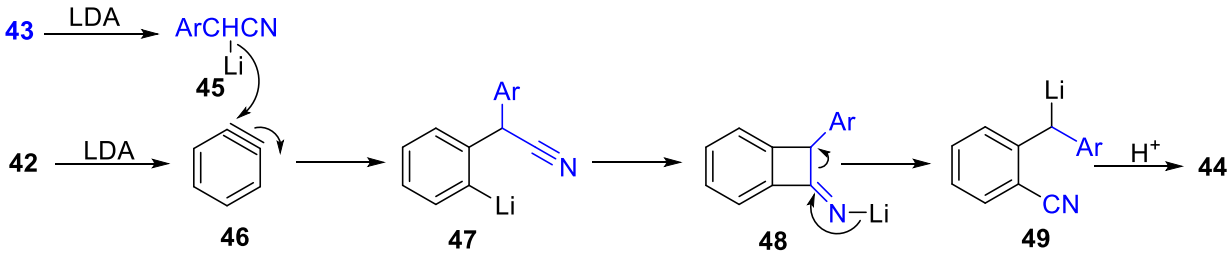
3.2 Tandem addition-rearrangement under aryne forming conditions

The addition of α-lithiated arylacetonitriles to arynes, followed by a tandem addition-rearrangement pathway provides an access to *ortho*-cyanated diarylmethanes.[56-60] Cao and co-workers have investigated the reaction of haloarenes with arylacetonitriles in the presence of LDA.[61] Scheme 17 focuses on the reaction between fluorobenzene **42** and arylacetonitriles **43** under the optimized conditions. The reaction was successful both with electron-donating (**44b**) and withdrawing (**44c**) groups in the aromatic ring of arylacetonitriles as well as with a more hindered substrate (**44d**). The reaction was extended to chloro and bromoarenes. When the initial halobenzene was substituted, regioisomers were usually obtained.

In the mechanism proposed, the elimination of fluorobenzene (**42**) with LDA leads to benzyne (**46**). LDA also deprotonates arylacetonitriles **43** to give the corresponding α-lithiated derivative **45**. The reaction of **45** with **46** yields the adduct **47**. After an intramolecular addition to the nitrile group (**48**), the 4-membered ring-opening (fragmentation step) gives the rearranged intermediate **49** precursor of **44** (Scheme 18). Interestingly, when the two *ortho* positions of fluorobenzene are substituted with methyl groups, no reaction takes place in agreement with the formation of the aryne intermediate **46**.



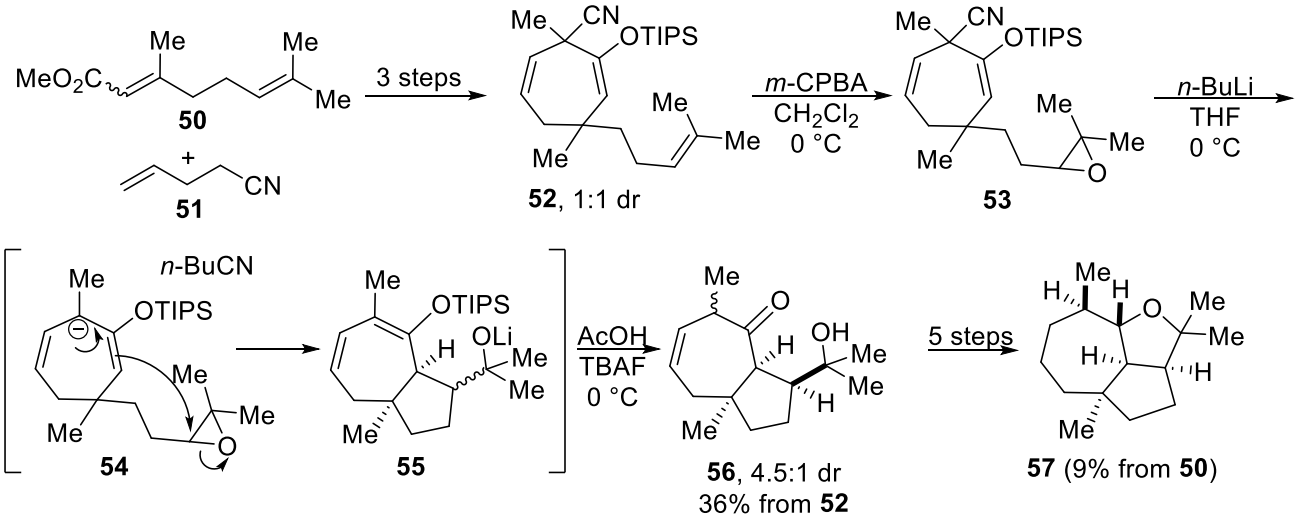
Scheme 17. Synthesis of *ortho*-cyanated diarylmethanes **44**.



Scheme 18. Proposed mechanism for the formation of *ortho*-cyanated diarylmethanes.

3.3 Addition-elimination on a bis(allyl)nitrile

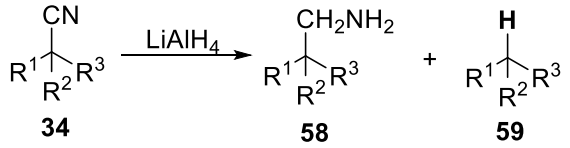
Although not related to α-aryl nitriles, this section describes the comparable bis(allyl)nitrile framework. Tanino et al. have investigated the total synthesis of the 6,11-epoxyisodaucane natural sesquiterpene **57**, an essential oil extracted from the *Tritomaria polita* liverwort (Scheme 19).[62] This synthesis starts from methyl geranate **50** and pent-4-enenitrile **51** and uses an anionic 8π electrocyclic reaction for the construction of the seven-membered ring. After the three first steps, the oxidation of cyclic nitrile **52** with *m*-CPBA leads to the epoxynitrile **53**. Treatment of crude **53** with *n*-BuLi triggers the addition-elimination process with formation of the stabilized bis-allylic carbanion **54** and release of *n*-BuCN. Interestingly, *n*-BuCN was isolated among other reaction products. The epoxide group then is opened by an intramolecular attack to give alkoxide **55**. A one-pot desilylation with tetrabutylammonium fluoride (TBAF) in acetic acid gives the keto alcohol **56** in 36% yield (from **52**, 2 steps). The desired 6,11-epoxyisodaucane **57** was obtained in 5 steps from **56**. This study allows the correction of the initial stereochemistry assigned to the natural product **57**.

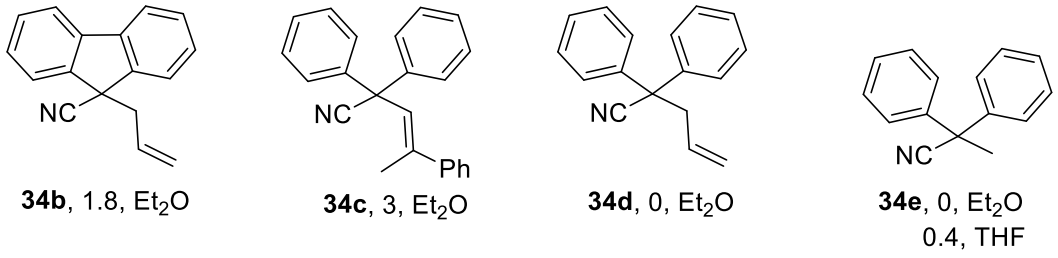


Scheme 19. Total synthesis of 6,11-epoxyisodaucane **57**. TIPS = triisopropylsilyl.

3.4 Decyanations with metal hydrides

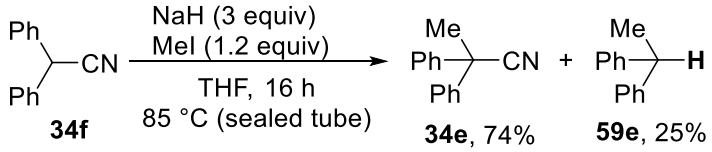
In 1978, Black and Doyle found that the $LiAlH_4$ reduction in Et_2O of 9-allylfluorene-9-carbonitrile (**34b**) and 2,2,4-triphenylpent-3-enenitrile (**34c**) yielded predominantly the decyanation product together with the expected primary amine.[63] In contrast, no decyanation was observed starting from 2,2-diphenylpent-4-enenitrile **34d** and related compounds.[64-66] They concluded that decyanation was observed with nitriles leading to the more stabilized carbanions in an addition-elimination process. They proposed that the initial hydride addition was "followed by elimination of a hydrogen cyanide complex and formation of a highly stabilized carbanion". Later, Chanon's group investigated the $LiAlH_4$ reduction of 2,2-diphenylpropionitrile **34e**, they observed decyanation in THF but not in Et_2O.[67] The use of $LiAlD_4$ led to quantitative deuterium incorporation while a basic and polar solvent such as HMPA favors the decyanation pathway. The authors proposed an addition-elimination pathway followed by a fast protonation of the leaving group (carbanion) with HCN in a solvent cage. Scheme 20 summarizes the reactivity observed.





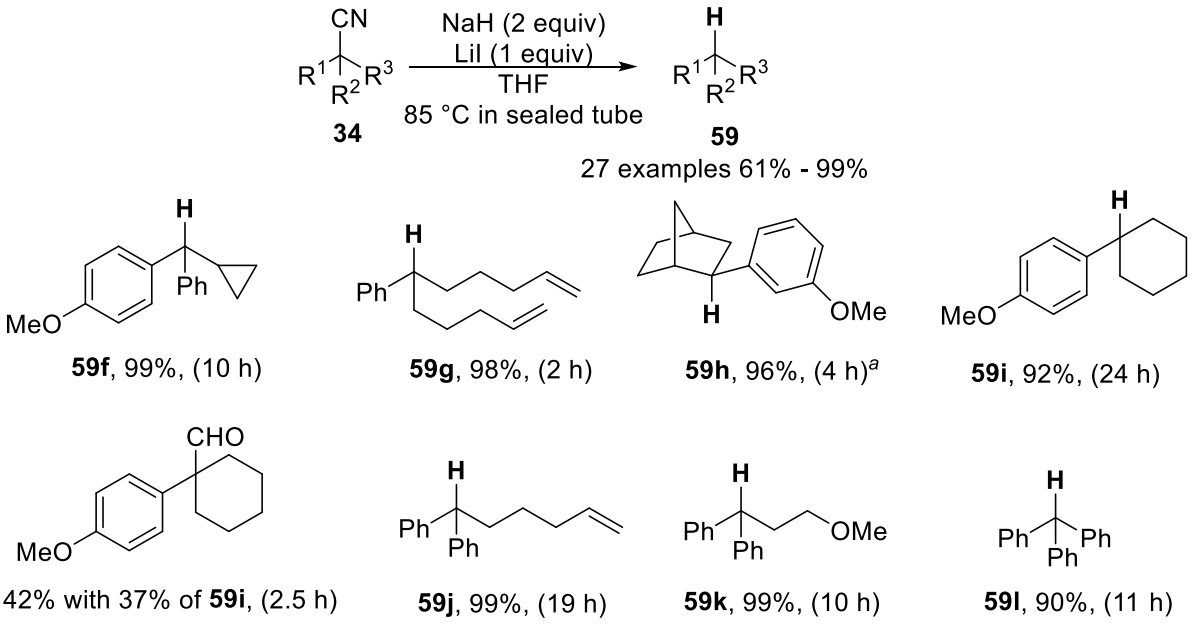
Scheme 20. $LiAlH_4$ slurry reduction of various α-diaryl nitriles: the decyanation/primary amine ratio (**59b**-**59e**/**58b**-**58e**) and the solvent used are given.

The addition-elimination mechanism was discussed again from the unusual nucleophilic properties of the NaH-NaI or LiI composite.[68-69] Indeed, Chiba and co-workers found an unexpected reactivity during the methylation of 2,2-diphenylethanenitrile **34f**: they obtained the alkylated nitrile **34e** (74% yield) and 1,1-diphenylethane (**59e**) in 25% yield (Scheme 21).[70]



Scheme 21. Unexpected decyanation upon alkylation of 2,2-diphenylethanenitrile **34f**.

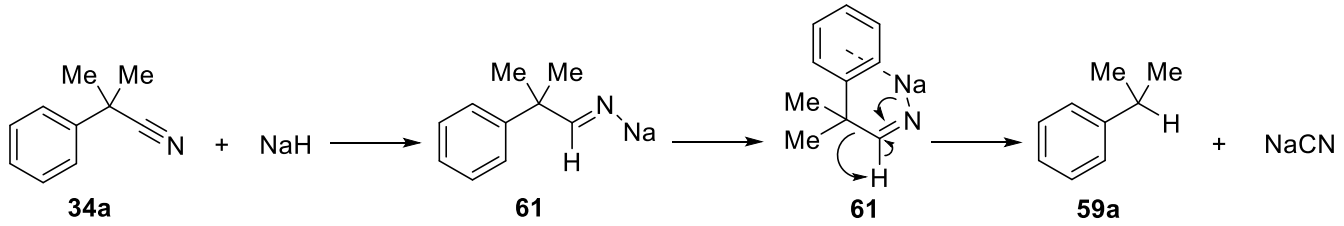
They assumed that **59e** was produced from the decyanation of 2,2-diphenylpropanenitrile **34e** and investigated the optimization of reaction conditions. They observed that NaH alone was ineffective. Since NaI was formed upon the methylation reaction, they explored the use of several additives and found that NaI and LiI gave the best results. After a set of experiments on stoichiometry and reaction time, the authors examined the scope of this new decyanation with conditions described in Scheme 22. The protocol was extended to 27 nitriles giving monoaryl- (**59g**-**59i**), diaryl- (**59f**, **59j**, **59k**) or triarylmethane (**59l**) derivatives from the corresponding nitriles.[71]



Scheme 22. Scope of the decyanation by sodium hydride-iodide composite. The reaction time is shown in brackets. [a] From the *endo* nitrile substrate **34h**.

The reaction of nitrile **34i** proceeded in a high yield (92%) after 24 h but when the reaction mixture was quenched after 2.5 h, aldehyde **60** was isolated in 42% yield together with the decyanated product **59i** (37%). This experiment suggests that the first step could be a hydride addition to the cyano group giving an N-metalated imine intermediate. The reduction of nitrile **34h** shows that this reaction proceeds with the retention of configuration (**59h**). No radical intermediates were trapped using radical probe substrates **34g**

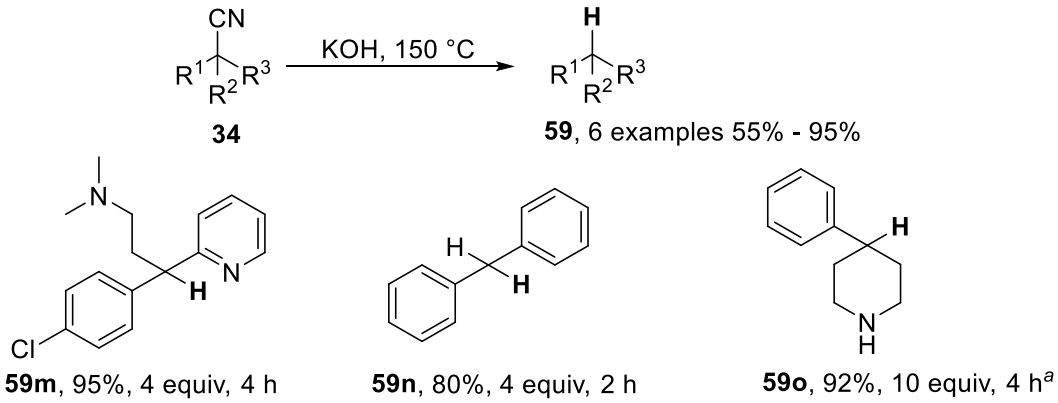
and **34j** (5-hexenyl cyclization) or **34f** (cyclopropylcarbinyl ring-opening). The absence of deuterium incorporation using THF-d_8 as solvent also fits with the absence of radical intermediates. DFT calculations performed on 2-methyl-2-phenylpropanenitrile **34a** support a mechanism involving nucleophilic attack of the hydride ion to give the intermediate **61** where a sodium cation-π interaction occurs. Then, a fast fragmentation involving an intramolecular proton transfer with retention of configuration gives the decyanation product **59a** (Scheme 23). The NaH-Na(Li)I composite in THF is composed of NaI interspersed with activated NaH. Synergistic cooperation between NaH and NaI at the surface could be crucial for the observed hydride reactivity.[68]



Scheme 23. Addition-elimination mechanism proposed for the decyanation by sodium hydride-iodide composite.

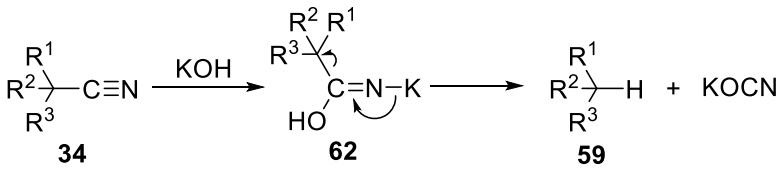
3.5 Decyanations with the hydroxide anion

Tertiary and secondary nitriles activated with phenyl groups are decyanated in the presence of molten 85% potassium hydroxide.[72] This transformation is described from α-mono and diaryl-substituted nitriles (Scheme 24).



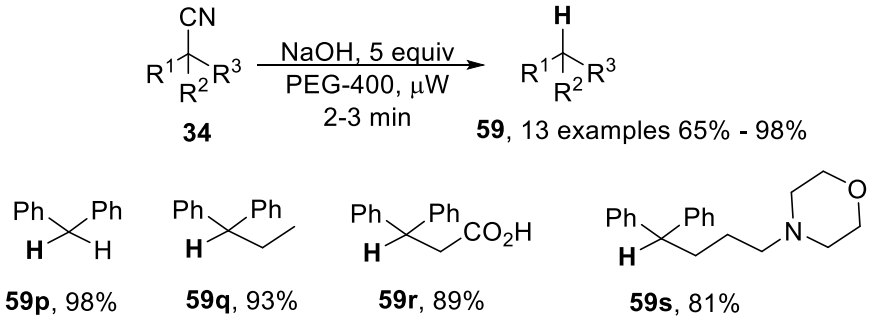
Scheme 24. Decyanation by alkali fusion. KOH excess and reaction time are given. [a] From the corresponding amine hydrochloride (**34o**).

The decyanation reaction in an acid or basic medium is a well-known transformation. The nitrile group is first hydrolyzed into a carboxylic acid, which is removed by decarboxylation.[73-74] However, in alkali fusion, the addition-elimination pathway proposed in Scheme 25 fits better with experimental data. Treatment of primary and unactivated secondary and tertiary nitriles does not afford the decyanation product but leads to the expected hydrolysis products (carboxylic acids and/or amides). Moreover, potassium cyanate (KOCN) was trapped with semicarbazide hydrochloride.



Scheme 25. Addition-elimination mechanism proposed for the decyanation reaction in molten KOH.

A similar decyanation can be performed under milder conditions. Khadilkar and co-workers have reduced alkyldiphenylacetonitriles with NaOH by microwave irradiation in PEG-400 (Scheme 26).[75] Under the reaction conditions, they were able to trap cyanic acid (HOCN) evolved by discoloration of an NH_4OH-$CuSO_4$ indicator.



Scheme 26. Decyanation under microwave irradiation. PEG = polyethylene glycol.

4. Conclusions

The addition-elimination mechanism on α-aryl nitriles and disubstituted malononitriles is well-established. This reaction leads to a cyanation product and an anionic leaving group. Disubstituted malononitriles appear as fruitful reagents for transnitrilation of organometallics. Subsequent reactions of the leaving group such as electrophilic trapping were successfully explored in one-pot reactions. The addition-elimination mechanism also was proposed using hydride donors and the hydroxide anion. Particularly, NaH-iodide composite and NaOH (or KOH) appear as efficient reagents for the decyanation of α-aryl nitriles. The extension of this process to a bis(allyl)nitrile offers an original perspective in organic synthesis. Recently, AIBN was described as a new electrophilic reagent for cyanation of aryllithiums. This new application illustrates the versitality of the addition-elimination pathway.[76]

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Author's Biography

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