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Cyanoalkylation: Alkylnitriles in Catalytic C–C Bond-Forming Reactions

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***A**lkylnitriles are one of the most ubiquitous nitrogen-containing chemicals and are widely employed in reactions which result in nitrile-group conversion into other functionalities. Nevertheless, their use as carbon pronucleophiles in carbon–carbon bond-forming reactions has been hampered by difficulties associated mainly with the catalytic generation of active species, that is, α-cyano carbanions or metalated nitriles. Recent investigations have addressed this challenge and have resulted in different modes of alkylnitrile activation. This review illustrates these findings, which have set the foundation for the development of practical and conceptually new catalytic, direct cyanoalkylation methodologies.*

1. Introduction

Cyanoalkyl moieties are found as structural motifs in several nitrile-containing natural products and important drugs (Figure 1).[1,2] Cyanoalkylation is also a synthetically useful reaction because the cyano group can be easily converted into other functional groups.[3]

During the last decade, there have been considerable advances in the catalytic generation and enantioselective addition of carbon nucleophiles (i.e., enolates and nitronates) to different types of electrophiles.[4] Nevertheless, catalytic reactions of alkylnitriles, a unique class of carbon pronucleophiles, represent an exception. From a synthetic point of view, alkylnitriles constitute a versatile building block with the same oxidation state as carboxylic acids. However, the generation of carbanions from simple alkylnitriles (pK_a 31.3 in DMSO and 28.9 in H_2O for acetonitrile)[5] requires the utilization of strong bases, generally in stoichiometric amounts, which are usually incompatible with base-sensitive substrates. The low chemoselectivity obtained by these types of bases means that only a few successful examples for the direct catalytic base-promoted α-cyano carbanion generation has been described.[6a–c] Obviously, this issue may be circumvented by using activated nitriles such as α-cyano esters, malononitriles, and α-sulfonyl nitriles wherein a mild Brønsted base is enough for deprotonation.[7] Nevertheless, methods which involve this type of nitrile-containing pronucleophile are outside the scope of this article, and have been omitted since they do not directly produce the product of a simple cyanoalkylation reaction. Likewise, α-amino nitriles[8] and their *N*-alkylidene derivatives have not been discussed here owing to the relatively easy generation of an active α-cyano carbanion nucleophile, a process which is assisted by the imino group.[9] In general, efforts to overcome the attenuated

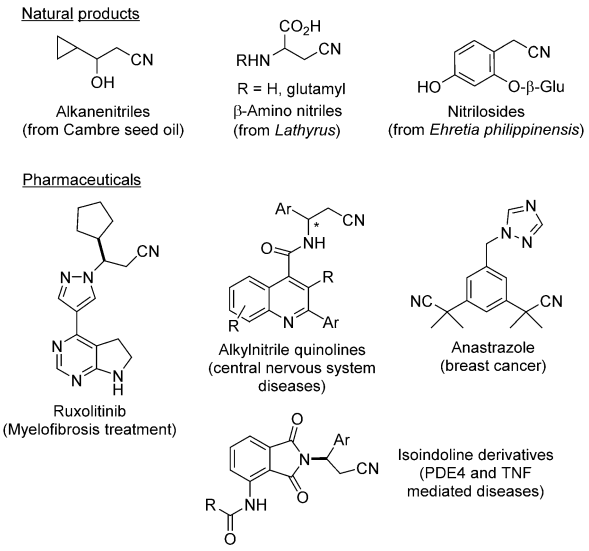

Figure 1. Natural products and pharmaceuticals containing alkylnitrile moieties.

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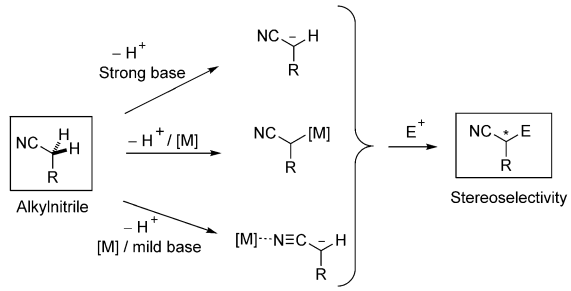
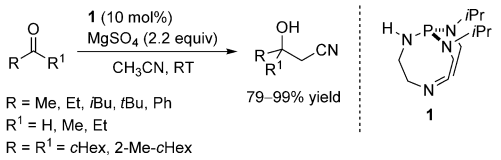


Scheme 1. Usual direct activation modes for α-cyanoalkylations.

reactivity of alkylnitriles have been focused on the catalytic generation of metalated nitriles and, more recently, cyanoalkyl radicals. Also, the direct activation of acetonitrile by Lewis acids, to allow deprotonation by relatively weak bases, represents the most general and successful strategy so far. Additionally, a few approaches that involve previous transformation of the nitrile into trialkylsilyl acetonitriles or trialkylsilyl ketimines have also been developed. This review provides, for the first time, an overview of the state of the art on this emerging area of research with a special focus on the challenges of the activation of alkylnitriles in catalytic cyanoalkylation reactions (Scheme 1).

2. Base-Promoted α-Deprotonation of Alkylnitriles

The interest in the synthesis of β-hydroxy nitriles and related compounds, without using the classical opening of epoxides by cyanide salts, motivated the search for base-catalyzed procedures for the generation of α-cyano carbanions. As previously mentioned, the necessity of using strong bases may trigger undesired side reactions, such as dehydration in the particular case of β-hydroxy nitriles. The first example of a base-catalyzed synthesis of β-hydroxy nitriles was effected by using a combination of the proazaphosphatrane **1**, a strong non-ionic base, and magnesium sulfate as a Lewis acid to activate the carbonyl group (Scheme 2).[10] The reaction proceeds at room temperature to give β-hydroxy nitriles in good yields. The α,β-unsaturated nitriles, usually obtained by dehydration, were not detected. Unfortunately, an enantioselective version of this approach is not yet available.



Scheme 2. Proazaphosphatrane-catalyzed synthesis of β-hydroxy nitriles.

Enantioselective cyanoalkylations based on the catalytic generation of α-cyano carbanions are clearly limited by the pK_a barrier for proton abstraction, and it usually lies between the pK_a values of 16 and 17. Compared to alkylnitriles, benzylnitrile exhibits a slightly enhanced acidity (pK_a 21.9 in DMSO), but it is still inadequate for catalytic generation of these species. Nonetheless, as shown in Figure 2,[5,11] the

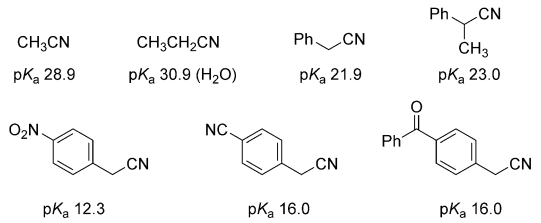
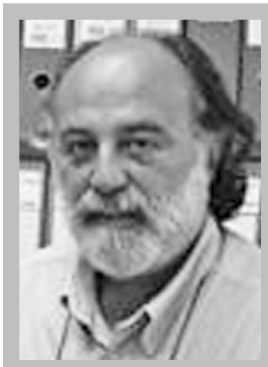


Figure 2. Selected pK_a values of substituted alkylnitriles in DMSO, unless stated otherwise.

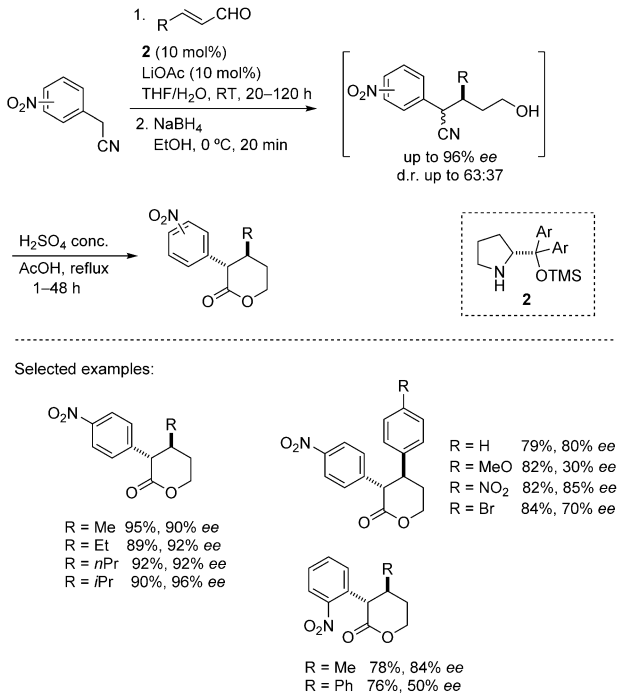
incorporation of an appropiate electron-withdrawing group at the aromatic ring provides an increase of the acidity of the benzylic carbon atom in substituted benzylic nitriles, and allows the generation of α-cyano carbanions by mild Brønsted bases.[12]

The first example of this strategy was reported by Cid, Ruano, and co-workers, who have shown that by using the secondary amine **2**, nitroarylacetonitriles, in the presence of a mild base (LiOAc), can react with α,β-unsaturated aldehydes through iminium catalysis (Scheme 3). Products were formed, after reduction of the corresponding intermediate adducts, in good yields and variable enantioselectivities, but with low diastereoselectivities as a result of facile epimerization during reduction.[13] Cyclization into the corresponding lactone essentially provided the most stable diastereomer.



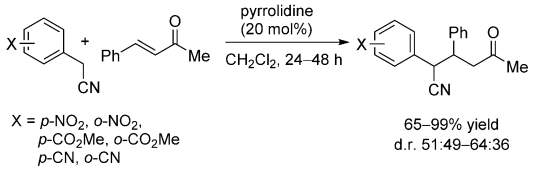
Claudio Palomo studied Chemistry at the Instituto Químico de Sarria, in Barcelona, where he received his Chemical Engineering Degree in 1975. He obtained his Licenciatura in Chemistry in 1979 at the University of Barcelona and his Ph.D. in 1983 at the University of the Basque Country under the supervision of Prof. R. Mestres. In 1989 he was promoted to Full Professor in Organic Chemistry and in 1991 he joined Prof. H. Rapoport at the University of California at Berkeley as a visiting professor. His current interests are in the area of asymmetric catalysis.

Rosa López studied Chemistry at University Autónoma de Madrid where she obtained her M.Sc. in 1990 and her Ph.D. in 1994 under the guidance of Prof. A. Fernández-Mayoralas. Between 1995 and 1997 she held postdoctoral positions at Harvard University with Prof. R. R. Rando and at MIT with Prof. G. C. Fu. She joined the University of the Basque Country in 1998. In 2001 she was awarded with a Ramón y Cajal contract from the Spanish Government and in 2012 she was appointed an Associate Professor.



Scheme 3. Organocatalytic conjugate addition of nitrophenylacetonitriles to α,β-unsaturated aldehydes. THF = tetrahydrofuran, TMS = trimethylsilyl.

A catalytic conjugate addition of arylacetonitriles, in which the aromatic moiety bears electron-withdrawing groups (NO_2, CO_2Me), to benzylideneacetone was also reported using pyrrolidine as catalyst (Scheme 4).[14] The corresponding racemic adducts were produced in good yields and negligible diastereoselectivity. As expected, the conjugate addition with the less acidic phenylacetonitrile did not proceed.



Scheme 4. Organocatalytic conjugate addition of 2-arylacetonitriles to benzylideneacetone.

3. Catalytic Generation of Metalated Alkylnitriles

The generation of metalated nitriles has been known for more than a century. Also, several studies have revealed how metal centers can interact with alkylnitriles to generate a reactive species through their interaction with either the electron-rich nitrile nitrogen atom, the α-carbon atom, or both nitrogen and carbon atoms (Figure 3).[15] Nevertheless, the use of these reactive metalated nitriles in α-cyanoalkylations has been little explored in comparison with other carbon–carbon bond-forming reactions.

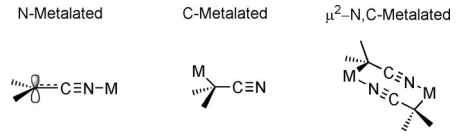
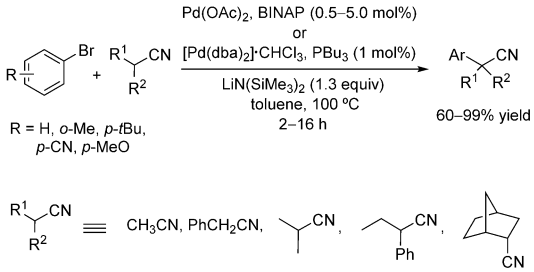


Figure 3. Usual metalated alkylnitriles.

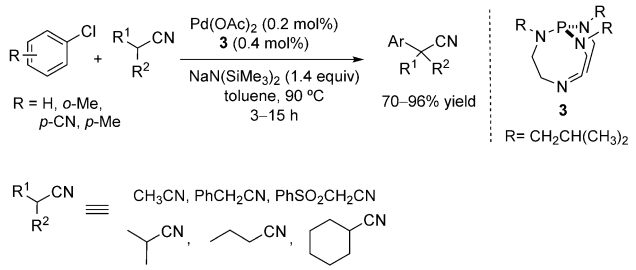
First reports consisted of α-arylations of α-arylacetonitriles. For instance, Miura and co-workers reported that phenylacetonitrile undergoes α-arylation upon treatment with bromo- or iodobenzene in the presence of catalytic $PdCl_2$ and Cs_2CO_3 in DMF at 100 °C.[16] Subsequent to this study, Culkin and Hartwig provided some insight into the preferred binding mode between the metal and the cyanoalkyl group by synthesizing and characterizing a series of arylpalladium cyanoalkyl complexes.[17] The obtained data showed that the α-cyano carbanion prefers to coordinate to palladium through the carbon atom in the absence of steric effects, whereas coordination through the nitrogen atom is observed when a highly hindered ligand is bound to the metal. When labile ligands are present, dissociation occurs and a bridged complex of the type μ^2-C,N are produced.

Information obtained from the study by Miura and co-workers was applied to effect the palladium-catalyzed arylation of alkylnitriles (Scheme 5).[18] The system tolerated hindered and electronically diverse aryl bromides and it was also compatible with secondary nitriles. The corresponding substituted benzylic nitriles were produced in good yields under the reaction conditions.



Scheme 5. Palladium-catalyzed α-arylation of alkylnitriles. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dba = dibenzylideneacetone.

Further studies showed that palladium-catalyzed α-arylation of secondary alkylnitriles could be conducted at room temperature by using zinc cyanoalkyl reagents generated in situ by quenching the corresponding alkali metal cyanoalkyls with zinc halides.[19] More recently, a related palladium-catalyzed arylation of zincated nitriles, using TMPZn-LiCl (TMP: 2,2,6,6-tetramethylpiperidyl), as a base, has been reported.[20] Another substantially improved version for the α-arylation of alkylnitriles consisted of the use of palladium acetate along with the commercially available proazaphosphatrane **3** as the ligand (Scheme 6). This combination allows aryl chlorides to participate in that reaction to produce adducts in good yields.[21]

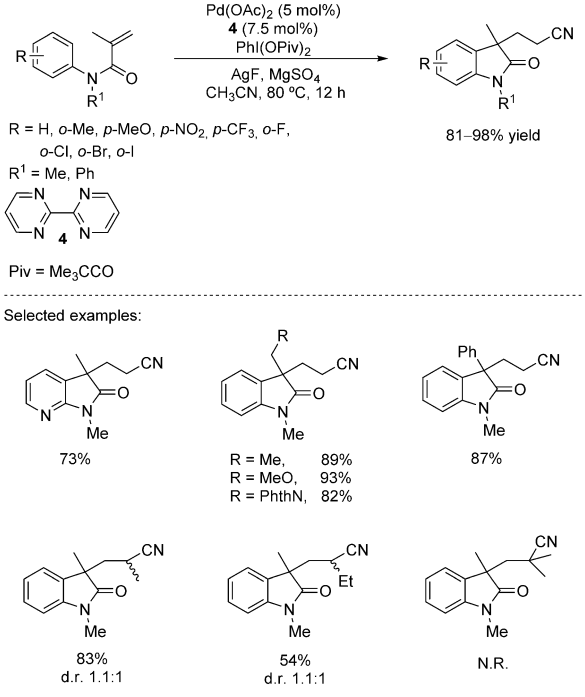


Scheme 6. Palladium-catalyzed α-arylation of alkylnitriles with aryl chlorides.

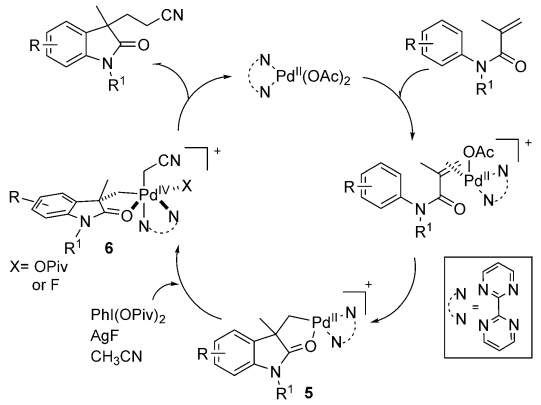
Despite these examples, and given the observations by Culkin and Hartwig noted above, as well as the impressive advances in the field of metal-catalyzed enantioselctive α-arylation of carbonyl compounds,[22] it is surprising that no asymmetric versions of the related α-arylation of alkylnitriles have been developed.

An interesting palladium-catalyzed oxidative arylalkylation of activated alkenes (Scheme 7) has been described for the synthesis of nitrile-bearing indolines.[23] Substrates that did not undergo transformation were restricted to olefins without substituents at the α-position and those which have an electron-withdrawing group at the nitrogen center. In contrast, a decrease in reactivity was observed by increasing the steric hindrance of the alkylnitrile; isobutyronitrile did not react.

Regarding the reaction mechanism, the authors propose the catalytic cycle, shown in Scheme 8, on the basis of the following considerations. First, a large primary isotope effect was observed for reactions run in CD_3CN, thus suggesting that



Scheme 7. Palladium-catalyzed oxidative arylalkylation of alkenes. N.R. = no reaction, Phth = phthaloyl, Piv = pivaloyl.

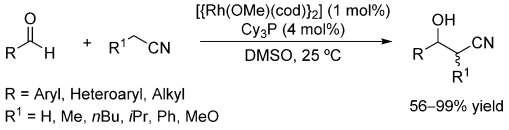


Scheme 8. Proposed mechanism for the oxidative arylalkylation of alkenes.

C–H bond activation of acetonitrile contributes to the rate-determining step. Second, the addition of $PhI(OPiv)_2$ and AgF was essential for the reaction to proceed, thus suggesting the oxidative formation of **6** from the complex **5**. Finally, the compatibility of halogenated substrates could imply a $Pd^{II/IV}$ catalytic cycle.

This transformation has also been achieved by using a combination of catalytic amounts of copper chloride and stoichiometric amounts of di-*tert*-butylperoxide. By using these reaction conditions, cyanomethyl radicals, instead of metalated species, have been proposed to induce the alkene addition and subsequent cyclization to generate the corresponding nitrile-bearing indolines.[24a]

The first example of metal-catalyzed aldol-type reaction was promoted by a rhodium(I) complex generated from $[\{Rh(OMe)(cod)\}_2]$ (Scheme 9).[25] Although no mechanistic

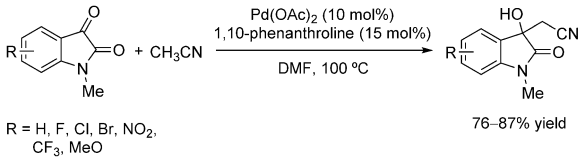


Scheme 9. Rhodium-catalyzed aldol-type reaction of alkylnitriles. cod = 1,5-cyclooctadiene, DMSO = dimethylsulfoxide.

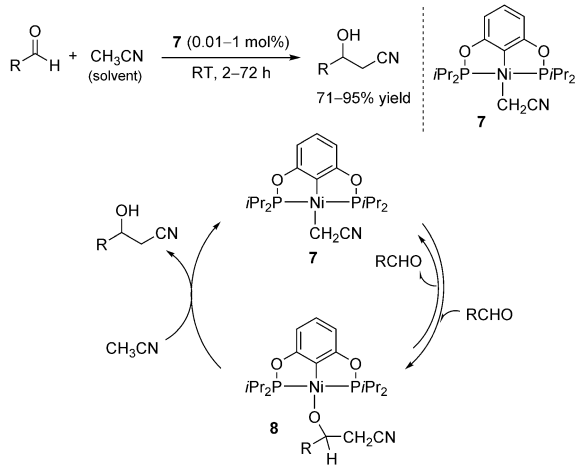
insights are given, aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes performed well in the reaction with acetonitrile and with other alkylnitriles. In the latter case, however, low diastereoselectivities (ca. 1:1.2) were obtained.

Yang and co-workers reported the palladium-catalyzed C–H activation of acetonitrile for the synthesis of 3-hydroxy-2-oxindoles, though relatively high catalyst loadings were required (Scheme 10).[26]

Concurrently with the above studies, the group of Guan reported a highly efficient nickel-catalyzed cyanomethylation of aldehydes (Scheme 11).[27] The nickel pincer complex **7** was used as a catalyst, which was previously synthesized by treatment of the corresponding chloride complex with lithium acetonitrile, and very low catalyst loadings (0.01–1 mol%) sufficed for producing the corresponding β-hydroxy nitriles in



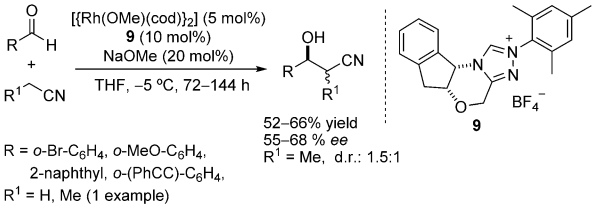
Scheme 10. Catalyzed addition of acetonitrile to isatins. DMF = *N*,*N*-dimethylformamide.



Scheme 11. Nickel-catalyzed cyanomethylation of aldehydes.

high yields under mild reaction conditions. A catalytic cycle is proposed based on experimental evidence which suggests reversible insertion of the aldehyde into the C-bound cyanomethyl complex **7** and acetonitrile activation by the resulting nickel alkoxide intermediate **8**.

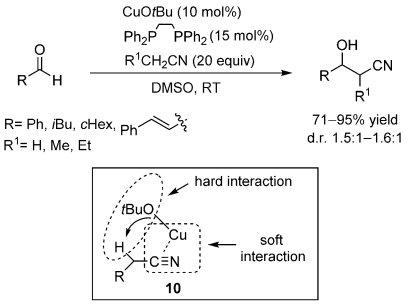
More recently, a complex consisting of a rhodium alkoxide and a chiral N-heterocyclic carbene, generated from the triazolium salt **9**, has been identified to promote aldehyde cyanomethylations with moderate yields and enantioselectivities (Scheme 12).[28]



Scheme 12. Rhodium/NHC-catalyzed aldol-type reaction of alkylnitriles. NHC = N-heterocyclic carbene.

4. Metal-Assisted Deprotonation of Alkylnitriles

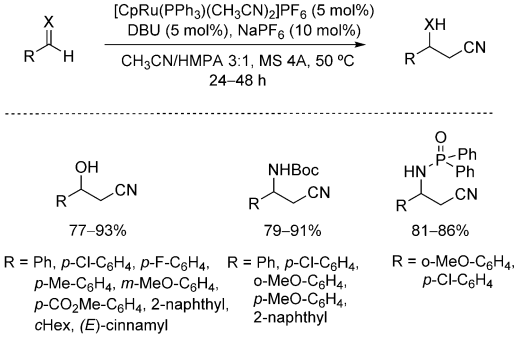
An alternative mode of alkylnitrile activation is based upon the use of a Lewis-acidic metal center to lower the pK_a value of the alkylnitrile, through coordination with the nitrogen atom, to facilitate deprotonation by the action of a mild base. The first direct catalytic aldol-type reaction based on this strategy was described by Shibasaki in 2003.[29] The



Scheme 13. Copper-catalyzed addition of alkylnitriles.

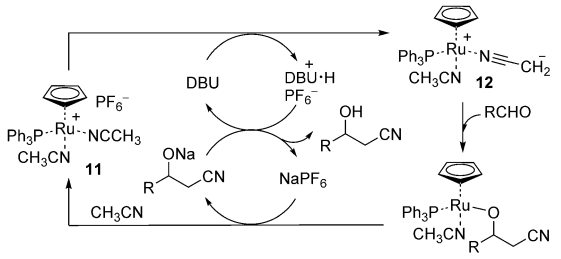
authors propose that the soft interaction between copper and the nitrile polarizes the α-carbon hydrogen bond and makes the α-proton in the complex **10** more susceptible to deprotonation by the alkoxide (Scheme 13).

Subsequent to this study Shibasaki and co-workers (Scheme 14) presented cationic ruthenium complexes as soft Lewis acids to promote the direct addition of acetonitrile to aldehydes and imines in the presence of common amine bases.[30] Cooperative action of the ruthenium complex, DBU, and $NaPF_6$ enables the aldol-type reaction with aromatic and aliphatic aldehydes, as well as activated imines to produce the corresponding β-hydroxy and β-amino nitriles in good yields.

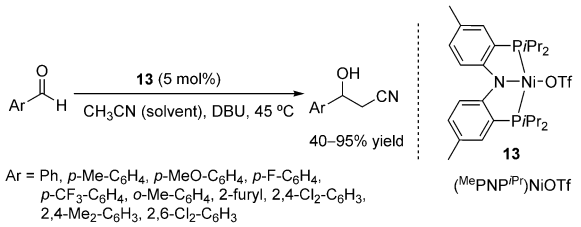


Scheme 14. Ruthenium-catalyzed addition of acetonitrile to aldehydes and imines. Boc = *tert*-butoxycarbonyl, Cp = cyclopentadienyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, HMPA = hexamethylphosphoramide, M.S. = molecular sieves.

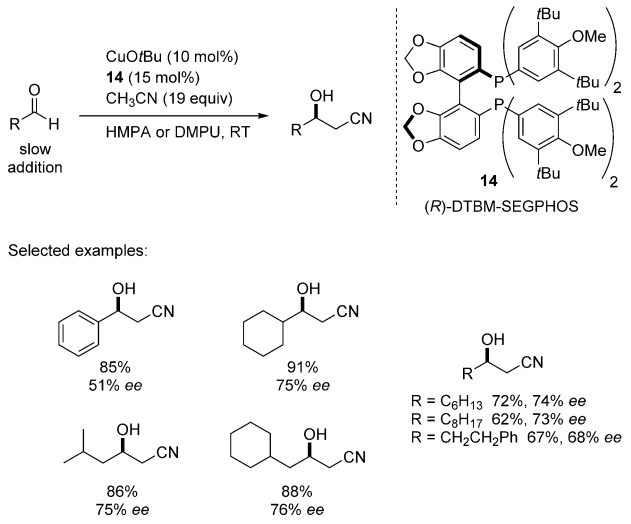
The role of each component in the catalytic triad was proposed based on experimental data obtained from NMR spectroscopy, ESI-MS analysis, and kinetic studies (Scheme 15). Ruthenium predominantly coordinates to acetonitrile, thus serving as a Lewis acid to form **11** and increase the acidity of the α-carbon atom to facilitate deprotonation by an amidine base to generate the reactive species **12**. A first-order rate dependence on DBU and a strong kinetic isotope effect ($k_H/k_D = 5.6$) indicate that deprotonation is the rate-limiting step. In contrast, the beneficial effect of $NaPF_6$ is explained by the equilibrium shift towards **11**, thus avoiding DBU coordination to the Ru center and consequently increasing the concentration of free DBU in the reaction media. This catalytic nucleophilic activation of acetonitrile



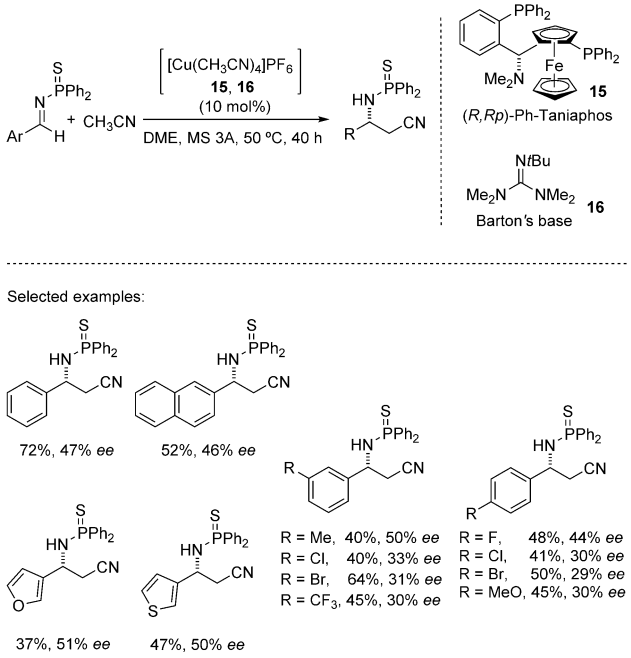
Scheme 15. Proposed catalytic cycle for the addition of acetonitrile to aldehydes.



Scheme 16. Nickel-catalyzed addition of acetonitrile to aldehydes. Tf = trifluoromethanesulfonyl.



Scheme 17. Copper-catalyzed enantioselective aldol-type reaction. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.



Scheme 18. Copper-catalyzed asymmetric addition of acetonitrile to *N*-thiophosphinoylimines. DME = 1,2-dimethoxyethane.

was extended to the reaction with enolizable aldehydes[31] and ketones[32] to produce the corresponding β-hydroxy nitriles in good yields, albeit in racemic form.

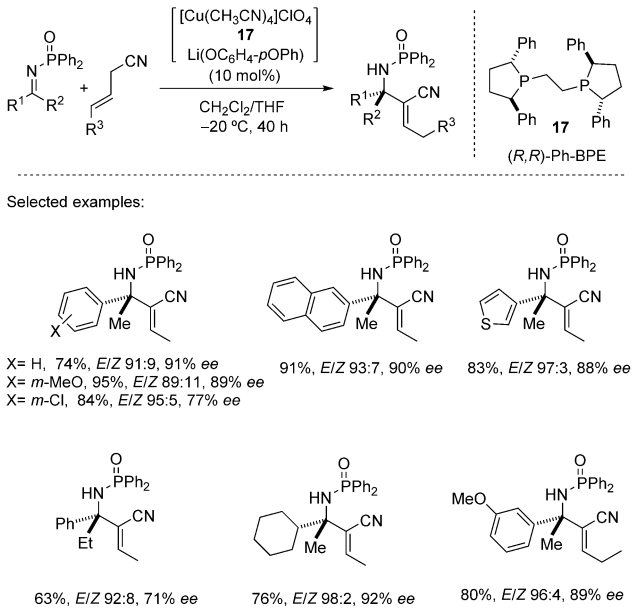
A nickel-complex of diarylamido-based PNP ligands, such as **13** (Scheme 16), also behaved as a Lewis acid to promote, as shown by Fan and Ozerov,[33] the coupling of acetonitrile with aldehydes in the presence of DBU. In general, electron-poor and neutral aromatic aldehydes provided β-hydroxy nitriles in good yields, whereas electron-rich aromatic aldehydes, such as *p*-methoxy benzaldehyde, afforded the corresponding adduct in a poor yield of 40%. Kinetic experiments support a mechanism similar to that proposed by Shibasaki.[30] The rate-limiting step occurs before the carbon–carbon bond formation step.

Although promising, essentially all the above examples provide racemic β-hydroxy and β-amino nitriles. The first asymmetric catalytic direct aldol reaction of acetonitrile was implemented using CuO*t*Bu in the presence of chiral phosphines, such as (*R*)-DTBM-SEGPHOS (**14**; Scheme 17).[34] The reaction proceeds to give adducts in good yields, albeit in moderate enantioselectivities.

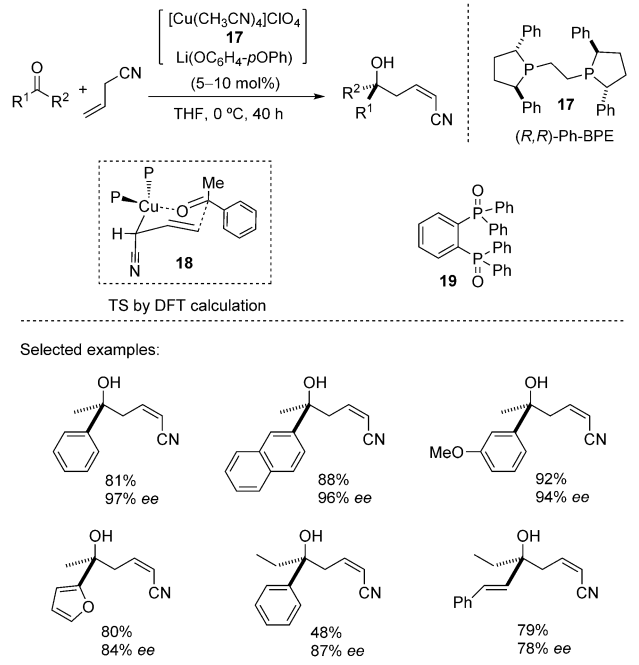
This mode of alkylnitrile activation was also been extended to the first enantioselective copper-catalyzed Mannich-type addition of acetonitrile to *N*-thiophosphinoylimines (Scheme 18), albeit with moderate yields and enantioselectivities.[35] In this case, the cooperative catalytic system consisted of the cationic copper source $[Cu(CH_3CN)_4]PF_6$, the chiral phosphine (R,R_p)-Ph-Taniaphos (**15**), and Barton's base (**16**). The authors propose that the soft Lewis-basic thiophosphinoyl protecting group on the imine leads to a productive association around the soft Lewis acid in the chiral environment, given that the reaction using analogous *N*-phosphinoylimines did not participate in the reaction.

Less-reactive ketimines can also participate in such an asymmetric Mannich-type reaction provided the more reactive allylic cyanides are employed. For example, the reaction of allylic cyanides with a survey of *N*-phosphinoyl ketimines (Scheme 19), in the presence of a cationic copper complex formed by combination of a copper(I) salt, (*R*,*R*)-Ph-BPE (**17**), and Li(OC_6H_4-*p*-OPh), proceeds to give the corresponding adducts from an α-addition. These adducts rapidly isomerize to α,β-unsaturated nitriles with good yields and *ee* values ranging from 71 to 92%.[36]

This cooperative catalyst system was also effective in the direct catalytic asymmetric addition of allyl cyanide to ketones (Scheme 20).[37] In contrast to the α-addition ob-



Scheme 19. Copper-catalyzed asymmetric addition of allylic cyanides to ketimines.



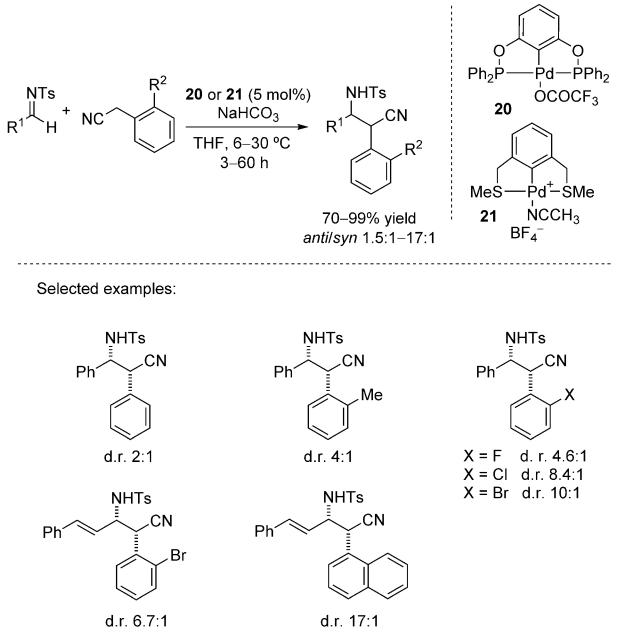
Scheme 20. Copper-catalyzed asymmetric addition of allyl cyanide to ketones.

served for ketimines, exclusive γ-addition occurs to afford the corresponding tertiary homoallylic alcohols with excellent enantioselectivities and complete *Z* selectivity for aryl methyl ketones. Only 1,2-addition was detected for α,β-unsaturated ketones, albeit with a disminished enantioselectivity. The authors suggest that the exclusive formation of a *Z* olefin might be explained by a six-membered cyclic transition state such as **18**, in which the nitrile group occupies a pseudoequatorial position to avoid steric interactions.

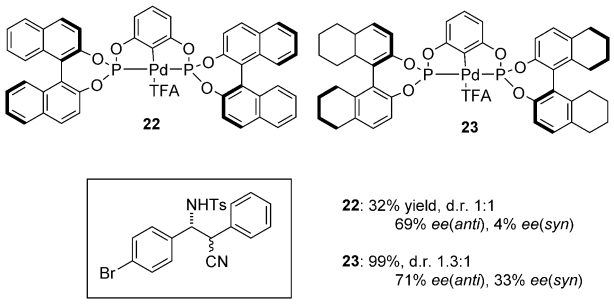
Subsequent mechanistic studies established that the addition of 1,1′-(1,2-phenylene)bis(1,1-diphenyl)phosphine oxide (**19**; Scheme 20), substantially accelerated the reaction rate by enhancing the Brønsted base basicity of $Li(OC_6H_4$-*p*-OPh), thus allowing the reaction to proceed in the presence of 0.5–1 mol% of the catalyst.[38] Under the same reaction conditions, the γ-addition pattern was also observed in the 1,2- and 1,4-addition reaction of allyl cyanide to aldehydes[39] and α,β-unsaturated thioamides, respectively.[40]

In general it is difficult to predict the ability of different metal complexes to activate the nitriles towards α-deprotonation, and combinations of Lewis acids and bases must be screened. α-Arylacetonitriles have been explored using this approach. Szabó and co-workers[41] showed that α-arylacetonitriles react with aromatic *N*-tosyl imines (Scheme 21) in the presence of either the palladium pincer complex **20** or **21** and sodium hydrogen carbonate to give products with variable diastereoselectivities. The reaction works particularly well for *ortho*-substituted benzylic nitriles, thus affording the highest stereoselectivities with the bulkiest substitutions. Nonetheless, no explanation of the assigned relative configuration of the major adducts was given. Attempts to develop the enantioselective addition of benzyl nitrile to *p*-bromophenyl *N*-tosyl imine were carried out in the presence of two different chiral pincer complexes, **22** and **23**, with moderate success (Scheme 22).

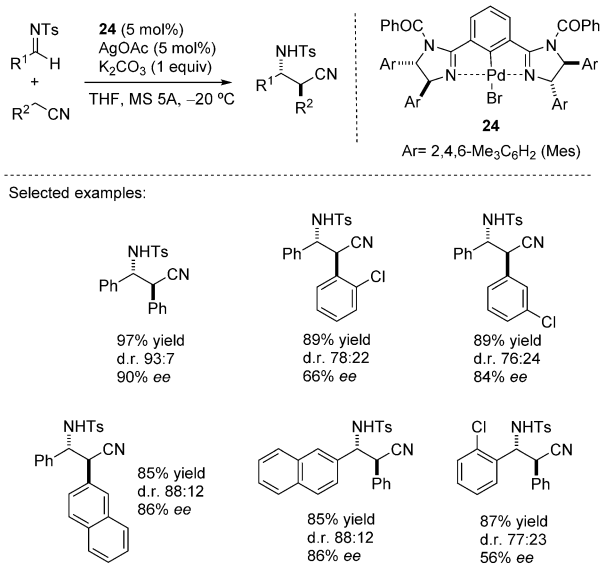
An improved enantioselective version for the above transformation was realized by Nakamura, Shibata, and coworkers by using the chiral bis(imidazoline) palladium pincer complex **24** (Scheme 23).[42] Herein, the effect of the size of the nitrile component appears to be less pronounced than that observed when employing **20** and **21** (see above), but products with high yields and enantioselectivities for the major diastereomers are obtained. The reaction also tolerates a wide



Scheme 21. Palladium-catalyzed addition of benzylic nitriles to *N*-tosyl imines. Ts = 4-toluenesulfonyl.



Scheme 22. Preliminary enantioselective results.



Scheme 23. Enantioselective palladium-catalyzed addition of benzylic nitriles to imines.

range of substituted benzylic nitriles, but no examples on alkylnitriles were reported. On the basis of the established absolute configuration of the major adducts by X-ray crystallography, the model shown in Figure 4 was proposed to account for the carbon–carbon bond-forming event assisted by **24**.

The ability of the chiral palladium pincer complexes to coordinate alkylnitriles has also been exploited not only to increase acidity of the α-carbon atom in alkylnitriles, but also to enhance electrophilicity towards Lewis bases. Using this methodology a highly enantioselective aza-Morita-Baylis–

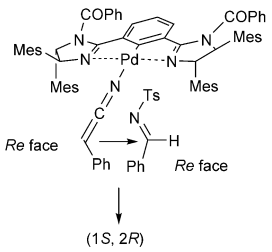
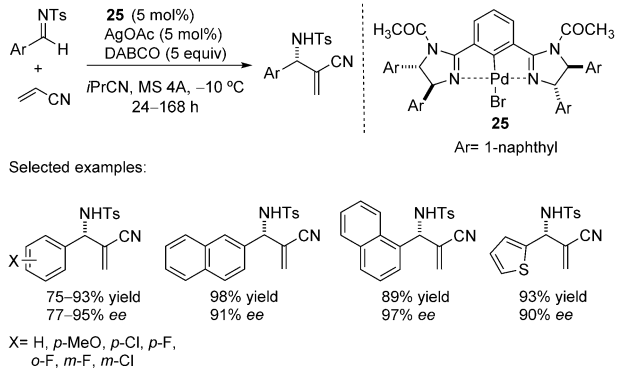


Figure 4. Proposed model for the reaction of benzylic nitriles and *N*-tosyl imines assisted by complex **24**.



Scheme 24. Enantioselective palladium-catalyzed aza-Morita–Baylis–Hillman reaction of acrylonitrile with imines. DABCO = 1,4-diazabicyclo[2.2.2]octane.

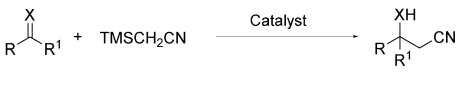
Hillman reaction of acrylonitrile with imines, catalyzed by **25**, was been described (Scheme 24).[43]

5. The Use of Synthetic Equivalents

As mentioned above, to circumvent the difficulties associated with the attenuated reactivity of alkylnitriles, more-reactive synthetic equivalents have been employed to effect cyanoalkylations. A versatile synthetic equivalent of acetonitrile is trimethylsilylacetonitrile ($TMSCH_2CN$). The C–Si bond is easily activated by Lewis bases, thus acting as a stable equivalent of α-cyano carbanions. This methodology has been mainly used in the catalytic synthesis of racemic β-hydroxy nitriles and β-amino nitriles (Scheme 25).[44,45]

Additionally, the cyanomethylation of chiral *N*-(tert-butylsulfinyl)imines (Scheme 26) using $TMSCH_2CN$ allowed the stereoselective synthesis of β-amino nitriles in good yields and excellent diastereoselectivities, although stoichiometric amounts of tetrabutylammonium phenoxide ($PhONnBu_4$) are required.[46]

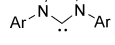
A methodology which complements the use of $TMSCH_2CN$, is one in which α-(dimethylsilyl)nitriles are used. These synthetic equivalents, which react spontaneously with aldehydes in DMSO and with ketones in the presence of lithium acetate, enable the synthesis of racemic but sterically congested β-hydroxy nitriles (Scheme 27).[47]



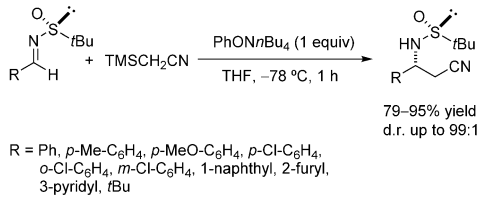
X	R^1	Cat. (mol%)	Yield [%]	Ref.
O	H	TASF(10)	50–93	[42a]
O	H	KF/AlO_3(20)	63–89	[42b]
		TTMPP(10)	65–97	[42c]
		NHC(5)	63–89	[42d]
O	Me,Et	TTMPP(10)	65–96	[42c]
NTs	H	LiOAc/LiOBz(10)	65–94	[42e]

TASF = difluorotrimethylsiliconate

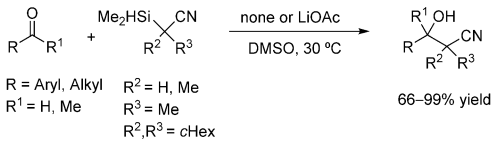
TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine

NHC =  Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

Scheme 25. Cyanomethylation of carbonyl compounds and aldimines.



Scheme 26. Diastereoselective cyanomethylation of chiral *N*-(*tert*-butylsulfinyl)imines.

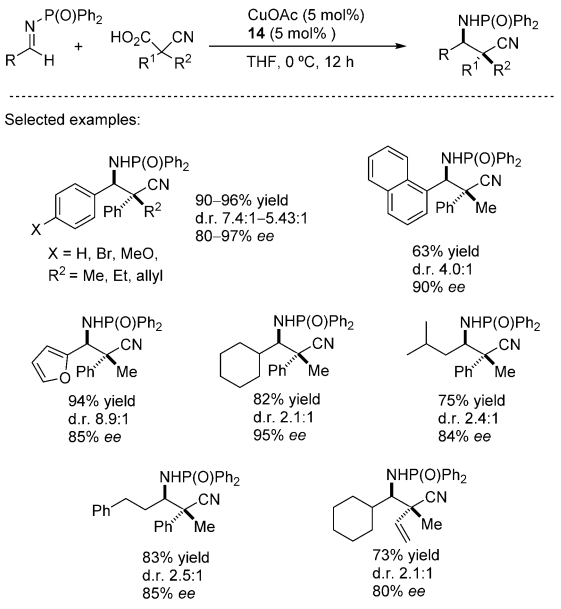


Scheme 27. Cyanomethylation of carbonyl compounds.

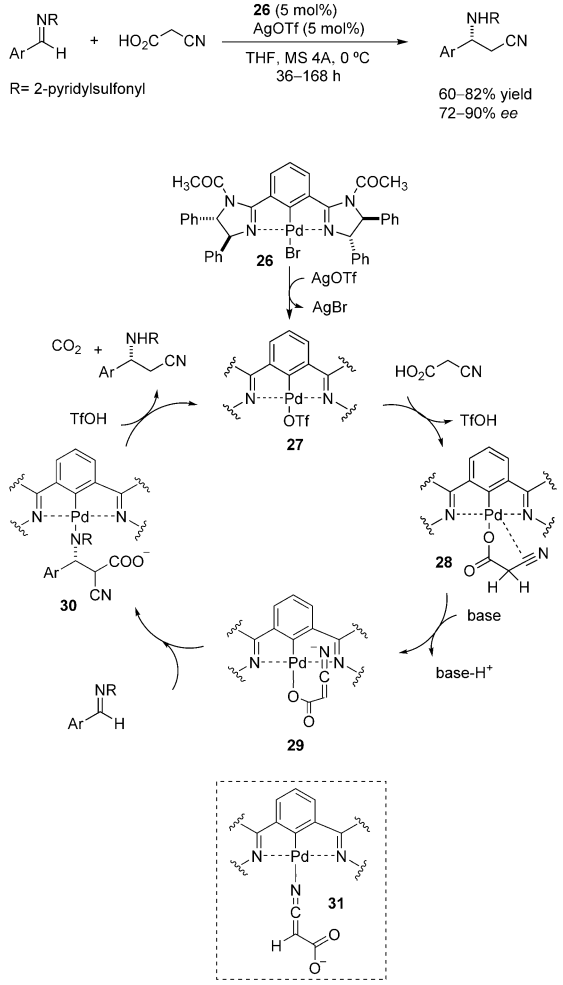
The decarboxylative nucleophilic generation, typically observed in the biosynthesis of polyketides, inspired Shibasaki's work on decarboxylative Mannich-type reactions using cyanocarboxylic acids as synthetic equivalents (Scheme 28).[48] The copper(I)-catalyzed extrusion of CO_2 from cyanocarboxylic acids generates α-cyano carbanions which react with *N*-phosphinoyl imines to produce adducts with contiguous trisubstituted and quaternary stereocenters, and serve as $\beta^{2,2,3}$-amino acid precursors. In general, the reaction proceeds with good levels of diastero- and enantioselectivity and, remarkably, is compatible with imines derived from enolizable aldehydes.

More recently, Nakamura and co-workers described a highly enantioselective decarboxylative Mannich-type reaction of cyanoacetic acid by using the chiral palladium pincer complex **26** to provide the corresponding β-amino nitriles in good yields and in moderate to good enantiomeric excesses (Scheme 29).[49] The authors propose a plausible catalytic cycle in which **26** is first transformed into **27**, which then reacts with cyanoacetic acid to form **28**. This complex, stabilized by the bidentate coordination to palladium, is deprotonated by any weak base present in the reaction media to produce the complex **29**. Reaction of **29** with the imine affords **30** to deliver the β-amino nitrile and regenerate **27**. However, despite their proposal being based on theoretical calculations and experimental data, alternatives might be considered. For example, cyanoacetatic acid coordination to Pd in **27** through the nitrile nitrogen atom and subsequent deprotonation to furnish **31** should not be disregarded given the ample precedent on palladium nitrile complexes. Another intriguing issue is the role of the 2-pyridyl sulfonyl moiety of the starting imine, a heteroaryl group whose high capability for metal coordination is well established.[50]

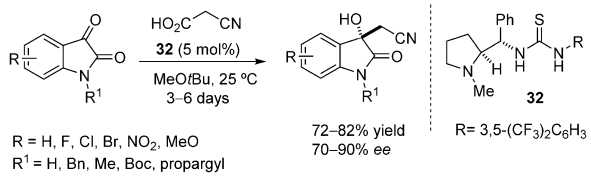
Only one example for the metal-free asymmetric decarboxylative cyanomethylation has been described so far. The L-proline-derived bifunctional thiourea **32** promotes the reaction of cyanoacetic acid with differently substituted isatins to produce enantiomerically enriched substituted 3-hydroxyindoles in good yields after long reaction times



Scheme 28. Catalytic asymmetric decarboxylative Mannich-type reaction.



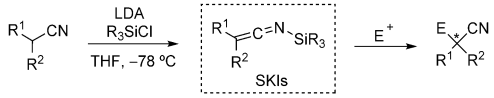
Scheme 29. Enantioselective decarboxylative cyanomethylation of *N*-sulfonyl imines.



Scheme 30. Enantioselective decarboxylative cyanomethylation of isatins.

(Scheme 30).[51,52] Although no mechanism has been proposed, it appears that **32** acts in a bifunctional manner by activating the keto function in the isatin substrate through hydrogen-bond interactions with the thiourea whilst the tertiary amine facilitates pronucleophile deprotonation and final decarboxylation.

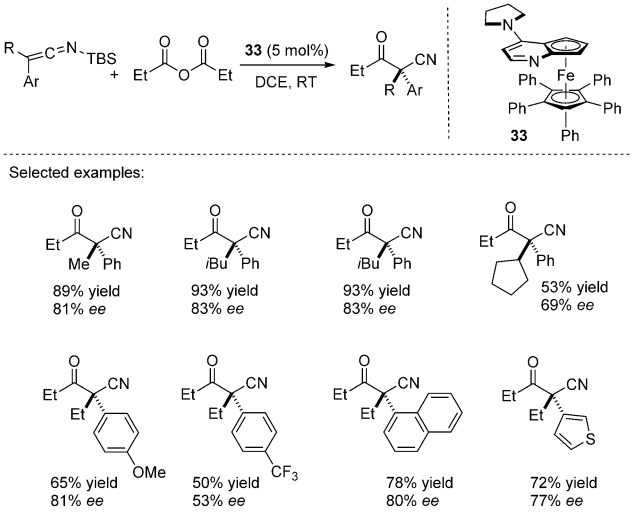
Silyl ketene imines (SKIs) constitute a particular type of α-cyano carbanion equivalent.[53] The α-deprotonation of alkylnitriles generates ambident anions which can undergo reactions at the nitrogen center to afford an N-substituted ketene imine or at the carbon atom to furnish a C-substituted nitrile. Site-selective procedures for the synthesis of *N*-silyl ketene imines mainly rely on the α-cyano carbanion generation, by treatment with LDA, and its subsequent trapping with substituted silyl chlorides (Scheme 31).[54,55] Disubstitution on the nitrile seems to be crucial for obtaining high selectivities and yields of SKIs. In general, geometrically well-defined SKIs may be produced and as a result a quaternary carbon stereocenter adjacent to a tertiary carbon atom may be constructed with very high diastereoselectivity.



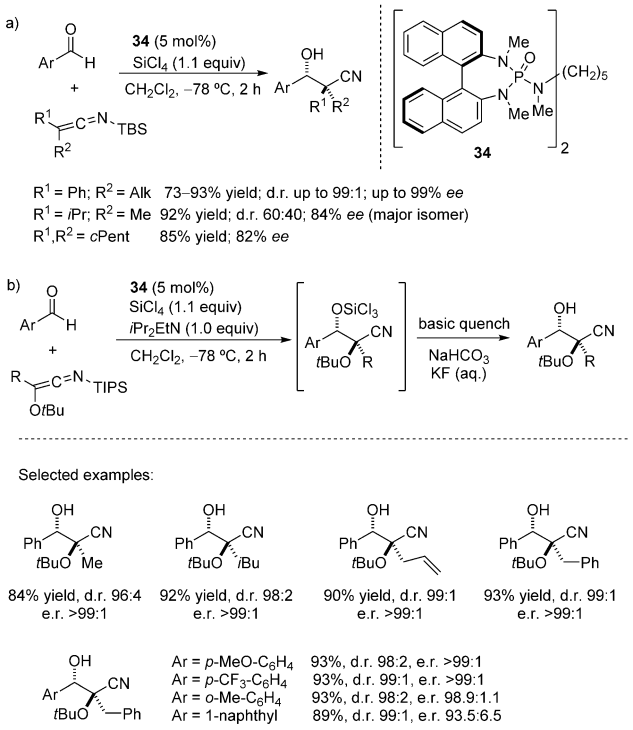
Scheme 31. Synthesis and reactivity of silyl ketene imines. LDA = lithium diisopropylamide.

The first catalytic asymmetric example of the use of SKIs as α-cyano carbanion equivalents was described by Fu and coworkers in 2005.[56,57] The chiral Lewis base **33** promotes the asymmetric acylation of alkyl,aryl-disubstituted SKIs using propionic anhydride (Scheme 32). The enantioselective acylation is proposed to proceed through a dual activation pathway which involves the generation of a reactive chiral acylpyridinium cation and the activation of the corresponding SKI by coordination of the propionate counterion to the silyl group.

A procedure for the synthesis of enantioenriched β-cyano alcohols bearing quaternary stereocenters was developed by Denmark et al. through the Lewis-base-catalyzed addition of SKIs to aldehydes (Scheme 33 a).[58] At low temperature, the bis(phosphoramide) **34**/$SiCl_4$ catalyst complex produces the corresponding β-hydroxy nitriles with good yields and excellent diastereo- and enantioselectivities. The transformation shows broad substrate scope for both the aromatic aldehyde and the disubstituted SKI. This combination of silicon tetrachloride and chiral phosphoramides was previously



Scheme 32. Nucleophile-catalyzed asymmetric acylation of silyl ketene imines. DCE = 1,2-dichloroethane.

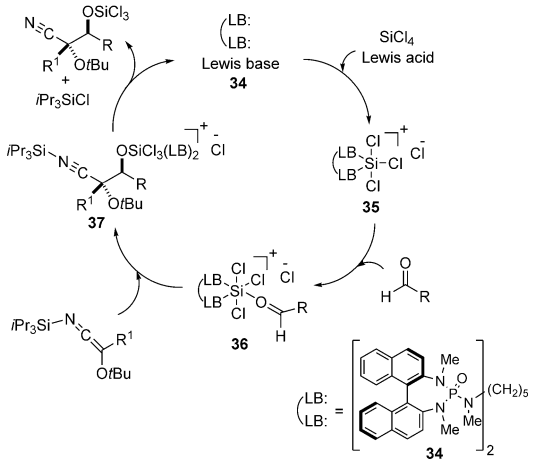


Scheme 33. Enantioselective catalyzed aldol reaction of silyl ketene imines (a) and silyloxy ketene imines (b). TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

employed by the same authors to catalyze the conjugate addition of SKIs to α,β-unsaturated aldehydes and ketones with moderate stereoselectivities (d.r. 68:32-91:9, up to 72% *ee*).[59]

N-Silyl oxyketene imines (Scheme 33 b) derived from *tert*-butyl-protected cyanohydrins also undergo Lewis-base-catalyzed aldol additions using similar reaction conditions.[60] The in situ generated intermediates afford, after a basic treatment,

the corresponding β-hydroxy cyanohydrins in good yields and high diastereo-and enantioselectivities. The proposed catalytic cycle (Scheme 34) starts with the binding of **34** to the weak Lewis acid silicon tetrachloride. This complexation of the Lewis base leads to polarization of $SiCl_4$ and eventually

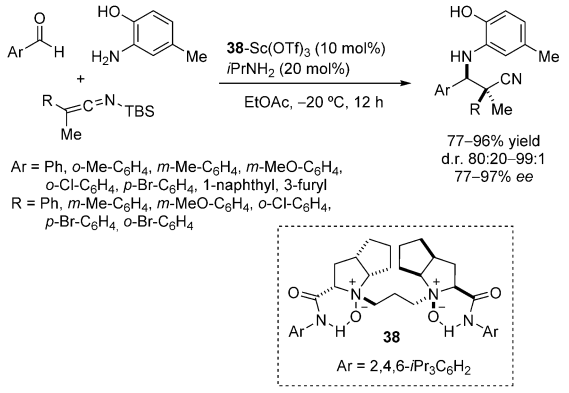


Scheme 34. Proposed catalytic cycle for silyloxy ketene imine additions to aromatic aldehydes.

ionization of a chloride ion to generate a chiral trichlorosilyl cation **35**. Coordination of the aldehyde to the activated Lewis acid **35** produces **36**. Then the enantioselective addition of the *N* -silyl oxyketene imine to **36** leads to the nitrilium ion intermediate **37**. Desilylation of the latter by nucleophilic chloride and subsequent regeneration of **34** delivers the aldol product as the trichlorosilyl ether.

The γ-addition of *N*-silyl vinylketene imines to aldehydes has been reported by the same authors using similar reaction conditions to produce α,β-unsaturated nitriles.[61]

Feng and co-workers have employed SKIs as nucleophiles in a scandium-catalyzed three-component Mannich-type reaction, using the ligand **38**, to produce enantiomerically enriched β-amino nitriles (Scheme 35).[62] The one-pot reaction conditions are compatible with a variety of aromatic aldehydes and methyl,aryl-disubstituted SKIs. The high



Scheme 35. Three-component catalytic asymmetric Mannich-type reaction of silyl ketene imines.

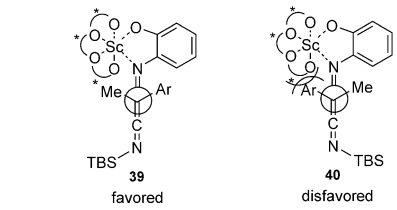
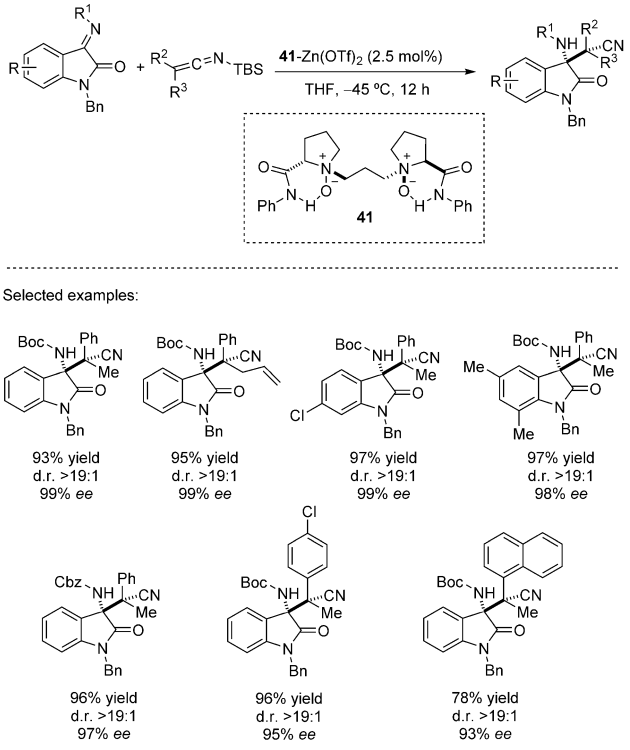


Figure 5. Proposed catalytic models for the Mannich-type reaction of SKIs.

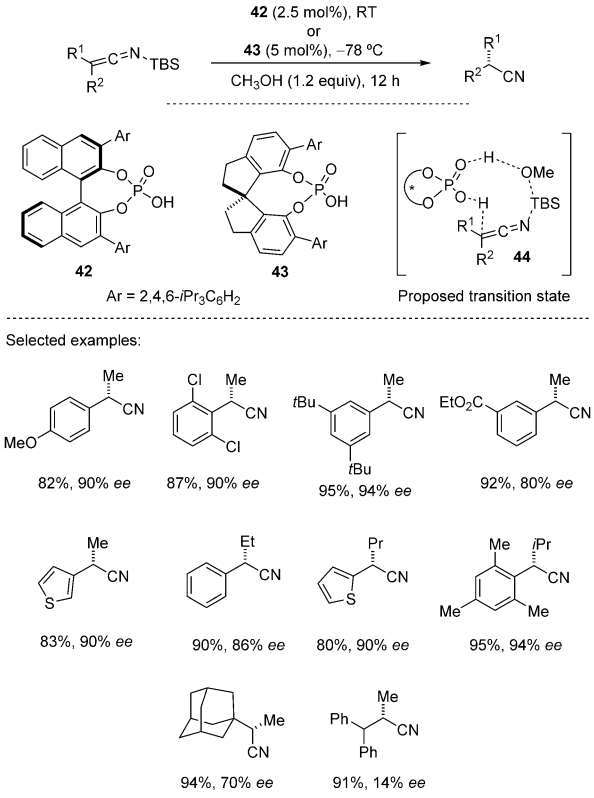
selectivity exerted by the catalytic system is attributed to the bidentate coordination of the aldimine, generated in situ, to the scandium center (Figure 5). Thus, the steric hindrance between the aryl group of SKI, the scandium(III) complex, and the aryl substitution of the imine seems to be the responsible for the model **39** being more favorable than the model **40**.

More recently, a related highly diastereo- and enantioselective method for the construction of vicinal tetrasubstituted stereocenters with isatin-derived ketimines was been reported by the same group (Scheme 36).[63] In this particular case, the chiral *N*,*N*′-dioxide **41**/Zn^{II} complex promotes the Mannich-type reaction of methyl,aryl-disubstituted SKIs to produce the corresponding functionalized 3-amino oxindoles in high yields and with excellent diastereo- and enantioselectivities.

List and co-workers have described the catalytic and enantioselective protonation of SKIs promoted by the chiral phosphoric acids **42** and **43** to produce highly enantioenriched nitriles (Scheme 37).[64] The procedure, which uses methanol



Scheme 36. Catalytic asymmetric Mannich-type reaction of silyl ketene imines and isatin-derived ketimines.



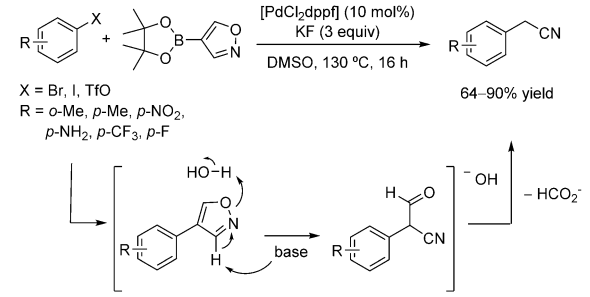
Scheme 37. Catalytic asymmetric protonation of silyl ketene imines.

as the stoichiometric proton source, is postulated to proceed through the formation of a methanol/phosphoric acid complex (**44**) which protonates the carbon center of the SKI enantioselectively.

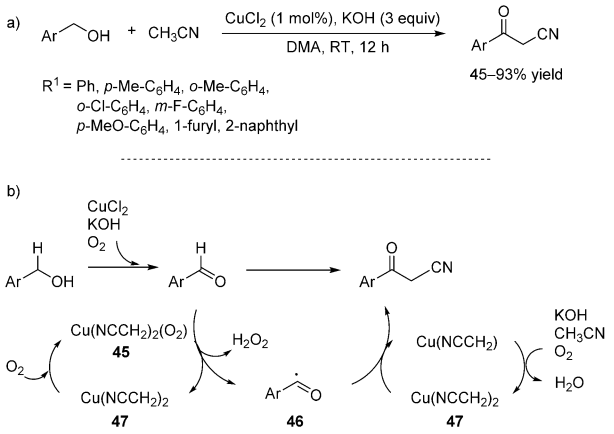
6. Miscellaneous Catalytic Cyanoalkylations

Isoxazolyl-4-boronic acid pinacol ester behaves as an acetonitrile anion equivalent for the synthesis of benzylic nitriles. The one-pot palladium-catalyzed Suzuki coupling between isoxazolyl-4-boronic acid pinacol ester and aryl halides, and subsequent base-induced isoxazole fragmentation produces, after a retro-Claisen-type process of the resulting α-formyl nitrile, the corresponding arylacetonitriles in good yields (Scheme 38).[65]

Recently, Liu and co-workers described an efficient preparation of β-ketonitriles by a copper-catalyzed aerobic oxidative coupling of aromatic alcohols and acetonitrile (Scheme 39 a).[66] The catalytic procedure is general for a wide range of benzylic alcohols, with only those having strong electron-withdrawing groups (NO_2) being unreactive. The authors propose a mechanism (Scheme 39 b) which primarily based on the absence of reactivity when molecular oxygen is not present in the reaction mixture. The reaction may proceed by the oxidation of the benzaldehyde, by the complex **45**, to generate the intermediate **46**, which further reacts with **47** to produce the corresponding β-ketonitriles.

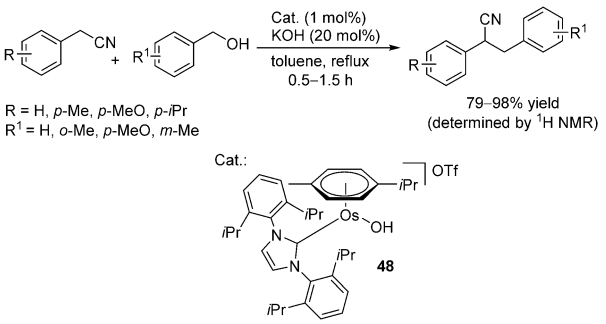


Scheme 38. Cyanomethylation of aryl halides. dppf = 1,1′-bis(diphenylphosphino)ferrocene.



Scheme 39. Catalytic synthesis of β-ketonitriles. a) Selected examples. b) Reaction mechanism proposal. DMA = dimethylacetamide.

In a related transformation, the osmium complex **48** in Scheme 40 promotes the alkylation of arylacetonitriles through the borrowing-hydrogen methodology.[67]



Scheme 40. Catalytic alkylation of arylacetonitriles with alcohols.

7. Summary and Outlook

During the last few years a considerable effort has been invested in investigating the catalytic generation of α-cyano carbanions, metalated nitriles, and/or related reactive species. The development of effective modes of alkylnitrile activation has been crucial and several direct catalytic α-cyanoalkylation

methodologies are now available. However, despite the progress achieved, much room for improvement remains. For example, the scope and generality of many of the current modes of activation of alkylnitriles still need to be established. Most work has been carried out with acetonitrile and benzyl and allyl cyanides, while nitriles bearing larger aliphatic or functionalized chains still have yet to be explored. As a result, very little is known about the influence of the size of the nitrile on the reactivity and reaction diastereoselectivity, another aspect which needs to be addressed properly. Also significant is the limited number of methods for enantioselective cyanoalkylation reactions. Base-promoted catalytic enantioselective cyanoalkylations, which represents a formidable task, are essentially restricted to nitrophenylacetonitriles (activated acetonitriles) in combination with highly reactive acceptors, and thus the search for efficient and more general catalyst systems is of great interest. There is essentially no asymmetric methodology, based on the catalytic generation of metalated alkylnitriles, and further development is clearly needed. In this respect, the progress made on metal-catalyzed cross-coupling reactions may help to fill this gap. In the context of metal-assisted deprotonation of alkylnitriles, predicting the ability of different metals to activate the nitriles towards deprotonation of the resultant complexes is difficult and thus research on this aspect would facilitate the design of new and more-efficient catalyst systems. Another weak point is the lack of catalytic enantioselective cyanoalkylation reactions with the commercially available $TMSCH_2CN$. In contrast, while silyl ketene imines have provided good entries for the generation of all-carbon quaternary stereocenters, direct methods for the asymmetric construction of tertiary nitriles still need to be developed. Additionally, the design of new catalytic activation modes for alkylnitriles is another challenge that would clearly increase the utility of alkylnitriles as synthetically useful reagents for direct carbon-carbon bond-forming reactions.[68]

Acknowledgements

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