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An overview of the direct vicinal cyano-acylation/-esterification of unsaturated hydrocarbons

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ABSTRACT

This review aims to summarize the current literature on the direct vicinal cyano-acylation and cyano-esterification of unsaturated hydrocarbons, with a particular focus on the mechanistic features of these reactions. This review is structured into four main sections. The first section covers the cyano-acylation of alkenes, followed by a discussion of cyano-esterification of alkenes in the second section. The third section consists of an overview of cyano-acylation of alkynes, while the final section focuses on the cyano-esterification of alkynes.

1. Introduction

The nitrile group (−CN) is a crucial functional group in medicinal chemistry, as it is found in over 60 small-molecule drugs available on the market, which are used to treat a wide range of diseases, ranging from viral infections to different types of cancer (Scheme 1) [1]. Nitrile- containing molecules are also abundant in nature and can be found in both prokaryotic and eukaryotic organisms [2]. Moreover, nitriles are versatile intermediates in organic synthesis and are easily diversified into various important functional groups such as amines, amides, imines, oximes, carboxylic acids, aldehydes, esters and various nitrogen-containing heterocycles [3-11]. Therefore, the development of new strategies for incorporating a nitrile group into organic compounds has always been an important topic in organic synthesis [12].

The direct difunctionalization of unsaturated hydrocarbons is a highly effective synthetic strategy enabling the conversion of readily accessible alkenes and alkynes into complex molecular structures by introducing two functional groups into the π system in a single step [13-17]. In this context, cyanative difunctionalization reactions have recently emerged as a highly powerful strategy for synthesizing β-substituted nitriles from alkene/alkyne feedstocks in a one-pot manner, without the need to isolation of intermediates [18]. Within this class of reactions, the carbonylative cyanation of

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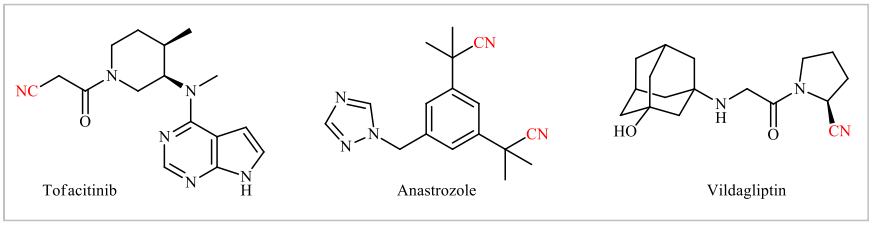
unsaturated hydrocarbons provides an effective approach for the selective synthesis of β-cyano carbonyl compounds by simultaneously introducing a cyano group and a carbonyl functional group on adjacent carbons (Figure 1). Despite considerable progress in this field over the past decades, no comprehensive review has yet been found in the literature covering this emerging area of research. In order to fill this gap, herein, we provide a detailed overview of recent advancements on the direct vicinal cyano-acylation/-esterification of unsaturated hydrocarbons, with a particular emphasis on the mechanistic aspects of the reactions.

2. Cyanoacylation of alkenes

In 2019, Bao and co-workers studied the possibility of synthesis of β-cyano ketones through the direct cyanoacylation of alkenes [19]. By employing styrene as the model substrate, along with benzaldehyde and trimethylsilyl cyanide (TMSCN) as the acyl and cyano sources, respectively, various reaction parameters such as catalysts, ligands, and solvents were carefully screened. The results demonstrated that the combination of 2.5 mol% of CuCl with 3.5 mol% of 4,4'-dibromo-2,2'-bipyridine (DBrBPy) and 2.5 equiv. of *tert*-butyl hydroperoxide (TBHP) constituted the most effective catalytic system for this transformation and among the various solvents tested (*e.g.*, DCM, DCE, MTBE, MeCN, ^{c}Hex, dioxane, toluene); MTBE was identified as the most suitable. Under the optimized conditions, 36 β-cyano ketone derivatives 3 were obtained in moderate to high yields by reaction of terminal (hetero)aromatic alkenes 1 with various aldehydes (aromatic, heteroaromatic, and aliphatic) and TMSCN (Scheme 2). The protocol was also applied to the efficient late-stage modification of estrone, a natural product derivative. Other substrates such as α-substituted styrene derivatives, α,β-unsaturated carbonyl compounds, and conjugated dienes were also found to be compatible with the reaction conditions, albeit affording only modest yields at best. Unfortunately, the applicability of unactivated alkenes as starting materials was not examined in this study. Several theoretical and experimental studies, such as radical trapping, radical clock, isotope-labeling, DFT calculation and others manifest that the mechanism of this difunctionalization reaction involves the initial formation of Cu(II) species A and ^{t}BuO$^{\cdot}$ through an inner-sphere single electron transfer (SET) process between LCu^{II} and ^{t}BuOOH. Subsequently, the ^{t}BuO$^{\cdot}$ radical abstracts a hydrogen atom from the aldehyde 2 to propagate an acyl radical B and a molecule of ^{t}BuOH. Next, the addition of radical B to the styrene 1 affords a more stable benzyl radical C, which after reaction with *in situ* generated cyanocopper(II) complex D delivers the observed acyl-cyanation product 3 *via* an outer-sphere cyano group transfer pathway through an outer-sphere electron transfer crossing point E (Scheme 3).



Scheme 1. Selected examples of marketed drugs with a nitrile moiety.

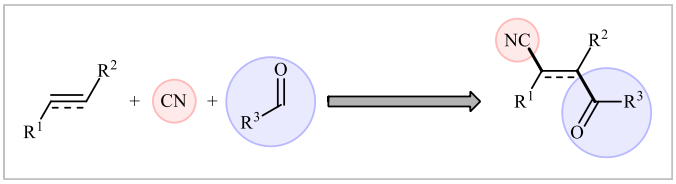
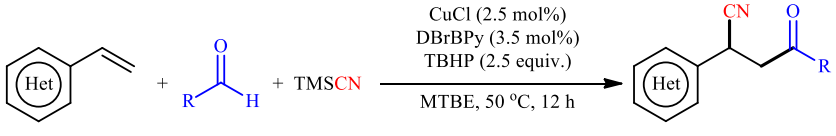


Fig. 1. Direct vicinal carbonylative cyanation of unsaturated hydrocarbons.



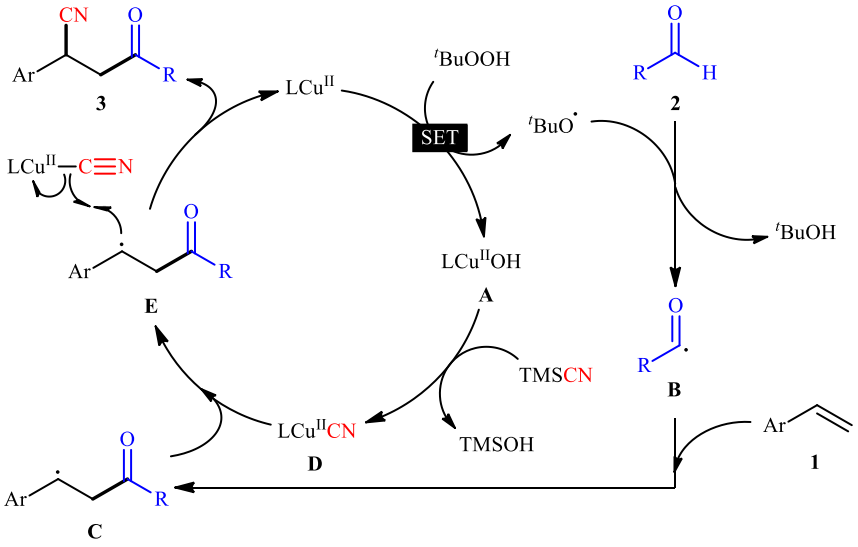
1 **2** **3**

36 examples (38-88%)

(Het)Ar= 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-OMe-C_6H_4, 4-CO_2Me-C_6H_4, 4-OCOMe-C_6H_4, 3-Me-C_6H_4, 2-Me-C_6H_4, 2-naphthyl, 5-(4-Me)-thiazolyl

R= ^{c}Pr, ^{i}Bu, ^{sec}Bu, ^{c}Hex, 4-^{c}Hex, -$(CH_2)_8CH{=}CH_2$, CH_2Bn, Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-CN-C_6H_4, 4-OH-C_6H_4, 4-SMe-C_6H_4, 3-Me-C_6H_4, 3-CF_3-C_6H_3, 3,4-$(Me)_2$-C_6H_3, 3,4-$(F)_2$-C_6H_3, 2-naphthyl, 2-furyl, 3-benzothienyl, phenylacetylenyl, TMS-acetylenyl

Scheme 2. Bao's synthesis of β-cyano ketones 3.



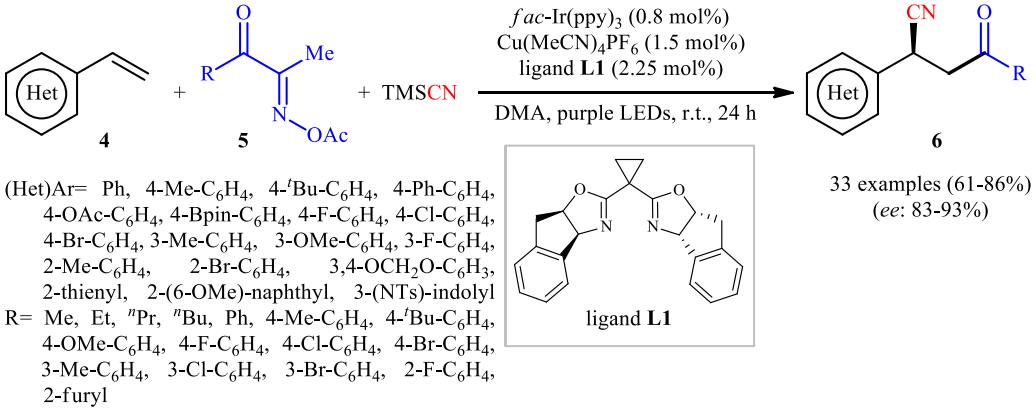
Scheme 3. Mechanistic explanation for the formation of β-cyano ketones **3**.

Shortly afterwards, Chen's group developed an efficient photoactivation strategy for asymmetric cyanoacylation of alkenes by merging a metallaphotoredox catalysis with a copper catalyst employing oxime esters as the acyl source and TMSCN as the cyano source [20]. Thus, in the presence of 0.8 mol% of *fac*-Ir(ppy)$_3$, as a photocatalyst and 1.5 mol% of Cu(MeCN)$_4$PF$_6$ as a transition-metal catalyst, in combination with 2.25 mol% of Box-type ligand L1 in DMA under irradiation of purple LEDs, the reaction of various (hetero)aromatic alkenes 4 bearing either electron-donating (*e.g.*, Me, ^{t}Bu, and Ph) or electron-withdrawing (*e.g.*, F, Cl, Br, OAc, and Bpin) functional groups with different aryl/alkyl ketone-derived oxime esters 5 and TMSCN furnished the corresponding β-cyano ketones 6 in good to high yields and excellent enantioselectivity (Scheme 4). Remarkably, the protocol was also successfully extended to pharmaceutically relevant compounds, including estrone, febuxostat-, and amino acid-derived alkenes. Unfortunately, the current catalytic system is not applicable to simple unactivated or electron-deficient alkenes, as well as cyclic oxime esters. Mechanistically, as stated by the authors, the reaction proceeds through two intertwined catalytic cycles as illustrated in Scheme 5. At first, the ground state photocatalyst (PC) undergoes photoexcitation under visible-light irradiation to produce the excited state (PC*), which subsequently reduces oxime ester 5 by a SET process to give iminyl radical A, with release of carboxylic anion. Then, radical A undergoes C–C bond β-cleavage to form acyl radical B that after addition to styrene 4 forms relatively more stable benzylic radical C. On the other hand, the initially formed carboxylic anion facilitates the ligand exchange between L1/Cu^I complex and TMSCN to form L1Cu^{I}CN species. Subsequently, oxidation of newly generated complex by the oxidizing photocatalyst (PC$^{\bullet+}$) *via* a SET process, followed by another ligand exchange with TMSCN affords L1Cu^{II}(CN)$_2$ complex with concomitant regeneration of ground-state photocatalyst. Finally, L1Cu^{II}(CN)$_2$ traps the prochiral benzylic radical C to form a chiral high-valent Cu^{III} complex D, which undergoes the reductive elimination to afford the target β-cyano ketone 6, with regeneration of L1Cu^{I}CN species.

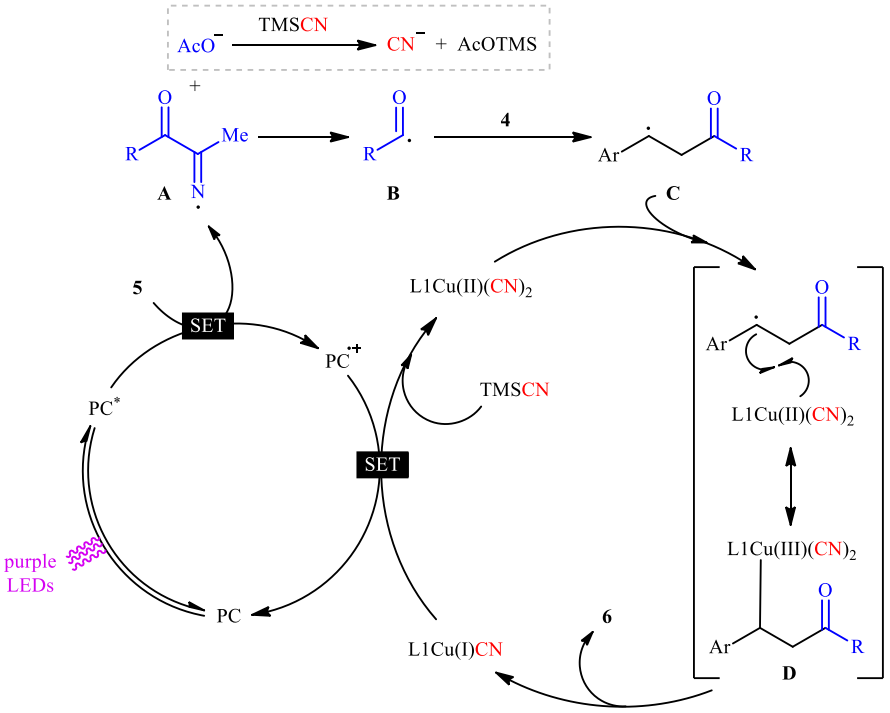
In a closely related study, Dong, Guan, and He disclosed that *fac*-Ir(ppy)$_3$ combined with CuOAc and pybox ligand L2 was highly effective catalytic system for the direct cyanoacylation of styrene derivatives 7 with aroyl chlorides 8 and TMSCN under blue LEDs irradiation at room temperature [21]. By this protocol, thirty-two β-cyano ketones 9 were synthesized in fair to high yields (Scheme 6). However, when aliphatic acyl chlorides were used as acyl donors under the optimal reaction conditions, no desired products were detected and most starting materials remained unchanged. The authors explained this observation by low reduction potential of aliphatic acyl chlorides. In order to expand the scope of this methodology, in this study, the reactivity of various sulfonyl chlorides was also examined. Interestingly, both aromatic and aliphatic sulfonyl chlorides reacted smoothly under the reaction conditions, providing a series of β-sulfonyl nitriles in satisfactory yields (8 examples, 62–76%). Mechanistic investigations revealed that the reaction proceeds *via* a SET pathway. Thus, the authors proposed a mechanism analogous to that of Chen's group depicted in Scheme 5.

In an attractive contribution in this field, Kong *et al*. disclosed an interesting electrocatalytic vicinal cyanoacylation of terminal alkynes 10 employing α-keto acids 11 and cyanobenziodoxolone 12 as radical sources of acyl and cyano groups, respectively [22]. The reactions were conducted in an undivided cell assembled with a

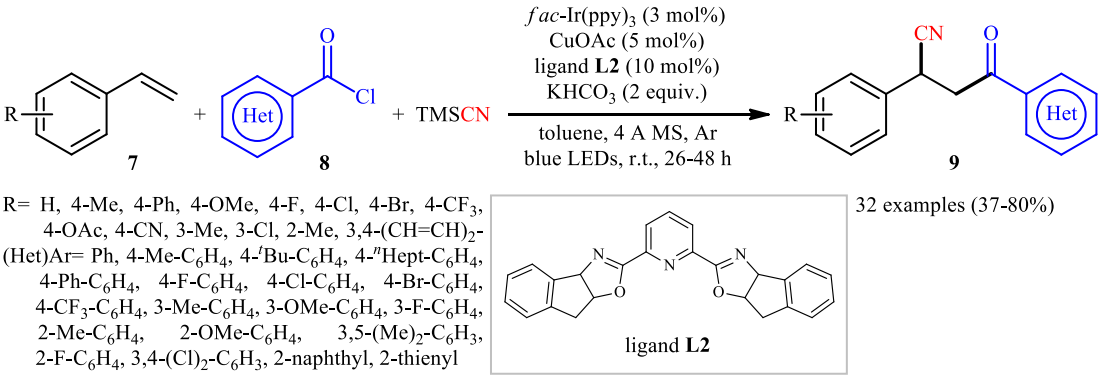
platinum anode and a carbon rod cathode using $LiClO_4$ as the supporting electrolyte under constant-current of 5 mA and provided the expected β-cyano ketones 13 in good yields, ranging from 61% to 81% yield (Scheme 7). The method showed a broad substrate scope including both aliphatic and aromatic alkenes and various alkyl/aryl/heteroaryl α-keto acids. On the basis of several control experiments and literature reports, the author proposed a possible mechanistic course for this electrochemical synthesis of β-cyano ketones, which is outlined in Scheme 8.



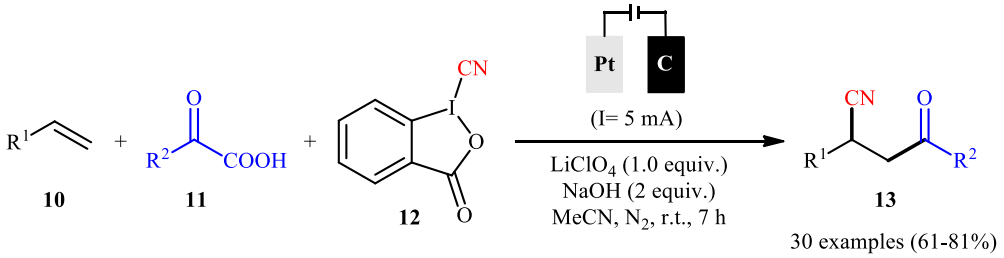
Scheme 4. Chen's synthesis of chiral β-cyano ketones **6**.



Scheme 5. Proposed mechanism for the reaction in Scheme 4.



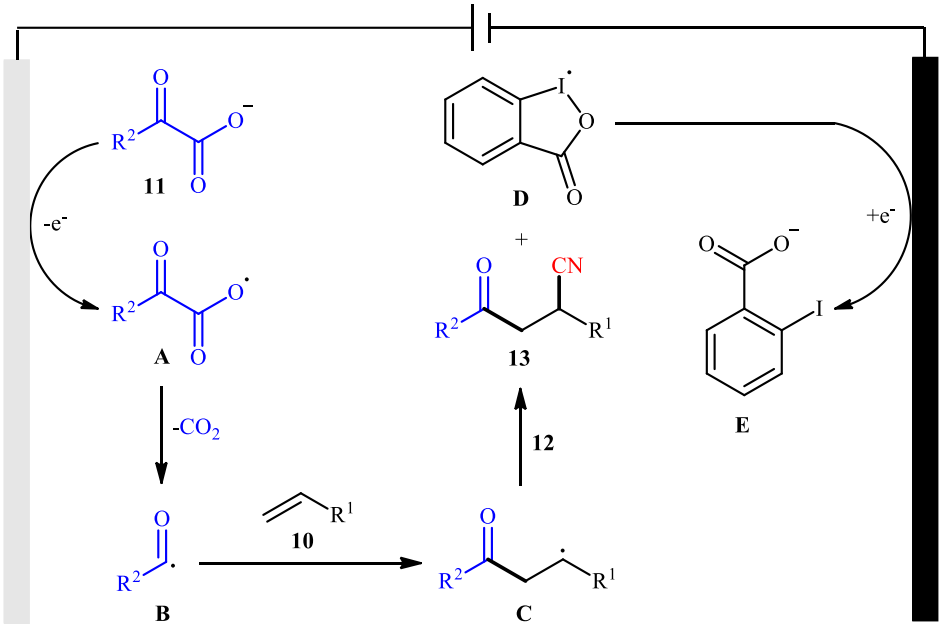
Scheme 6. He's synthesis of β-cyano ketones 9.



R^1= ^{n}Bu, ^{n}Pent, ^{n}Hex, ^{c}Hex, CH_2Bn, Ph, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 4-CO_2Me-C_6H_4, 4-OAc-C_6H_4, 3-Me-C_6H_4, 2-Br-C_6H_4, 2-naphthyl

R^2= ^{c}Pr, ^{t}Bu, Ph, 4-Me-C_6H_4, 4-^{t}Bu-C_6H_4, 4-Ph-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-Br-C_6H_4, 1-naphthyl, 2-naphthyl, 2-thienyl

Scheme 7. Kong's synthesis of β-cyano ketones 13.



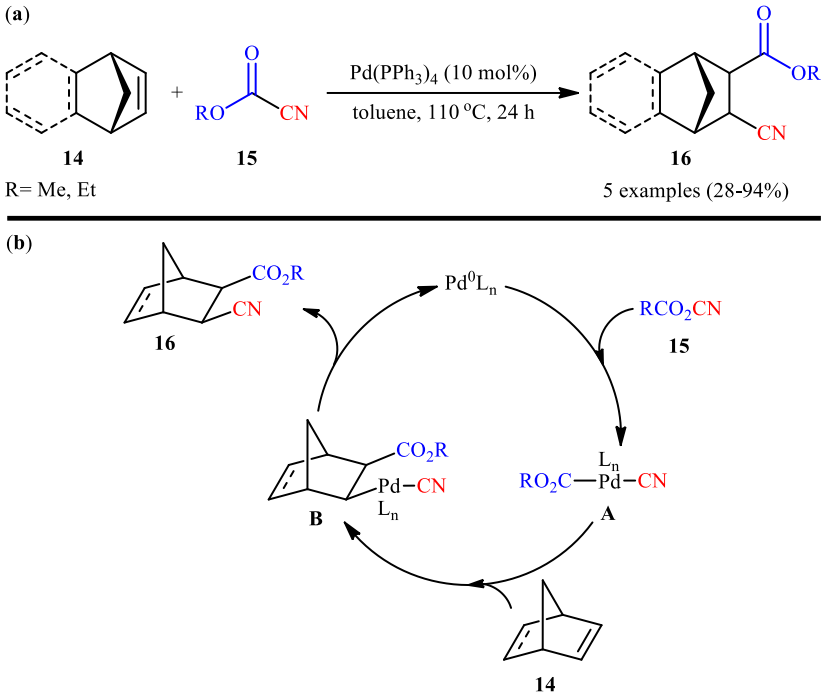
Scheme 8. Presumable pathway of the formation of β-cyano ketones 13.

3. Cyanoesterification of alkenes

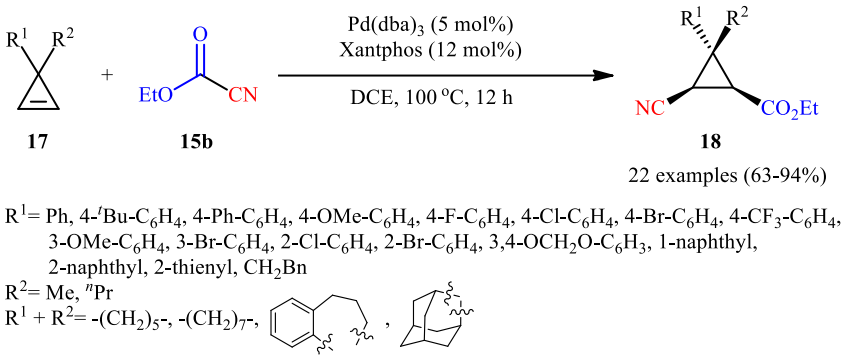
One of the earliest protocols for the direct vicinal cyanoesterification of olefinic double bonds has been reported by Nishihara and co-workers in 2005 [23]. They disclosed that the treatment of norbornene derivatives 14 with commercially available cyanoformates 15 as both cyanation and esterification agents in the presence of a catalytic amount of $Pd(PPh_3)_4$ in refluxing toluene, resulted in the formation of the corresponding β-cyano esters 16 in poor to excellent yields and outstanding 2-*exo*,3-*exo* stereoselectively (Scheme 9a). Various alkyl and benzyl cyanoformates worked well under optimized conditions, but extension of the reaction to aryl cyanoformates was failed [24]. According to author's proposed mechanistic cycle (Scheme 9b), this reaction may proceed through an oxidative addition/ alkoxycarbonylpalladation/reductive elimination sequence. A decade later, the authors investigated the detailed mechanism of this cyanoesterification reaction with the aid of density functional theory (DFT) calculations to elucidate the origin of the observed *exo*-selectivity [25]. The results suggested that this strong selectivity originates from the steric and agostic hydrogen interactions between the methylene and the ethylene bridges of the norbornene and the adjacent *cis*-ligands at the Pd^{II} center. It should be mentioned that this innovative research group also successfully extended the substrate scope of this chemistry to 1,2-dienes [26, 27].

In this realm, Fang and co-workers disclosed an interesting asymmetric cyanoesterification of cyclopropenes employing ethyl cyanoformate as the sources of the cyano group and ester group [28]. Herein, catalytic amounts of $Pd(dba)_3$ in presence of Xantphos enabled direct cyanoesterification of various f aryl/alkyl-substituted cyclopropenes 17 with ethyl cyanoformate 15b to dispense the targeted cyclopropanecarbonitriles 18 with high functional group compatibility (Scheme 10). The synthetic application of this transformation was

also demonstrated by the conversion of the cyclopropane nitriles to the corresponding amino alcohols. Moreover, the scalability of process was demonstrated by performing two reactions on gram scales.



Scheme 9. Nishihara's synthesis of β-cyano ketones 16.



Scheme 10. Fang's synthesis of cyclopropanecarbonitriles 18.

4. Cyanoacylation of alkynes

One of the earliest reports on the direct cyanoacylation of alkynes to form acrylonitrile derivatives have been published by Takaya and co-workers in 1994 [29, 30]. They showed that treatment of phenylacetylene derivatives 19 with acyl cyanides 20 in the presence of 20 mol% PPh_3 and 10 mol% dppb as mixed ligands and 20 mol% of $Pd(OAc)_2$ as a catalyst in DCE at 70 °C, resulted in β-cyano α,β-unsaturated ketones 21 in moderate to good yields with excellent (*Z*)-selectivity (Scheme 11).

The results demonstrated that the stereochemical effect of the reaction was strongly dependent on the nature of the ligand employed. Performing the process in the absence of dppb resulted in a mixture of both (*Z*)- and (*E*)-products, indicating reduced stereoselectivity. Moreover, the outcome of this reaction was also strongly dependent on the selected solvents. For example, when the reaction was carried out in THF, the corresponding acetylenic ketones were exclusively obtained without any of β-cyano α,β-unsaturated ketone products. As shown in Scheme 12, the authors proposed two potential mechanisms for the formation of β-cyano α,β-unsaturated ketones 21.

After two decades, Ohmiya-Sawamura's research group described an alternative cyanoacylation of alkynoates with acyl cyanides under transition-metal free conditions [31]. Thus, by using dimethylphenylphosphine ($PPhMe_2$) as a Lewis base catalyst in toluene, various alkynoates 22 regioselectively cyanoacylated with acyl cyanides 23 to afford tetrasubstituted acrylonitrile derivatives 24 in good to almost quantitative yields with high *anti* selectivities (Scheme 13a). The reaction scope appears to be broad as various alkynoates with either electron-donating or electron-withdrawing groups at different positions of aromatic rings of the β-substituent were well tolerated.

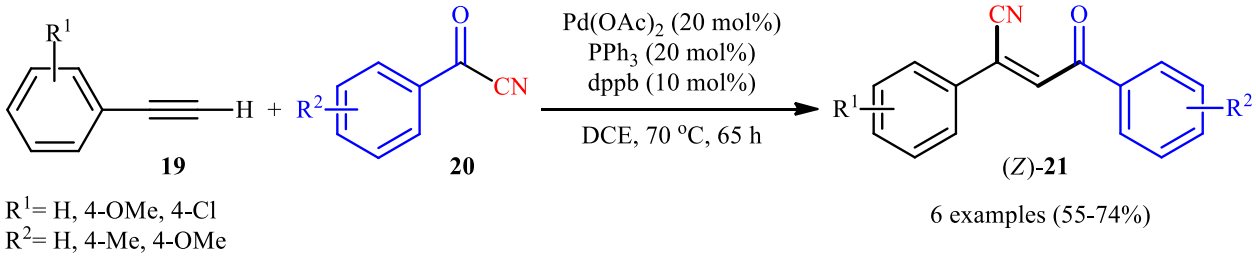
Notably, natural products such as sugar and cholesterol derivatives were also compatible with this scenario. However, 2-tolyl- and 4-benzonitrile-substituted alkynoate did not react at all. According to the author proposed mechanism (Scheme 13b), this cyanoacylation reaction proceeds through the formation of zwitterionic allenolate intermediate A *via* the conjugate addition of the phosphine to the alkynoate 23. Subsequently, a nucleophilic acyl substitution of acyl cyanide 22 with zwitterion A affords phosphonium cyanide B. Afterwards, conjugate addition of the cyanide ion into the β-phosphonium acrylate counterpart in B leads to the intermediate C. Finally, elimination of phosphine from C affords the observed acrylonitriles 24.

5. Cyanoesterification of alkynes

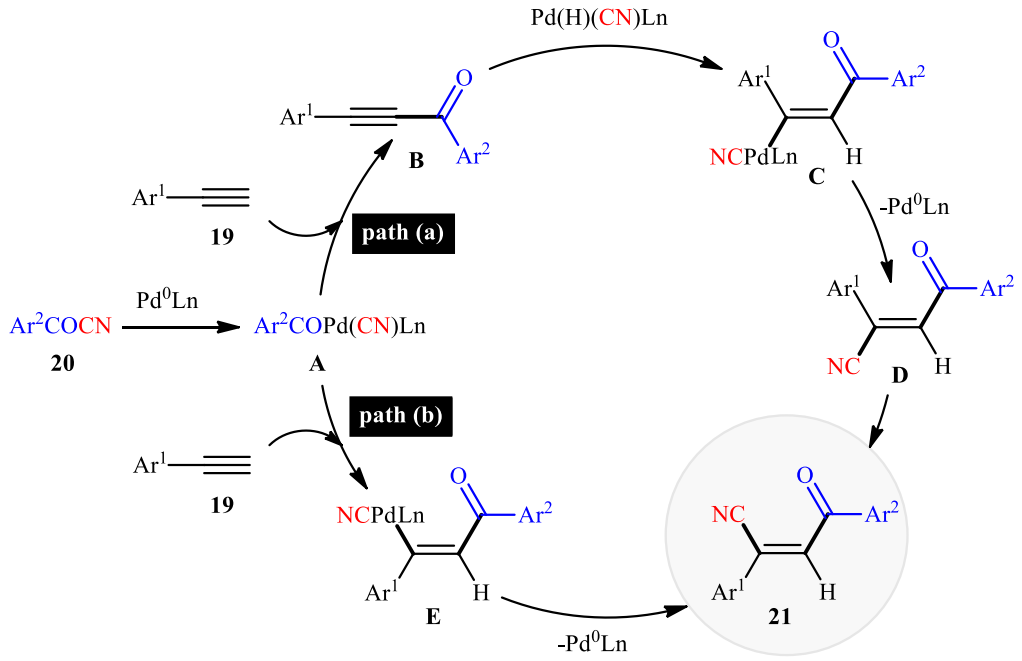
In 2010, Nakao and Hiyama along with their co-workers reported the first and only example of the direct cyanoesterification of alkynes into β-cyano-substituted acrylates [32]. They showed that various internal alkynes 25 underwent smooth cyanoesterification with alkyl cyanoformates 15 in the presence of 5 mol% of $Ni(cod)_2$ as a catalyst, 20 mol% of tris[3,5-bis(trifluoromethyl)phenyl]phosphine ($P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$) as a ligand, and 20 mol% of an organoboron Lewis acid [$B(C_6F_5)_3$ or BPh_3] in toluene or 1,4-dioxane at 35°C.

The corresponding β-cyano-substituted acrylates 26 were obtained in fair to high yields (Scheme 14). Notably, the nature of Lewis acid and solvent had a major impact on the regioselectivity of products. Thus, when the reaction was performed in toluene using $B(C_6F_5)_3$ as a Lewis acid, the cyano group is predominantly placed on the carbon atom adjacent to the bulkier substituent and carbonyl group added to the carbon atom near the sterically less hindered substituent.

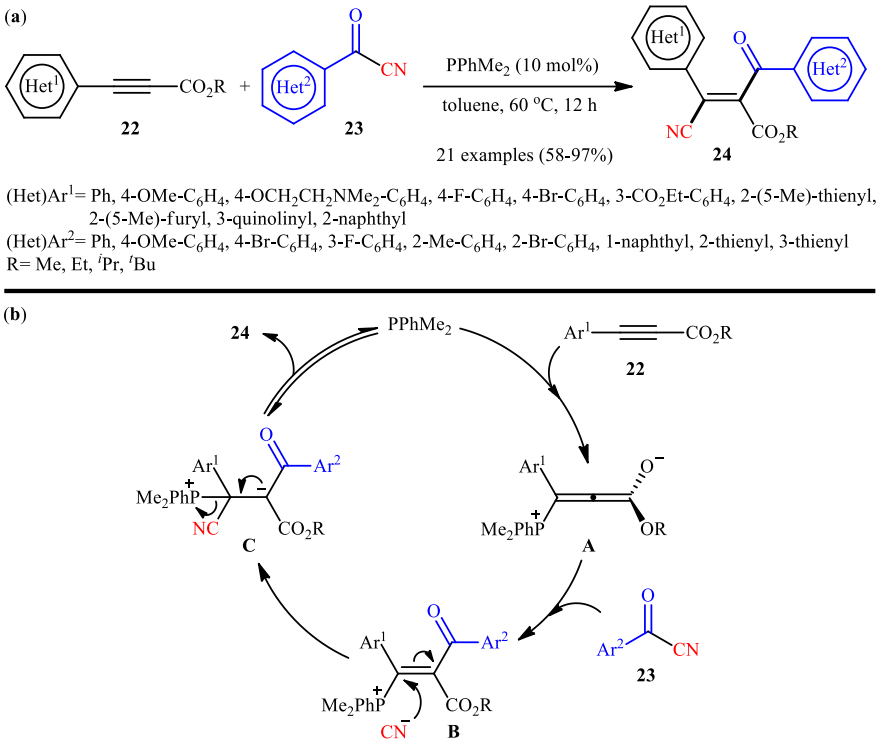
On the other hand, performing the process in 1,4-dioxane in the presence of BPh_3 provided products with opposite regioselectivity. It is worth noting that in this study, a library of nine β-cyano-substituted acrylamides was also efficiently synthesized through the direct cyanoamidation of corresponding alkynes with cyanoformamides. In 2017, Zhu *et al* theoretically investigated the mechanistic details of this cyanoesterification reaction with the DFT method and provide a rational explanation of the "Lewis acid effect" [33].



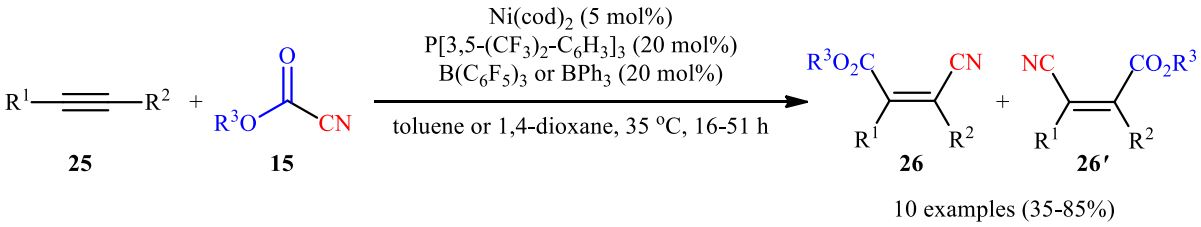
Scheme 11. Takaya's synthesis of β-cyano α,β-unsaturated ketones 21.



Scheme 12. Plausible mechanism for the formation of β-cyano α,β-unsaturated ketones 21.



Scheme 13. Ohmiya-Sawamura's synthesis of tetrasubstituted acrylonitrile derivatives 24.



R[1]= Me, *i*Bu, *n*Hex, $(CH_2)_2OSiMe_2{}^tBu$, $(CH_2)_3CO_2Me$, $(CH_2)_3NPhth$, $(CH_2)_2CH{=}C(Me)(CH_2)_2CH{=}C(Me)_2$, $SiMe_3$
R[2]= *i*Pr, *t*Bu, $SiMe_3$
R[3]= Me, Et

Scheme 14. Nakao-Hiyama's synthesis of β-cyano-substituted acrylates 26.

6. Conclusion

The direct vicinal cyano-acylation/-esterification of unsaturated hydrocarbons has recently emerged as the reliable and powerful approach for the one-pot synthesis of β-cyano carbonyl compounds from easily accessible starting materials, featuring high atom and step efficiency while minimizing waste generation. Despite the remarkable progress made in this intriguing research arena, the field is still in its early stages and requires further research and improvements to reach maturity.

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