Enantioselective Carbocyanations

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Asymmetric Intramolecular Carbocyanation of Unsaturated Olefins via C-C Bond Activation**

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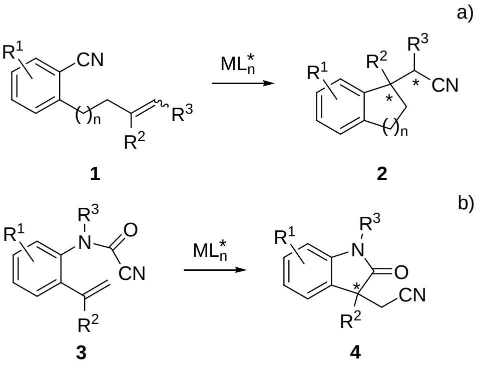
Keywords:
asymmetric catalysis · carbocyanation · nickel
· palladium · carbon-carbon bond

Every organic functional group coordinates with each transition metal in a characteristic manner. Upon coordination, the reactivity of these functional groups is often dramatically altered. In this way the normal reactivity patterns of functional groups can be inverted, and unconventional transformations can be achieved with facility. Most organometallic reactions are highly specific, able to discriminate between structurally similar sites, thus avoiding the standard protection-deprotection sequences. Transition metal complexes containing metal-carbon σ-bonds are intermediates to a majority of transformations leading to the formation of carbon-carbon bonds (with identical or different hybridization), which are of supreme importance in organic synthesis.[1]

The generation of an all-carbon quaternary center is always a complicated task, mainly due to the steric repulsions between the four substituents.[2,3] The situation in which the four substituents differ, quaternary stereocenters become an extraordinary challenge for achieving an efficient asymmetric synthesis of chiral organic compounds.[4] In this way, the development of new strategies in this particular asymmetric catalysis represents a very active research area worldwide, which was boosted by Knowles, Noyori, Sharpless, and Kagan. Moreover, and compared to enzymatic processes, these chemical methods exhibit a broader substrate range, providing separately both enantiomers of each product by a simple switch of the absolute configuration of the catalyst.

At present, few methods are reported in the literature concerning the catalytic enantioselective construction of all-carbon quaternary stereocenters,[2,3] one of them being the intramolecular aryl- and acyl-cyanation of unactivated olefins (Scheme 1a and 1b, respectively), where benzo-condensed cyclic compounds **2** and **4** can be prepared.

Due to its strength (>100 kcal/mol) the target carbon-carbon σ-bond (C-CN) is kinetically inert and its activation is limited to systems in which relief of strain or aromatization serves as driving force.[1b] A notable exception to this is the oxidative addition of unstrained C-CN bonds of nitriles without neighboring coordinating groups. It is well known the usefulness of nitriles as ligands in transition metal complexes, and the overall stability of them. However, a group of low valent transition metals such as Ni^{0},[5] Rh^{III},[6] Pd^{0},[5a,f] Pt^{0},[5a,f,7] Fe^{II},[8] Cu^{II},[9] and Mo^{II},[10] are able to cleave this carbon-carbon bond under thermal or, in less extension, photolytic conditions. In spite of the high dissociation energy of the aromatic nitriles versus aromatic halogenides ($D_{\text{Ar-X}}$ decreases I < Br < Cl < CN < F),[11] substituted benzonitriles have been used in cross-coupling[12] and amination reactions,[12c] although the most important application of this homolitic C-CN bond cleavage can be found in the carbocyanation of unactivated alkenes and alkynes.



M = Ni^{0}, Pd^{0}
L* = chiral ligand

Scheme 1. General intramolecular aryl- and acylcyanation approaches.

The direct cleavage of an R-CN bond, followed by addition of both R and CN groups to a carbon-carbon double or triple bond, namely carbocyanation reaction, provides ready access to highly functionalized nitriles with perfect atom economy. Unlike the cross-coupling reaction involving benzonitriles, here the cyano group is incorporated to the final structure of the product. Thus, nickel-catalyzed arylcyanation of norbornene and norbornadiene[13] took place with a broad scope of substrates in a range of 56-95% yield (Scheme 2a). In the case of norbornadiene, the product **5** was generated in higher proportion, and, in both examples, a high *exo*-selectivity was achieved. Similarly, the C-CN bond of the alkyl,[14] allyl,[15] alkenyl,[14] alkynyl,[16] and aryl cyanides[14, 17] were successfully cleaved and added to a carbon-carbon triple bond affording α,β-unsaturated nitriles **6** and **7** (Scheme 2b). The double insertion reaction occurred, as expected, by the same face of the unsaturated bond.

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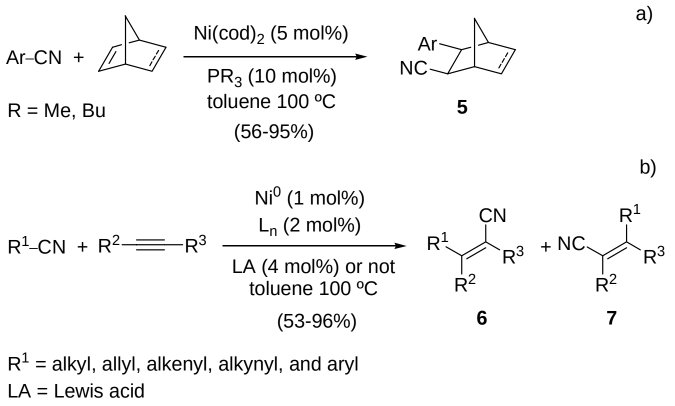
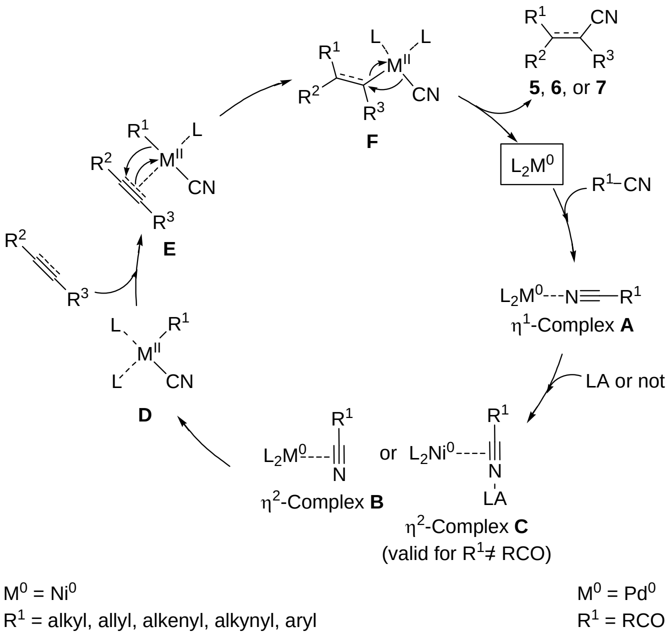

a)
Ar–CN +
Ni(cod)$_2$ (5 mol%)
PR$_3$ (10 mol%)
toluene 100 ºC
(56-95%)
R = Me, Bu
Ar
NC
5
b)
R^1–CN + R^2—≡—R^3
Ni^0 (1 mol%)
L$_n$ (2 mol%)
LA (4 mol%) or not
toluene 100 ºC
(53-96%)
6
7
R^1 = alkyl, allyl, alkenyl, alkynyl, and aryl
LA = Lewis acid

Scheme 2. Intermolecular carbocyanation reactions.

In the carbocyanation of alkynes shown in the Scheme 2b, the presence of the Lewis acid has a dramatic effect in the acceleration of the reaction rate. This co-catalyst activated selectively the R-CN bond in all type of nitriles such as it is shown in the general mechanism described in Scheme 3 (η^2-complex **C**). The driving force of this reaction would be attributable to: a) the high affinity exhibited by transition metals to nitriles (η^1-complex **A** and η^2-complexes **B** and **C**, Scheme 3); b) the withdrawing nature of the cyano group; and c) the strong M-CN linkage (complexes **D**, **E**, and **F** of the Scheme 3) resulting from the activation of the C-CN bond. In particular, η^2-coordination triggers the activation of the C-CN bond via oxidative addition affording the nickel(II) complex **D**, which undergoes the double insertion of the R and the CN groups into the unsaturated system yielding compounds **5**, **6**, or **7** and the catalytic M^0 species.[17c] The planar Ni^{II} complexes **D**, **E**, and **F** are the responsible of the *exo*-selectivity in bicyclic alkenes and also of the preferred approach of the R^1 group towards the region occupied by the smaller R^2 or R^3 alkyne substituents. In other words, the geometry of the coordination complex **E** is valid exclusively when R^2 is smaller than R^3.

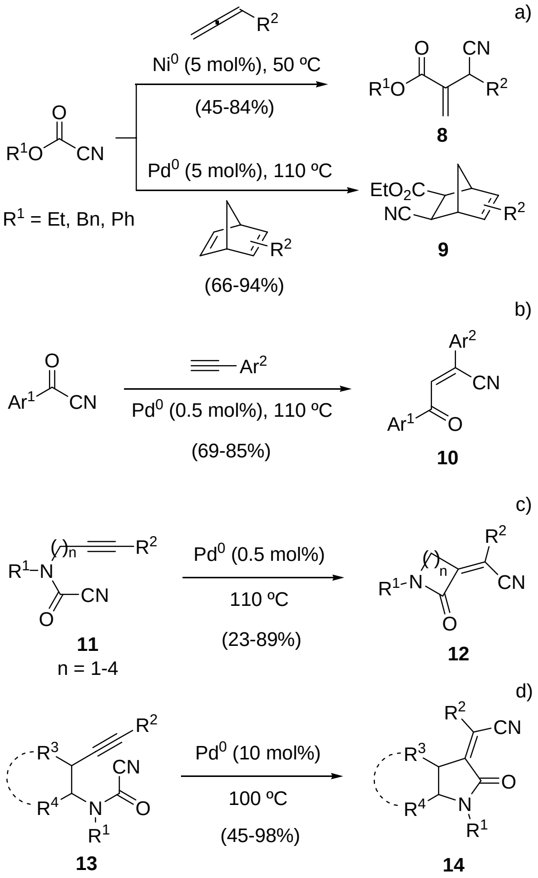
The acylcyanation consists on a direct cleavage of a RCO-CN bond, followed by the addition of both RCO and CN groups to an unsaturated carbon-carbon bond. The acyl cyanides are activated by palladium(0) complexes at high temperatures. In fact, aroyl cyanides underwent decarbonylation and further coupling of the aryl and the cyano groups to yield benzonitriles.[18] This process has been successfully redirected to the acylcyanation of allenes,[19] alkenes,[19b, 20] and alkynes.[19b,20b, 21] Inter- and intramolecular processes afforded different type of attractive polyfunctionalized linear products (Scheme 4a and 4b) as well as carbo- and heterocycles (Scheme 4c and 4d). For example, the synthesis of the racemic compound **2** has been described with Pd^0 complexes as catalysts in 68->99% yield at 130 ºC (Scheme 1b).[20b]

The so called cyanoesterification takes place by cleavage of the corresponding cyanoformate. The double insertion onto allenes (central and proximal carbon atoms) and bicyclic olefins gave raise stereoselectively to products **8** and **9** in good yields (Scheme 4a). Although the acylcyanation is almost exclusively a Pd^0 governed process, the unique Ni^0-promoted transformation was described for the double insertion onto this allene moiety.[19] The cyanoamidation of alkenes and alkynes **11** and **13** is a different version of the last described strategy, able to generate interesting small and medium size heterocycles of the type **12** and **14** in good yields (Scheme 4c and 4d).[19b,20b,21]


R^1 CN
R^2 R^3
5, 6, or 7
L$_2$M^0
R^1–CN
L$_2$M^0---N≡—R^1
η^1-Complex A
LA or not
L$_2$M^0---
R^1
N
or L$_2$Ni^0----
N
LA
η^2-Complex B
η^2-Complex C
(valid for R^1≠ RCO)
D
E
F
M^{II}
L
CN
M^0 = Ni^0
R^1 = alkyl, allyl, alkenyl, alkynyl, aryl
M^0 = Pd^0
R^1 = RCO

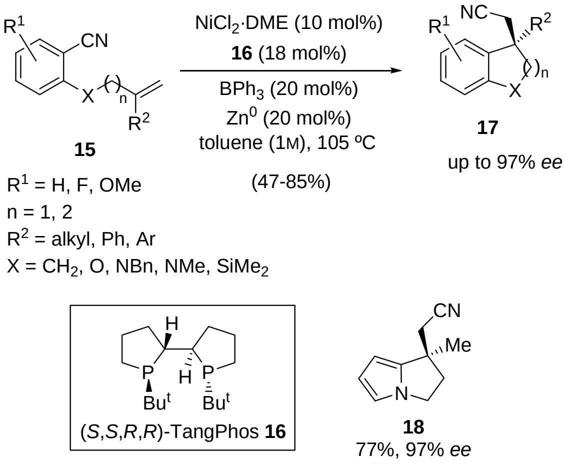
Scheme 3. General mechanism for the carbocyanation of unsaturated systems.

The most accepted mechanism is described in the general carbocyanation process shown in Scheme 3. Here, the different R^1 nature (RCO group) makes possible the undesired side reaction exhibited by complexes **D** and **E**, which can undergo decarbonylation before the direct insertion reaction to give complexes **F**. Fortunately, the rate of the decarbonylation step is somewhat slower than the transfer of the whole acyl group.


a)
R^2
Ni^0 (5 mol%), 50 ºC
(45-84%)
R^{1}O CN
R^1 = Et, Bn, Ph
Pd^0 (5 mol%), 110 ºC
(66-94%)
8
EtO$_2$C
NC
9
b)
Ar^1 CN
Ar^2
Pd^0 (0.5 mol%), 110 ºC
(69-85%)
10
c)
R^1–N
11
n = 1-4
Pd^0 (0.5 mol%)
110 ºC
(23-89%)
12
d)
R^3
R^4
13
Pd^0 (10 mol%)
100 ºC
(45-98%)
14

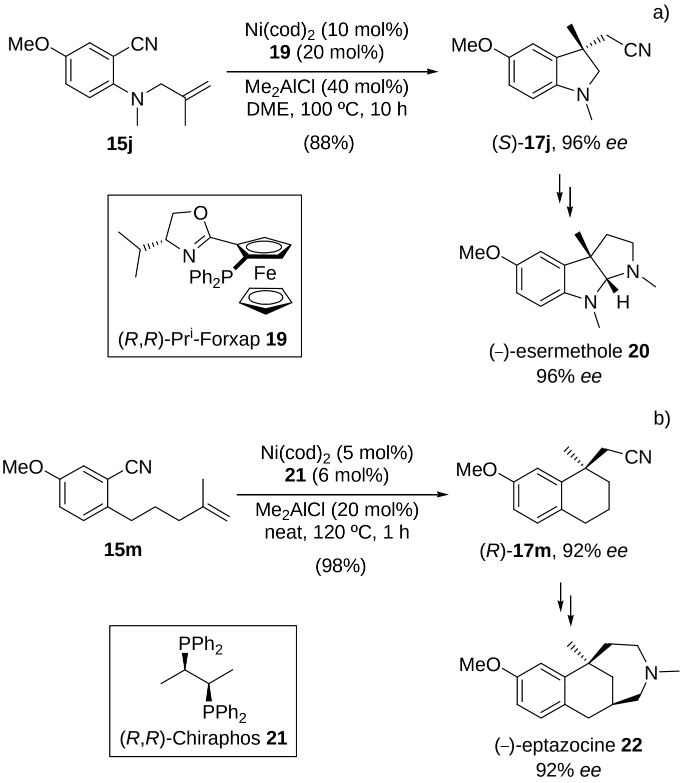
Scheme 4. Several examples of acylcyanations.

To the best of our knowledge, there are only two simultaneous recent publications dealing with an enantioselective arylcyanation of unactivated alkenes. The first one described the use of chiral Ni^0 complexes in the presence of a Lewis acid (BPh_3) as co-catalyst.[22] The presence of zerovalent Zn was found to be crucial in order to avoid the isomerization of the olefin **15** as major competing pathway. This detail was observed in the initial isomerization of cycloocta-1,5-diene towards cycloocta-1,3-diene. The reactions involving starting materials **15** (X = CH_2 or O) and chiral monophosphanes were generally low yielding and displayed poor enantioselectivity. Bidentate ligands were also tested in this 5- or 6-*exo-trig*-cyclization obtaining the highest enantioselections when (*S*,*S*,*R*,*R*)-TangPhos ligand **16** was employed. Compounds **17** were obtained in good yields (47-85%) and very high enantioselectivity (up to 97% *ee*, Scheme 5). This methodology also allowed to obtain fused nitrogenated heterocycles, demonstrating its applicability to construct heteroaromatic frameworks. The proposed mechanism involves species represented in Scheme 3, the Lewis acid coordinated to the nitrile moiety being an activation towards oxidative addition.[22]



Scheme 5. First catalytic enantioselective arylcyanation.

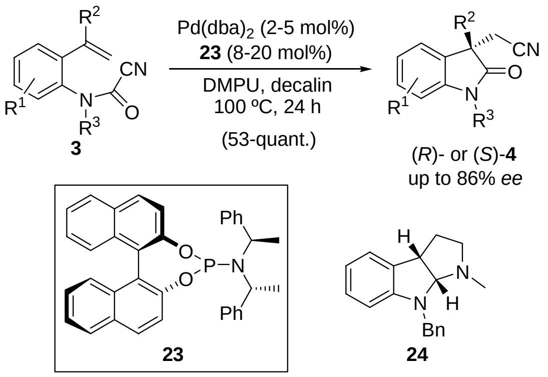
In the second publication alkenes **15** (X = CH_2, NMe, NBn, $SiMe_2$) were used to study the synthesis of racemic mixtures of **17** (48-95% yield) but employing Me_2AlCl as Lewis acid instead of BPh_3 in toluene at 100 ºC.[23] The authors suggested that the insertion step through a tetra or a pentacoordinate intermediate (**D**→**E**, Scheme 3) or the omitted ligand exchange was the rate determining step. The asymmetric version of this reaction was focused on the synthesis of natural products such as (–)-esermethole **20**,[24] precursor of potent acetylcholinesterase inhibitors, and compound (*R*)-**17m**, which is a synthetic precursor of (–)-eptazocine **22**,[25] an analgesic substance commercially available (Scheme 6). This nickel(0)-catalyzed enantioselective acylcyanation of compounds **15j** and **15m**, using almost identical reaction conditions, was performed in the presence of different chiral ligands. Thus, the best enantioselection for the product (*S*)-**17j** (96% *ee*) was achieved by intermediacy of ferrocenylphosphane (*R*,*R*)-Pr^i-Forxap **19**, whilst (*R*,*R*)-Chiraphos **21** was the most appropriate chiral diphosphane to catalyze the cyclization of the alkene **15m** furnishing (*R*)-**17m** in both excellent yield (98%) and enantioselectivity (92% *ee*), avoiding the non-desired isomerization of the alkene (Scheme 6).



Scheme 6. Synthetic applications of the catalytic enantioselective arylcyanation.

The first catalytic enantioselective acylcyanation (also called cyanoamidation) was recently reported in the synthesis of oxindoles **4** using cyanoformamides **3**.[26] These chiral heterocyclic structures are of paramount importance in the synthesis of a wide number of natural products based on this specific heterocyclic framework.[27] The process was catalyzed by palladium(0) species (2-5 mol%) and chiral binol-derived phosphoramidite **23** (8-20 mol%), and the corresponding oxindoles **4** were isolated in good to quantitative yield and high enantioselections (up to 86% *ee*, Scheme 7). Initially, the reaction was performed in xylene at 130 ºC, but the addition of polar additives allowed to reduce the reaction temperature to 100 ºC, the best combination being *N*,*N*-dimethylpropyleneurea (DMPU, 1 equiv) in decalin. Although there is not an explicit explanation of this effect, it can be assumed that the transition state can be stabilized by this type of polar agents in an extreme hydrophobic environment promoted by decalin. The absolute configuration of the resulting new stereogenic center was confirmed by converting the corresponding enantioenriched product **4** (R^1 = H, R^2 = H, R^3 = Bn) into the (–)-esermethole surrogate **24** through two conventional steps (Scheme 7). The approach to the natural products **20** and **22** (Scheme 6) would be more advantageous employing this last Pd^0-catalyzed enantioselective acylcyanation.

Similarly to carbon-carbon bond generation, other different reagents such as TMSCN employing Ni^0 complexes[28] or cyanoboranes using Pd^0 complexes[29] can be inserted into an alkene, allene or alkyne giving rise to new C-Si/C-CN and C-B/C-CN bond formations, respectively. Another open research line would be the palladium-catalyzed three-component coupling of aryl halides, internal alkynes or alkenes, and an external cyanide source such as the environmentally friendly $K_4[Fe(CN)_6]$.[30] Obviously, this is not a proper carbocyanation reaction but it can be an interesting alternative/variant for obtaining the same compounds described in this highlight.



Scheme 7. Catalytic enantioselective acylcyanation.

In conclusion, it is very relevant the elaboration of all-carbon quaternary stereocenters through an enantioselective carbon-carbon bond formation involving a total atom economy. These asymmetric transformations are at their infancy and more active Pd^0 or Ni^0 catalytic complexes are needed in order to decrease the operation temperature with the objective of increasing the enantioselection of the process. In general, Ni^0 and Pd^0 catalytic complexes are preferred for the arylcyanation and acylcyanation, respectively, obtaining in both cases good yields and excellent enantioselections. These reactions are also much more attractive because they are versatile and tolerate a large number of functional groups, especially in the case of oxindole derivatives, which are precursors of a myriad of natural or biologically active products. The improvements of the enantioselective reactions depicted in Schemes 6 and 7, the search for an intermolecular enantioselective carbocyanation of alkenes affording products collected in Schemes 2 and 4, and the possibility to recover the chiral catalytic complex would be important goals to achieve by synthetic organic chemists.

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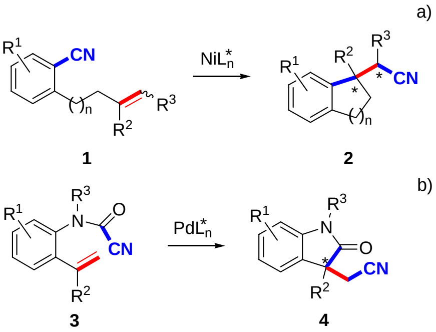

L^* = chiral ligand

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