Enantioselective Carbocyanations

DOI: 10.1002/anie.200805601

Asymmetric Intramolecular Carbocyanation of Alkenes by C–C Bond Activation**

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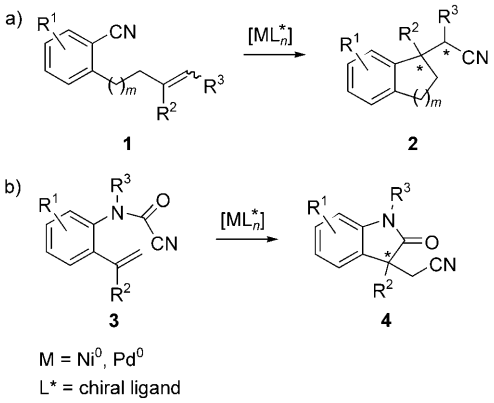
asymmetric catalysis · carbocyanation · nickel · palladium

Each organic functional group that coordinates with a transition metal does so 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 and able to discriminate between structurally similar sites; thus standard protection–deprotection sequences can be avoided. Transition-metal complexes containing metal–carbon σ bonds are intermediates in most transformations leading to the formation of carbon–carbon bonds (with identical or different hybridization)—reactions of supreme importance in organic synthesis.[1]

The generation of an all-carbon-substituted quaternary center is always a demanding task, mainly because of the steric repulsion between the four substituents.[2,3] Chiral organic compounds in which the quaternary stereocenter has four different substituents present an extraordinary challenge for achieving an efficient asymmetric synthesis.[4] The development of new strategies in asymmetric catalysis is a very active research area worldwide, which has been boosted by Knowles, Noyori, Sharpless, and Kagan. Moreover, compared to enzymatic processes, these chemical methods exhibit a broader substrate range, providing separately both enantiomers of the product by a simple switch of the absolute configuration of the catalyst.

At present, few methods have been reported for the catalytic enantioselective construction of all-carbon-substituted quaternary stereocenters;[2,3] one of these is the intramolecular aryl- and acylcyanation of unactivated olefins (Scheme 1 a and b, respectively), whereby the benzo-fused cyclic compounds **2** and **4** can be prepared.



Scheme 1. General intramolecular aryl- and acylcyanation approaches.

Owing to its strength (> 100 kcal mol^{-1}), the carbon–carbon σ bond to be broken, C–CN, is kinetically inert, and its activation is limited to systems in which relief of strain or aromatization serves as the driving force.[1b] A notable exception to this is the oxidative addition of unstrained C–CN bonds of nitriles without neighboring coordinating groups. The usefulness of nitriles as ligands in transition-metal complexes and their overall stability are well known. However, a number of low-valent transition-metal complexes containing 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 photolytic conditions. Although the dissociation energy of aryl nitriles is high relative to that of aryl halides ($D_{Ar\text{-}X}$ increases I < Br < Cl < CN < F),[11] substituted benzonitriles have been used in cross-coupling[12] and amination reactions.[12c] The most important application of this homolytic cleavage of the C–CN bond is the carbocyanation of unactivated alkenes and alkynes.

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 a 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, the nickel-catalyzed arylcyanation of norbornene and norbornadiene[13] took place with a broad range of substrates in 56–95% yield (Scheme 2 a). In the case of norbornadiene, the product **5** was generated in higher proportion, and, in both examples,

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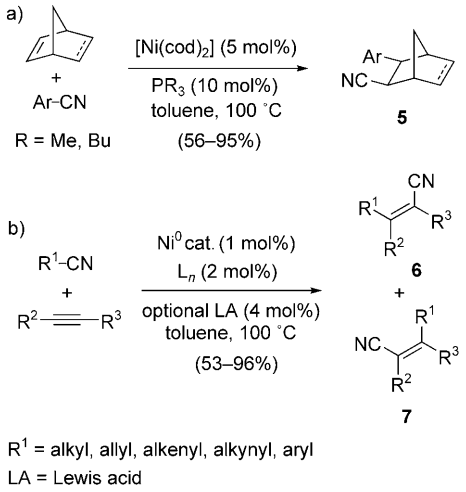
[**] We thank the Spanish Ministerio de Ciencia e Innovación (Consolider INGENIO 2010 CSD2007-00006, CTQ2007-62771/BQU), Generalitat Valenciana, and the University of Alicante for financial support.



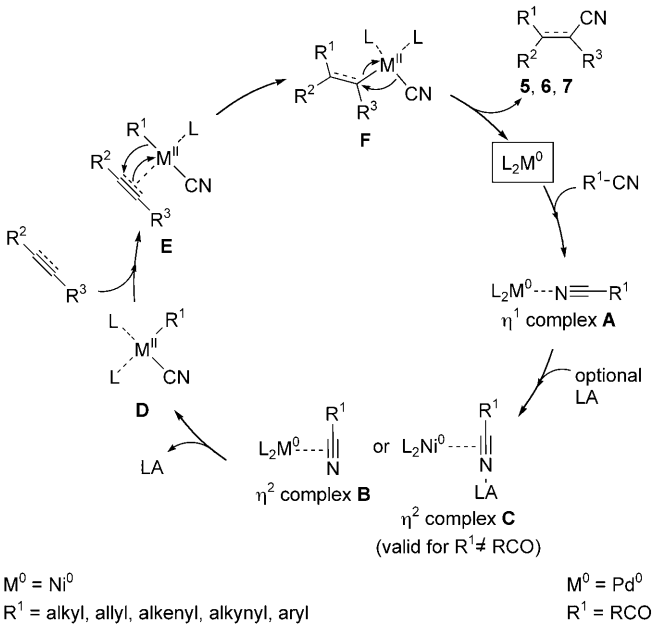
Scheme 2. Intermolecular carbocyanation reactions. cod = cycloocta-1,5-diene.

high *exo* selectivity was achieved. Similarly, the C–CN bond of alkyl,[14] allyl,[15] alkenyl,[14] alkynyl,[16] and aryl cyanides[14,17] was successfully cleaved and added to alkynes affording α,β-unsaturated nitriles **6** and **7** (Scheme 2b). The two insertions occurred, as expected, on the same face of the unsaturated bond.

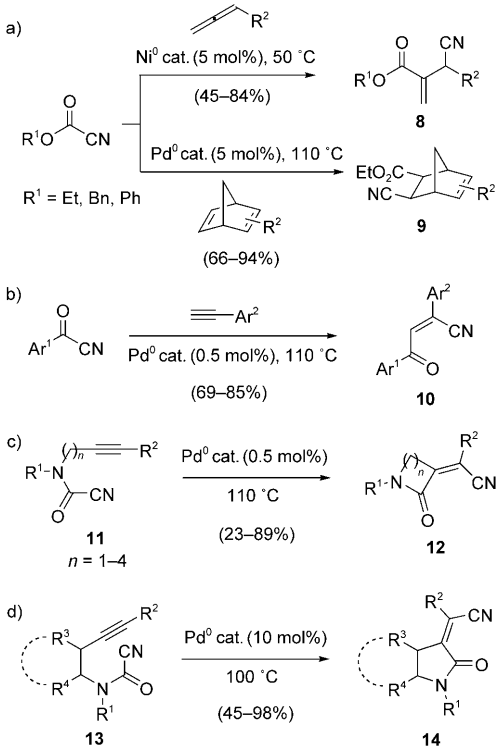
In the carbocyanation of alkynes shown in the Scheme 2b, the presence of a Lewis acid has a dramatic effect on the acceleration of the reaction rate. This co-catalyst selectively activates the R–CN bond in all types of nitriles, as depicted in the general mechanism shown in Scheme 3 (η^2 complex **C**). The driving force of this reaction is attributable to 1) the high affinity of transition metals for nitriles (η^1 complex **A** and η^2 complexes **B** and **C**); 2) the withdrawing nature of the cyano group; and 3) the strong M–CN linkage (complexes **D**–**F**) resulting from the activation of the C–CN bond. In particular, η^2 coordination triggers the activation of the C–CN bond by oxidative addition, affording the nickel(II) complex **D**, which mediates the double insertion of the R and the CN groups into the unsaturated system yielding compounds **5**, **6**, or **7** and the catalytic L_2M^0 species.[17c] The planar Ni^{II} complexes **D**–**F** are responsible for the *exo* selectivity in reactions with bicyclic alkenes and also for the preferred approach of the R^1 group towards the region occupied by the smaller R^2 or R^3 substituents on the alkyne. In other words, the geometry of the coordination complex **E** is valid only when R^2 is smaller than R^3.

The acylcyanation consists of the direct cleavage of an RC(O)–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 afford different types of attractive polyfunctionalized linear products (Scheme 4a,b) as well as heterocycles (Scheme 4c,d). For example, the synthesis of racemic **2** has been described with Pd^0 complexes as the catalyst in 68 to 99% yield at 130 °C (Scheme 1b).[20b]

The so-called cyanocarboxylation takes place by cleavage of the corresponding cyanoformate. The double insertion into allenes (central and proximal carbon atoms) and bicyclic olefins gives rise stereoselectively to products **8** and **9** in good



Scheme 3. General mechanism for the carbocyanation of alkenes and alkynes.

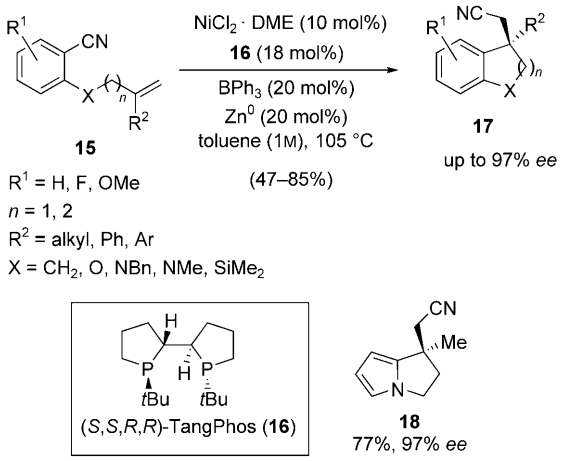


Scheme 4. Several examples of acylcyanations.

yields (Scheme 4a). Although acylcyanation is almost exclusively a Pd^0-governed process, the unique Ni^0-promoted transformation was described for the double insertion into this allene moiety.[19] The cyanoamidation of alkenes and alkynes **11** and **13** is a different version of this strategy and generates interesting small and medium-sized heterocycles of type **12** and **14** in good yields (Scheme 4c, d).[19b,20b,21]

The accepted mechanism for cyanoesterification follows along the lines of the general carbocyanation process (Scheme 3). In this case, since $R^1 = RCO$, the undesired decarbonylation of complexes **D** and **E** is possible before the direct insertion reaction to give complexes **F**. Fortunately, the rate of the decarbonylation step is somewhat lower than the transfer of the whole acyl group.

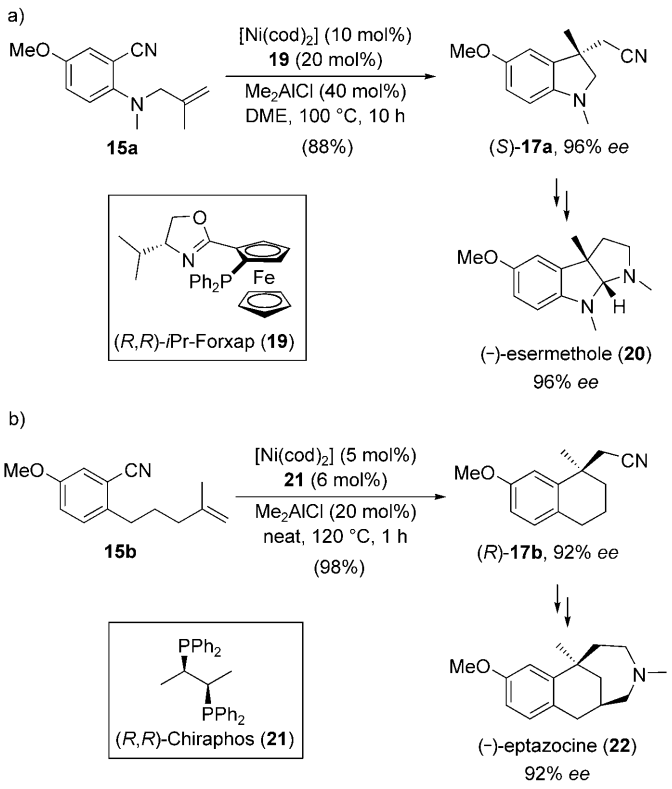
To the best of our knowledge, there are only two simultaneous recent publications dealing with the enantioselective arylcyanation of unactivated alkenes (Scheme 5). The



Scheme 5. First catalytic enantioselective arylcyanation. DME = 1,2-dimethoxyethane.

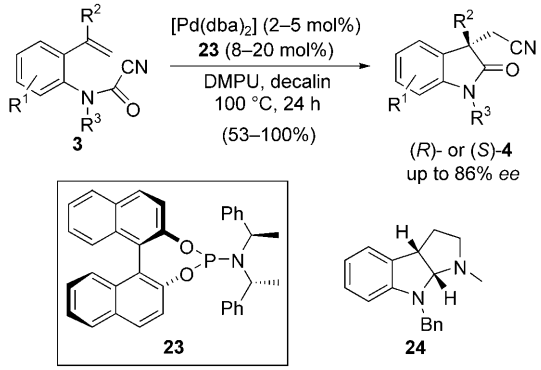
first describes the use of chiral Ni^0 complexes in the presence of a Lewis acid (BPh_3) as co-catalyst.[22] The presence of Zn^0 was found to be crucial to prevent the isomerization of the olefin **15**. This detail was observed in the initial isomerization of cycloocta-1,5-diene to cycloocta-1,3-diene. The reactions of 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, and the highest enantioselectivities were obtained when the ligand (*S*,*S*,*R*,*R*)-TangPhos **16** was employed. Compounds **17** were obtained in good yields (47–85%) and very high enantioselectivities (up to 97% *ee*, Scheme 5). This methodology provided access to benzo-fused N-heterocycles and is applicable for the construction of heteroaromatic frameworks. The proposed mechanism involves species represented in Scheme 3; activation towards oxidative addition results from coordination of the Lewis acid to the nitrile moiety.[22]

In the second publication, alkenes **15** (X = CH_2, NMe, NBn, $SiMe_2$) were used to generate racemic mixtures of **17** (48–95% yield); Me_2AlCl served as the Lewis acid instead of BPh_3 and the reactions were conducted in toluene at 100 °C.[23] The authors suggested that either the insertion step via a tetra- or a pentacoordinate intermediate (**D**→**E**, Scheme 3) or ligand exchange (not shown) was the rate-determining step. The asymmetric version of this reaction focused on the synthesis of natural products such as (−)-esermethole (**20**),[24] a precursor of potent acetylcholinesterase inhibitors, and compound (*R*)-**17b**, which is a synthetic precursor of (−)-eptazocine (**22**),[25] a commericially available analgesic (Scheme 6). This nickel(0)-catalyzed enantioselective arylcyanation of compounds **15a** and **15b** was performed under almost identical reaction conditions with various chiral ligands. Thus, for the synthesis of (*S*)-**17a** the best results (96% *ee*) were obtained in the presence of ferrocenylphosphane (*R*,*R*)-*i*Pr-Forxap **19**, whilst (*R*,*R*)-Chiraphos **21** was the most appropriate chiral diphosphane for the cyclization of alkene **15b** to furnish (*R*)-**17b** (98% yield, 92% *ee*), avoiding the undesired 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** (Scheme 7).[26] These chiral heterocyclic structures are of paramount importance in the synthesis of numerous natural products based on this specific heterocyclic framework.[27] The process was catalyzed by a palladium(0) species (2–5 mol%) and a chiral binol-derived phosphoramidite **23** (8–20 mol%), and the corresponding oxindoles **4** were isolated in good to quantitative yield and high enantioselectivitiy (up to 86% *ee*, Scheme 7).



Scheme 7. Catalytic enantioselective acylcyanation. dba = dibenzylideneacetone.

Initially, the reaction was performed in xylene at 130 °C, but when a polar additive was included the reaction temperature could be reduced to 100 °C; the best conditions proved to be *N*,*N*-dimethylpropyleneurea (DMPU, 1 equiv) in decalin. Although this effect cannot be explained explicitly, it can be assumed that the transition state is stabilized by the polar agent in the extremely hydrophobic environment provided by the decalin solvent. 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 by this last Pd^0-catalyzed enantioselective acylcyanation.

In analogy to reagents used in carbon–carbon bond generation, other compounds such as TMSCN (with Ni^0 catalysis) [28] or cyanoboranes (with Pd^0 catalysis) [29] can be reacted with alkenes, allenes, or alkynes giving rise to new C–Si/C–CN and C–B/C–CN bonds, respectively. Another open line of research 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 method for obtaining the same compounds described in this Highlight.

In conclusion, the elaboration of all-carbon-substituted quaternary stereocenters through enantioselective carbon–carbon bond formation with total atom economy is very relevant. These asymmetric transformations are in their infancy, and more active Pd^0 or Ni^0 catalytic complexes are needed in order to lower the operation temperature and increase the enantioselectivity of the process. In general, Ni^0 and Pd^0 complexes are preferred for the arylcyanation and acylcyanation, respectively; in both cases good yields and excellent enantioselectivities are obtained. These reactions are also 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 and/or biologically active products. Improvements of the enantioselective reactions depicted in Schemes 6 and 7, the search for an intermolecular enantioselective carbocyanation of alkenes affording products shown in Scheme 2 and 4, and the possibility of recovering the chiral catalytic complex are important goals for synthetic organic chemists.

Published online: February 6, 2009

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