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Efficient and clean nickel catalyzed α-allylation reaction of nitriles

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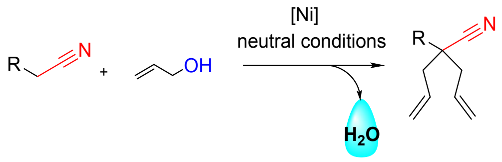
Abstract. A clean method has been developed for the α -allylation of phenyl and alpha alkyl phenyl acetonitrile with allylic alcohols. The reaction is catalyzed by nickel complexes in situ generated from a combination of $Ni(cod)_2$ and the dppf ligand and performed at 80°C in methanol as reaction solvent. Accordingly to this simple and base-free protocol that only yields water as a side-product, many allylic nitriles were synthetized with good yields.

Keywords: allylation; nickel; nitrile; allylic alcohol

Introduction

Allylic alkylation reactions remain one of the most powerful tools for the formation of homo (C-C) and hetero (C-O, C-N, C-S) bonds.[1] The introduction of the allylic moiety is particularly attractive as it allows subsequent chemical transformations based on the C=C bond reactivity.[2] Commonly used allylation reagents bear good leaving groups like acetate, carbonate or halide. Such reagents are however limited to the low atom economy related with their use that often results in the production of large amounts of side products such as salts. In comparison to other reagents, allylic alcohols could be advantageously used. At a first stand, it is noteworthy that most of the commonly used allylation reagents are synthesized from allylic alcohols. The direct use of allylic alcohols in allylation reactions is more straightforward and consistent with a step economy. It is also noteworthy that their use generates only water as byproduct. In such case, this is related to the fact that the hydroxyl group acts as a base toward the nucleophile. On the point of view the accessibility, allyl alcohol is industrially produced from propene oxydation[3] and potentially accessible form vegetal feedstock like glycerol.[4] The main limitation with the use of allylic alcohols is related to the low reactivity of this reagent as the hydroxyl group is recognised as a weak leaving group. To activate allylic alcohols, catalytic amounts of transition metals are generally needed.[5] We reported very simple protocols of Ni-catalyzed allylic alkylation with allylic alcohol for the transformation of nucleophiles such as amides,[6] ketoesters and diketones,[7] malonates,[8] aldehydes[9] and ketones. [10] Beyond the use of more precious metals such as palladium,[11] iridium,[12] ruthenium,[13] platinum[14] and rhodium,[15] the use of nickel has opened up interesting prospects. This metal is abundant and inexpensive and it is noteworthy that nickel based catalysts prevent the addition of bases or other additives. [16] The highly efficient α-allylation of carbonyl compounds obtained with nickel-based catalysts [7-10] opens the question of the reactivity of nitriles (Scheme 1).

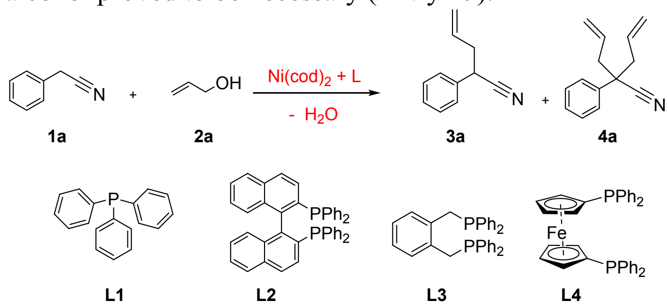
Nitriles are industrially used as precursors to many other functional groups such as carboxylic acids, aldehydes, ketones, and amines.[17] They are also available in many natural products and medicinal compounds.[18] In order to perform the alpha-allylation of this family of compounds, palladium-based catalysts have been commonly used. As examples, the direct coupling of allylic alcohols with weakly acidic pronucleophiles has been efficiently performed using catalytic $Pd(PPh_3)_4$ via activation of C-OH bonds with CO_2.[19] Allylic alcohols were also used as allylic reagents during the palladium catalyzed deacylative allylation of ketone enolates, α-arylcyanoacetones and α -arylcyanoacetic esters.[20] Other metals were likewise used as rhodium in the enantioselective metal-catalyzed allylic alkylation of nitriles with allyl benzoate[21] or iridium during allylation of cyanoacetates with allyl carbonate.[22] Herein, we wish to report the first nickel catalyzed α-allylation of nitriles with allyl alcohol performed under neutral conditions (Scheme 1).



Scheme 1. The nickel-catalyzed α-allylation of nitriles with allyl alcohol.

Results and discussion

The optimization of the reaction parameters was carried out with phenylacetonitrile **1a** and allyl alcohol **2a** (Table 1). The reaction led to the mono **3a** and the bis-allylated **4a** compounds (Scheme 2). Ni(cod)$_2$ associated with phosphorus ligands was used as catalyst precursor. The first experiments were performed in MeOH as solvent at 80°C for 17 h. The triphenylphosphine (PPh$_3$) ligand **L1** gave only 16 % yield into the monoallylnitrile **3a** although 2 equivalents of allyl alcohol were used (Entry 1). The use of diphosphines gave better results such bis(diphenylphosphino)-1,1'-binaphtyle (BINAP **L2**) with a global yield of 74 % (34 % monoallylated product **3a** and 40 % of bisallylated product **4a**) (Entry 2). The use of 1,2-bis[(diphenylphosphino)methyl]benzene **L3** (dppmb) gave similar results with a mixture of mono (36 %) and bis-allylated (35 %) products. It is noteworthy that **3a** was partially hydrolyzed in the corresponding amide (11 %) that has been isolated and fully characterized by ^{1}H and ^{13}C NMR whereas no product of hydrolysis of **4a** was never observed (Entry 3). Significantly better yields were obtained with the ferrocenyl ligand **L4** (dppf) that led to 25 % of **3a** and 60% yield of **4a** (Entry 4). In order to improve the conversion of the nitrile, the reaction temperature was increased to 100°C and 120°C (Entries 5 and 6). However, a higher temperature did not lead to better results but favored the hydrolysis of **3a**. Moreover the increase of the temperature up to 120°C resulted to a lower catalytic efficiency probably due to a catalyst decomposition at that temperature (Entry 6). As observed in previous studies that involved ketones and aldehydes as nucleophile,14, 15 the use of aprotic solvents such as toluene (Entry 7) or solvent-free conditions (Entry 8) led to reduced yields along with a larger part of hydrolysis. A remarkable yield of 80 % in **4a** was expectedly observed with sodium hydroxide as additive (Entry 9). The addition of a base probably favorably increased the concentration of the deprotonated nucleophile. On the other hand, it is thus not surprising that poor results were obtained in the presence of a strong acid such as PTSA (Entry 10). Finally, we varied the amount of the allyl alcohol **2a**. Reducing the number of allyl alcohol equivalents to 1 did not promote the monosubstitution in respect to the disubstitution but only contributed to reduce the overall conversion of **1a** (Entry 11). By increasing the number of equivalents up to 3, a comparable conversion of **1a** was observed (90 %) with yields in **3a** and **4a** of 20 % and 70 % respectively (Entry 12). Nevertheless, the yield in **4a** remained limited to 70 % with 2 equivalents of allylic alcohol (entry 14). In order to achieve a full conversion of the starting material and a very high selectivity in **4a**, a combination of higher catalyst loading up to 1.5 mol % and 3 equivalents of allyl alcohol proved to be necessary (Entry 15).



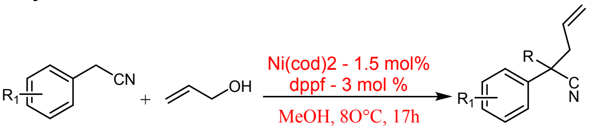
Scheme 2. Allylation of phenylacetonitrile **1a** and ligands used in the initial study.

Table 1. Optimization of the nickel catalyzed allylation of phenylacetonitrile with allyl alcohol.[a]

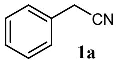
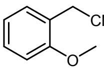
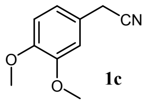
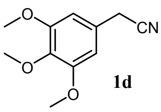
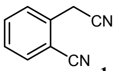
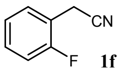
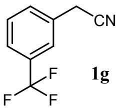
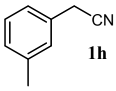
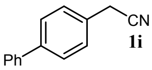
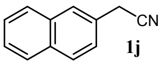
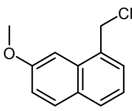
Entry	L	T (°C)	Solvent	Nb eq 2a	Yield (%)[b] 3a	4a
1	L1	80	MeOH	2	16	0
2	L2	80	MeOH	2	34	40
3	L3	80	MeOH	2	25+11[d]	35
4	L4	80	MeOH	2	25	60
5	L4	100	MeOH	2	25+5[d]	60
6	L4	120	MeOH	2	26+10[d]	5
7	L4	80	Toluene	2	24+34[d]	28
8	L4	80	neat	2	24+33[d]	28
9	L4	80	MeOH + 10 % NaOH	2	5	80
10	L4	80	MeOH + 2 % PTSA	2	2	0
11	L4	80	MeOH	1	30	14
12	L4	80	MeOH	3	20	70
13[c]	L4	80	MeOH	1	36	40
14[c]	L4	80	MeOH	2	30	70
15[c]	L4	80	MeOH	3	0	>99

[a] Conditions: **1a** (1.8 mmol), Ni(cod)$_2$: 1 mol%, $L_{diphosphine}$/Ni = 2, $L_{(monophosphine)}$/Ni = 4 , 17 h, in a sealed Schlenk tube.
[b] Determined by GC
[c] 1.5 mol% of catalyst
[d] Hydrolysis to the corresponding amide

Table 2. Reaction scope of the nickel catalyzed direct allylation of the alpha-aromatic acetonitriles with allyl alcohol. [a]



1a 2a R = H 3a-k R = H 4a-k

Entry	Nitrile 1a-k	GC Yield (%) 3	GC Yield (%) 4	Isolated yield of the major product (%)[b]
1	 1a	0	100	87(4a)
2	 1b	100	0	51(3b)
3	 1c	15	85	70(4c)
4	 1d	0	100	62(4d)
5	 1e	21	79	62(4d)
6	 1f	0	100	60(4f)
7	 1g	0	100	66(4g)
8	 1h	9	91	60(4h)
9	 1i	0	100	65(4i)
10	 1j	0	100	89(4j)
11	 1k	70	0	57(3k)

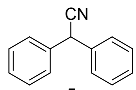
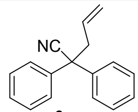
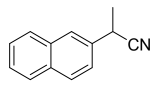
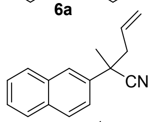
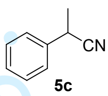
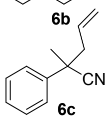
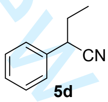
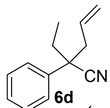
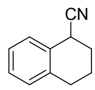
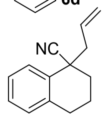
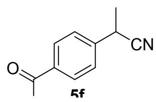
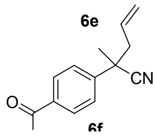
[a] Reaction conditions: **1a-k** (1.8 mmol), **2a** (5.4 mmol), $Ni(cod)_2$ (0.027 mmol), dppf (0.054 mmol), MeOH (0.5 mL), 17 h, T = 80°C in a sealed Schlenk tube.

[b] Isolated yield after silica gel chromatography.

Using the optimized conditions, we then examined the possibility to perform this reaction with alpha-monosubstituted acetonitriles bearing aromatic rings (Table 2). After isolation of the product, phenylacetonitrile 1a led to 87 % of **3a** yield (Entry 1, Table 2). The presence of a methoxy group on the ortho position oriented the synthesis toward the sole formation of the monoallylated derivative **3b** with a yield of 51 % (Entry 2). Good yields into the bisallylated product were observed with 3,4-dimethoxyphenylacetonitrile **1c** and 3,4,5-trimethoxyphenylacetonitrile **1d**, 70 and 62 % respectively (Entries 3 and 4). These results showed that the presence of methoxy groups on the meta and para positions of the aromatic ring did not bring significant steric hindrance. 2-cyanophenylacetonitrile **1e** and 2-fluorophenyl acetonitrile **1f** were efficiently diallylated and the compounds **3e** and **3f** were thus isolated with 70 % and 60 % yields respectively (Entries 5-6).

Table 3: Reaction scope of the nickel catalyzed direct allylation of the α,α disubstituted acetonitriles with allyl alcohol. [a]

5a-f 2a 6a-f

Entry	Nitrile 5a-f	Allylated product	Yield[b] 6a-f (%)
1	 5a	 6a	94
2	 5b	 6b	85
3	 5c	 6c	73
4	 5d	 6d	65
5	 5e	 6e	61
6	 5f	 6f	91

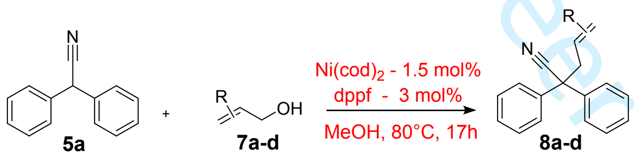
[a] Reaction conditions: **5a-f** (1.8 mmol), **2a** (5.4 mmol), $Ni(cod)_2$ (0.027mmol), dppf (0.054mmol), MeOH (0.5 mL), 17 h, T = 80°C in a sealed Schlenk tube. [b] Isolated yield after silica gel chromatography.

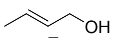
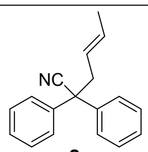
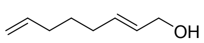
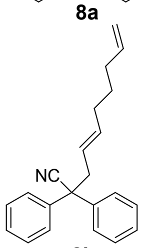
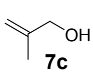
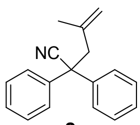
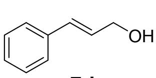
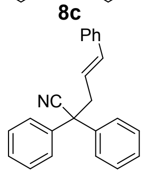
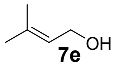
Very similar results were obtained with the fluorinated phenylacetonitrile **1g** (Entry 7). The 3-methylphenylacetonitrile **1h** and 4-biphenyl acetonitrile **1i** were converted in derivatives **3h** and **3i** with yields of 60 % and 65 % respectively (Entries 8-9). A very good yield was observed with naphthylacetonitrile **1j** of 89 % (Entry 10) while 7-methoxy-2-

naphthylacetonitrile **1k** gave only the monoallylated product **3k** with an isolated yield of 57 % (Entry 11). The higher steric hindrance due to the presence of the methoxy group likely impeded further substitution on the carbon atom.

Using the same conditions, the scope of the nitriles was extended to α,α-disubstituted acetonitriles. In that case, only monoallylation could be performed. It is noteworthy that in all cases reported in Table 3, complete conversions of the starting materials were observed. High isolated yields were obtained with diphenylacetonitrile **5a** and methyl-2-naphthylacetonitrile **5b** of 94 % and 85 % respectively (Entries 1 and 2). A slight decrease of yield with substrates bearing an electrodonor group was observed after isolation: α-methylphenylacetonitrile **5c**, α-ethylphenyl acetonitrile **5d** and 1,2,3,4-tetrahydronaphthalene-1-carbonitrile **5e** were converted with yields of 73 %, 65 % and 61 % respectively (Entries 3, 4 and 5). The 4-benzoyl-α-methylbenzeneacetonitrile **5f** was isolated with an excellent yield of 91 % (entry 6).

Table 4: Scope of the Ni-catalyzed allylation of diphenyl acetonitrile 5a with various allylic alcohols. [a]

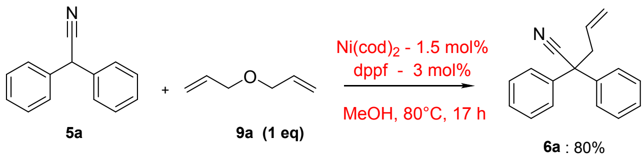


Entry	Allylic alcohol	Allylated product	Yield[b] 8a-d (%)
1	 7a	 8a	85
2	 7b	 8b	80
3	 7c	 8c	80
4	 7d	 8d	62
5	 7e	No product	0

[a] Reaction conditions: **5a** (1.8 mmol), **7a-d** (5.4 mmol), Ni(cod)$_2$ (0.027mmol), dppf (0.054mmol), MeOH (0.5 mL), 17 h, T = 80°C in a sealed Schlenk tube. [b] Isolated yield after silica gel chromatography. [c] 2 mol% of Ni(dppf)$_2$.

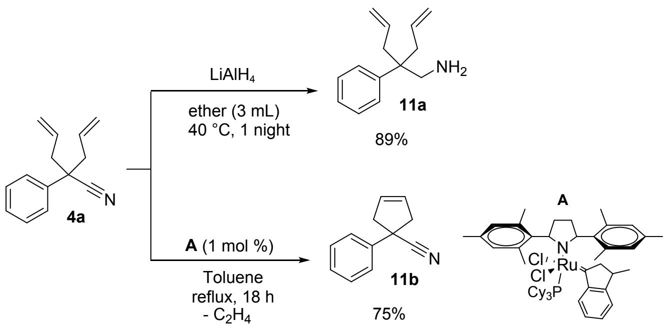
We further investigated different allylic alcohols with diphenylacetonitrile **5a** as substrate (Table 4). High yields were obtained with the allylic linear alcohols such as crotyl alcohol **7a** and octa-2,7-dien-1-ol **7b**, 85 % and 80 % respectively (Entries 1 and 2). A very similar result was obtained with 2-methyl-2-propen-1-ol **7c** as a branched alcohol (Entry 3). Cinnamyl alcohol (entry 4) could also be converted in the allylated derivative **8d** with 62% isolated yield. The linear allylic structure was selectively obtained and the branched isomer was not observed. However, the reaction with a more substituted alcohol such as 3-methyl-2-buten-1-ol **7d** did not give the allylated nitrile. The fact that this alcohol is more substituted disfavors the oxidative addition to a low valent Ni(0) intermediate.

As we previously reported for the allylation of ketones,[15] diallylether **9a** could also been involved in that reaction. As example with 2,2-diphenylacetonitrile **5a**, a good isolated yield of 80 % was then obtained by using 1 equivalent of diallylether **9a** (Scheme 3).



Scheme 3. The nickel-catalyzed α-allylation of α,α-diphenylacetonitrile with diallyether.

The diallylated nitriles can be further used in other transformations that involve either the allylic or the nitrile moieties. The reduction of the nitrile in the corresponding primary amine was accomplished with lithium aluminum hydride in ether leading to the diallylamine **11a**. The ruthenium catalyzed ring closing metathesis was also performed in high yield in refluxing toluene to form the cyclopentene ring along with the release of ethylene (Scheme 4).



Scheme 4: Transformations of diallylnitrile **4a.**

Conclusion

In conclusion, we have developed an efficient and very clean nickel-catalyzed process for the direct allylic alkylation of α-substituted nitriles with allyl alcohol. The reaction was carried out under neutral conditions giving only water as side product. A large variety of allylic nitriles were synthesized and different allylic alcohols were also investigated. Similar results were observed with diallylether in place of allyl alcohol. The thus obtained allylated derivatives can be further chemically modified through nitrile reduction or olefin metathesis reactions to generate a primary amine or a cyclopentene ring respectively. We believed that this methodology is relevant to straightforwardly produce new allyl compounds and derivatives.

Experimental Section

α-Allylation of phenylacetonitrile **1a** with allyl alcohol **2a**: In a Schlenk tube were placed first the catalytic precursor $Ni(cod)_2$ (1.5 mol %), then the ligand (3 mol %), the nitrile (1.8 mmol, 1 equiv.). Under nitrogen, freshly distilled and degassed allyl alcohol (3 eq.) or diallyl ether (1 eq.) were then added. Degassed MeOH (0.5 mL) was added under nitrogen and the reaction mixture was stirred at 80°C for 18 h. The reaction mixture was then concentrated under reduced pressure and the product was purified by silica gel column chromatography with petroleum ether/ethyl acetate (90/10) as eluent.

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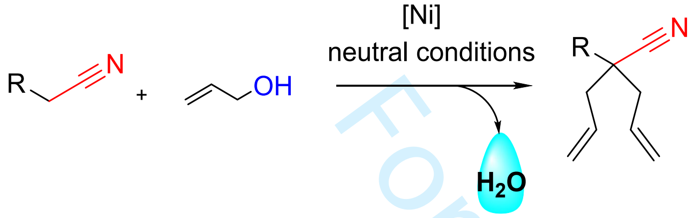

Nickel-based catalysts allow the alpha-allylation of nitriles under neutral conditions (no added base or co-reagent)