ARTICLE

The salt-free Nickel-Catalysed α-Allylation Reaction of Ketones with Allyl Alcohol and Diallylether

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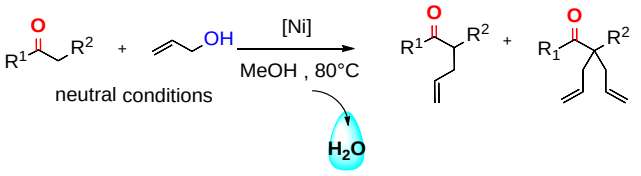
The nickel-catalysed α-allylation of ketones with allyl alcohol and diallylether has been performed under neutral conditions. As no base is involved, the products are synthesized without salts as side products. The dppf / Ni(cod)2 catalytic system in MeOH at 80°C has been shown as the most performant reaction conditions to afford tetrasubstituted derivatives from various cyclic and acyclic ketones with one or two mobile protons. This process combined with a metathesis step yields spirocyclic compounds according to a salt free synthetic sequence.

Introduction

Allylation reactions are among the most important reactions in organic chemistry for the formation of C-C, C-N and C-S bonds.[1] The terminal double bond of the unsaturated C3 building block can be involved in further chemical steps such as metathesis,[2] oxidation[3] reactions thus widening the library of compounds that can be obtained. Alternatively, the allylic group can be simply used as protective group on an heteroatom.[4] Allylation reactions can be performed thanks to the reaction between an allyl halide and a nucleophile in the presence of a base. Such approach, despite of its high effectiveness, necessitates the use of harmful allyl halides and leads to the generation of large amounts of salts as side products. The use of halide free allylic reagents is in this point of view particularly relevant for more sustainable synthetic processes. In particular, the use of prop-2-en-1-ol (allyl alcohol)[5] is attractive as this compound is industrially produced and moreover accessible form vegetal feedstock like glycerol.[6] Moreover, its use essentially leads to the formation of water as side-product. The hydroxyl group is however a much less efficient leaving group than halides. Hence, transition metal such as palladium, iridium, ruthenium, platinum and rhodium (Pd,[7] Ir,[8] Ru,[9] Pt,[10] Rh[11]) often associated with stoichiometric reagents are needed to activate the allyl alcohol and promote the allylation reaction. Remarkable examples involve the use of nickel based catalysts. In addition to the low cost of the metal, nickel catalysed transformations are advantageous as they don't necessitate the use of any additional chemical activators. Additive free transformations have been performed for the catalytic *N*-allylation of amides[12] and *C*-allylation of activated nucleophiles (diketones, ketoesters).[13] The use of appropriate nickel-based catalysts also allowed the α-allylation, under neutral conditions, of aldehydes and enals that bear much less acidic protons.[14] Ketone functionality is found in several industrially relevant natural compounds, terpenic ketones are for example widely used for the production of flagrances, cosmetics or pharmaceutical compounds. The α-allylic alkylation of ketones has been mostly performed from Claisen rearrangement of allyl enol ether[15] or from an allylic alkylation of enolate anions.[16] Stabilized enols such as allyl enol carbonates,[17] potassium enoxyborates have been reacted in the presence of an organometallic catalyst.[18] Stoichiometric reagents or strong bases are needed for the synthesis of the reactants. Alternatively, enols are catalytically generated from the reaction of a ketone with proline [19] or pyrrolidine,[20] the allylic alkylation is promoted by palladium based catalysts. We now wish to report that nickel based catalytic systems are able to promote the direct α-allylation of ketones with allyl alcohol under additive free conditions (Scheme 1).



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

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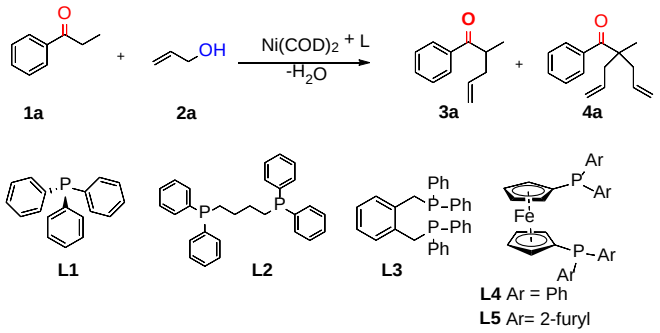
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and discussion

In order to assess the feasibility of the reaction and optimize the catalyst and reaction conditions, 1-phenylpropan-1-one (propiophenone) **1a** and allyl alcohol **2a** were chosen as model substrates. Nickel based catalysts were *in situ* generated from the combination of $Ni(cod)_2$ with a phosphine and evaluated in the α-allylation of propiophenone (Scheme 2).



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

Results are reported in Table 1. Thus, the triphenylphosphine ligand (PPh_3, **L1**) associated with the nickel precursor ($Ni(COD)_2$) gives a low ketone conversion of 15% (Entry 1). Diphosphines such as 1,4-bis(diphenylphosphino)butane (dppb, **L2)** or 1,2-bis[(diphenylphosphino)methyl]benzene (dppmb, **L3**) allowed a substantial increase of the conversion of the starting material up to 25 % and 40 % respectively (Entries 2-3). Such as in the case of the reaction performed with aldehydes, the best results were obtained with the ligand 1,1'-bis(diphenylphosphine) ferrocenediyl (dppf, **L4**) which allows to reach a conversion of 60 % (entry 4). The ligand Hiersophos-3 **(L5)** with furyl substituents in place of phenyl groups was tested but no conversion was observed on two successive tests (Table 1, entry 5). Then the optimization was directed towards the variation of temperature. At 70 °C, the kinetics of the reaction is not sufficient to achieve a good conversion after 18 h (entry 6). By increasing the temperature up to 90 °C, a slightly lower conversion was observed (compare entries 4 and 7). The use of THF and toluene as aprotic solvents does not lead to any conversion, while the use of the protic solvents ^{t}BuOH, ^{i}PrOH and MeOH respectively lead to 8 %, 27 % and 62 % of ketone conversions respectively (Table 1, entries 8 - 11). The proticity of the solvent appears as an important parameter for the success of the reaction. This has been also observed in the case of the palladium[21] and nickel catalysed α-allylation of aldehydes and was attributed to the activation of the allyl alcohol through hydrogen bondings with the solvent. Protic solvents can also promote hydrogen bonds with the oxygen of the ketone and that would also contribute to enhance the nucleophilicity of the carbon in the alpha position. In order to evaluate the impact of the water formed on the course of the reaction, an experiment was performed after addition of 18 µL of H_2O introduced at the beginning of the reaction. This test indeed gave a result very similar to that obtained under conventional conditions thus giving an evidence of a negligible effect of the water formed in the course of the reaction on the reaction yield (compare entries 4 and 12). After choosing methanol as the best solvent, we found that the amount of solvent also had an influence on the reaction outcome (Entries 4 and 13-16). The best quantity of methanol proved to be 0.5 mL while 1 ml of MeOH afforded the same result as the solvent free conditions. Thus, the conversion of **1a** was increased from 60 % (1 mL of methanol) to 80 % with 0.5 mL of methanol. A much lower amounts of solvent doesn't lead to further improvement in the reaction yield (Entry 16). Finally we evaluated the influence of the catalyst quantity. The use of 1.5 mol % or 2 mol % of catalyst is important to further improve the conversion of **1a** and yield in mono-substituted derivative **3a** while a lower catalyst loading led to an important decrease of the conversion (Entries 15 and 17 - 19). Finally, the reaction was performed with non-distilled methanol (presence of water and oxygen – entry 20). The reaction yielded the product with comparable yields thus showing that the catalyst is water and oxygen tolerant under those reaction conditions.

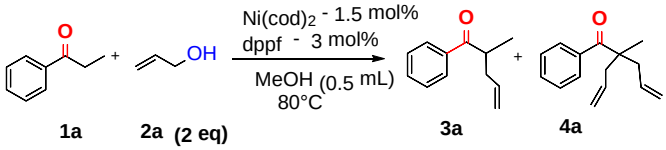
Table 1. Optimization of the nickel(0) catalyzed allylation of propiophenone with allyl alcohol.

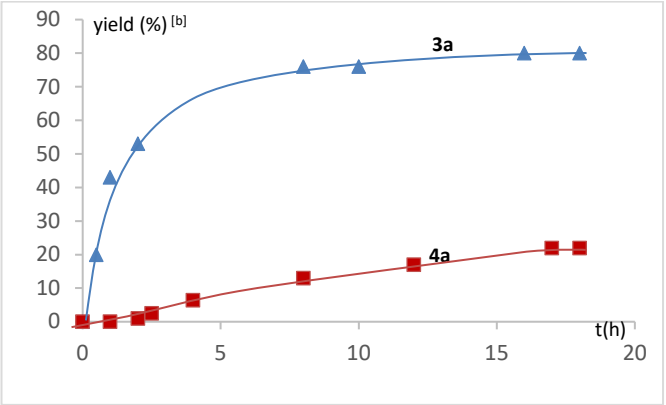
Ent.	[Ni] (mol%)	L	T (°C)	Solvent (mL)	conv. (%)[b]	Yield (%)[c]	
					1a	3a	4a
1	1.0	**L1**	80	MeOH (1.0)	15	13	<1
2	1.0	**L2**	80	MeOH (1.0)	25	20	<1
3	1.0	**L3**	80	MeOH (1.0)	40	36	<1
4	1.0	**L4**	80	MeOH (1.0)	60	53	2
5	1.0	**L5**	80	MeOH (1.0)	0*	0	0
6	1.0	**L4**	70	MeOH (1.0)	16	12	<1
7	1.0	**L4**	90	MeOH (1.0)	56	47	5
8	1.0	**L4**	80	Toluene (1.0)	0	0	0
9	1.0	**L4**	80	THF (1.0)	0	0	0
10	1.0	**L4**	80	*i*PrOH (1.0)	27	25	<2
11	1.0	**L4**	80	*t*BuOH (1.0)	8	8	<1
12	1.0	**L4**	80	MeOH (1.0) +H_2O (18 µL)	62	55	3
13	1.0	**L4**	80	Neat	59	50	3
14	1.0	**L4**	80	MeOH (2.0)	0	0	0
15	1.0	**L4**	80	MeOH (0.5)	80	65	5
16	1.0	**L4**	80	MeOH (0.25)	66	61	3
17	2	**L4**	80	MeOH (0.5)	92	82	10
18	1.5	**L4**	80	MeOH (0.5)	94	80	14
19	0.5	**L4**	80	MeOH (0.5)	25	20	<1
20[d]	1,5	**L4**	80	MeOH (0.5)	93	73	20

[a] Conditions: **1a** (1.8 mmol), **2a** (3.6 mmol), $Ni(cod)_2$/ligand (1:2 ratio), 18 h, in a sealed Schlenk tube [b] Determined by GC, [c]Determined by ^{1}H NMR. On the crude product using trimethoxybenzene as internal standard. [d] The reaction was performed with non-distilled methanol

Whatever the catalytic conditions, it is noteworthy that the diallylation of **1a** turned out to be very difficult to achieve even in the presence of 2 mol % of nickel (10 % yield in diallylated derivative, entry 17). The yields in products of monoallylation **3a** and diallylation **4a** have then been followed in respect to the time (Figure 1). The curves show a rapid formation of the monallylated product within the first four hours of reaction. The conversion of **3a** into **4a** is very slow and reaches a yield of 17 % after 18 hours.

Figure 1: Evolution curve of α-allylation reaction of propiophenone **1a** with allyl alcohol **2a**. [a]

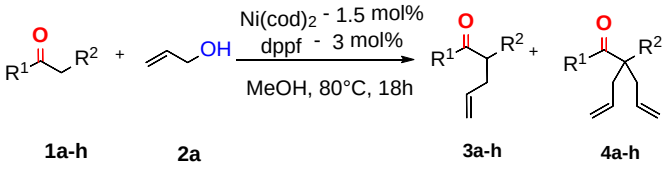


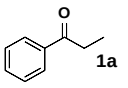
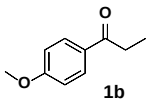
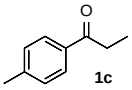
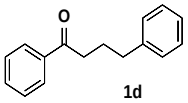
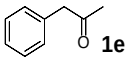
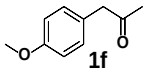
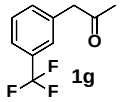
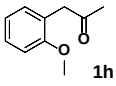


Reaction conditions: **1a** (1.8 mmol), **2a** (3.6 mmol), Ni(cod)$_2$ (0.027 mmol), dppf (0.054 mmol), MeOH (0.5 mL), T = 80°C in a sealed Schlenk tube. [b] Determined by GC.

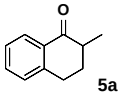
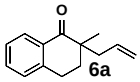
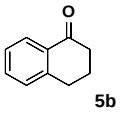
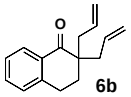
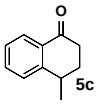
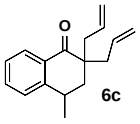
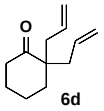
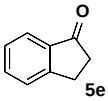
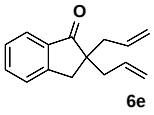
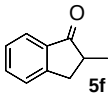
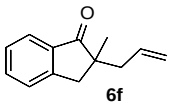
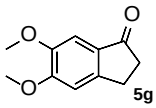
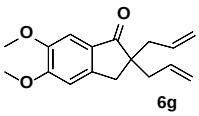
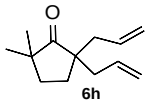
Using the optimized conditions, different products were synthesized by varying the nature of the ketone. The study targeted the conversion of arylalkylketones and arylpropan-2-ones (Table 2). As evidenced by the kinetic study, arylalkylketones are essentially monoallylated and the diallylation is much slower (Table 2, entries 1-4). Thus, the same trend was observed with *p*-methoxyphenylethylketone and *p*-tolylethylketone for which yields of 70 % and 67 % in the monoallylated derivatives **3b** and **3c** respectively were obtained. A very similar yield (65 %, entry 4) was obtained from the use of compound **1d**. Phenylpropan-2-one **1e** was efficiently converted in the bisallylated derivative **4e** with 65 % yield (Entry 5). Very similar results were obtained from the use of the para-methoxyphenylpropan-2-one **1f** and meta-trifluoromethylphenylpropan-2-one **1g** (Entries 6 and 7). The introduction of more sterically hindered aryl substituents favors the formation of the product of monoallylation. For example, the presence of the methoxy group on the ortho position of the phenyl group orientates the synthesis toward the sole formation of the monoallylated derivative **3h** obtained with 91 % yield (Entry 8). The higher steric hindrance due to the presence of the methoxy group might impede further substitution on the carbon. Interestingly no allylation on the methyl group was observed for susbtrates **1e-h**. It is noteworthy that acetophenone did not show any reactivity toward the allylation reaction.

Table 2. Reaction scope of the nickel(0) catalyzed direct allylation of ketones with allyl alcohol.



Entry	Ketone 1a-h	3 a-h yield (%) [b]	4a-h yield (%) [b]
1	 1a	70	11
2	 1b	70	0
3	 1c	67	0
4	 1d	65	0
5	 1e	15	65
6	 1f	16	67
7	 1g	14	72
8	 1h	91	0

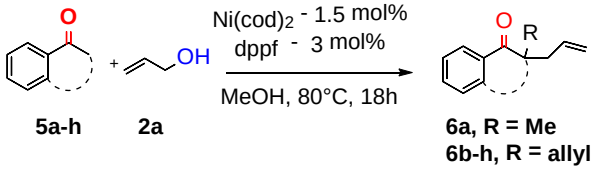
[a] Reaction conditions: **1a-h** (1.8 mmol), **2a** (3.6 mmol), Ni(cod)$_2$ (0.027mmol), dppf (0.054mmol), MeOH (0.5 mL), 18 h, T = 80 °C in a sealed Schlenk tube.

Entry	Ketone **5a-h**	Products of allylation	Isolated yields (%)[b]
1	 **5a**	 **6a**	72
2	 **5b**	 **6b**	72
3	 **5c**	 **6c**	87
4	 **5d**	 **6d**	66
5	 **5e**	 **6e**	94
6	 **5f**	 **6f**	97
7	 **5g**	 **6g**	88
8	 **5h**	 **6h**	87

[b] Isolated Yield of products after silica gel chromatography.

Cyclic ketones showed a higher reactivity toward the formation of tetrasubstituted carbons (Table 3).

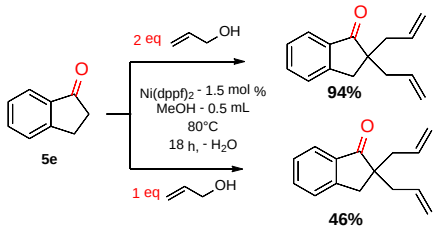
Table 3. Reaction scope: allylic alkylation of cyclic ketones with allyl alcohol.



[a] Reaction conditions: **5a-h** (1.8 mmol), **2a** (3.6 mmol), $Ni(cod)_2$ (0.027 mmol), dppf (0.054 mmol), MeOH (0.5 mL), 18 h, T = 80 °C in a sealed Schlenk tube. [b] isolated Yields of products after chromatographic purification.

The tertiary carbon in **5a** was readily allylated and the corresponding product **6a** was isolated with a high yield of 72 % (Table 3, entry 1). The 1-indanone **5b**, its derivative **5c** were efficiently diallylated and the compounds **6b** and **6c** were thus isolated with 72 % and 87 % yields respectively (Entries 2-3). Cyclohexanone was also efficiently converted and only the diallylated product **6d** on the same carbon was observed and isolated with 66 % yield (Entry 4). A similar behavior was also observed with substrates that bear a cyclopentanone moiety as exemplified with the catalytic transformation of compounds **5e-h** (entries 5-7). Such as in the case of the cyclohexanone series, the fused aromatic ring doesn't appear as a prerequisite to reach interesting reactivities and it is noteworthy that **5h** was diallylated with a high yield (Entry 8).

In all cases, with cyclic substrates, the diallylated derivatives have been isolated with high yields. Control experiments with various amounts of allyl alcohol **2a** have been performed with indanone **5e** as starting material. Performing the reaction with one or two equivalents of allyl alcohol afforded in both cases, the diallylated derivative in almost stoichiometric amount in respect to the allylating reagent and no product of monoallylation could be isolated. This result shows that the monoallylated intermediate has a higher reactivity than the starting ketone in the case of a cyclic structure.

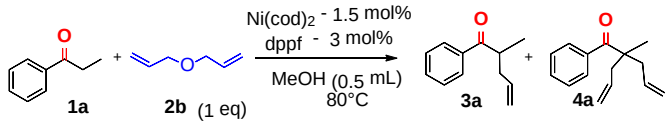


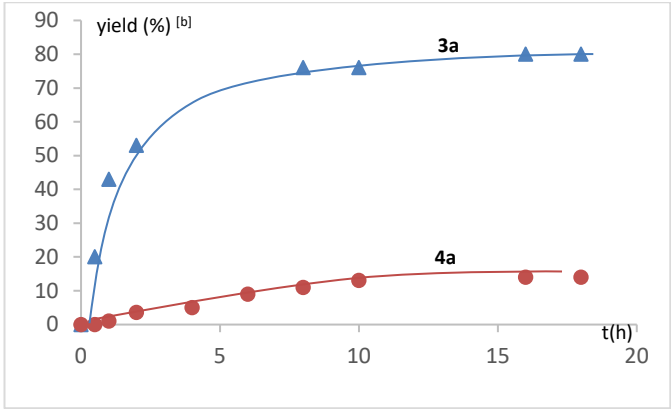
Scheme 3. Allylation of **5e** selectivity as function of allyl alcohol equivalents.

Further experiments targeting salt free α-allylation of ketones have been performed with diallylether **2b**. It is known that diallylether can be formed by self-etherification of allyl alcohol. This reaction catalysed by nickel complexes is not limiting to the transformation of allyl alcohol and diallylether can also be involved as allylation reagent. The allylic alkylation of phenylpropan-1-one **1a** involving diallylether **2b** (1 equivalent) has been performed and the yields in products have been followed in respect to the reaction time (Figure 2). After 18 h, the reaction leads to the formation of monoallylated **3a** and

diallylated **4a** products in very similar proportions to the initial catalytic test that involved allyl alcohol. It has to be noticed that the tests have been performed with comparable amounts of allylic group. The reaction rates obtained with diallylether and allyl alcohol are very close while the concentration of allyl alcohol is twice higher than the concentration of diallylether. This shows that diallylether is more reactive than allyl alcohol and if the compound is formed during the reaction from the self-etherification of allyl alcohol, this should not impact the progression of the reaction.

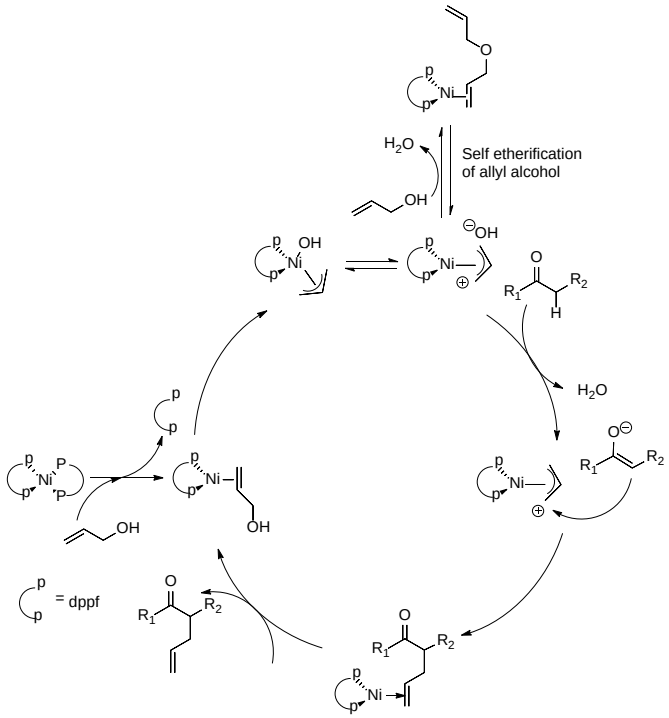
Figure 2: Evolution of α-allylation reaction of propiophenone **1a** with diallyether as function of time.[a]





[a] Reaction conditions: **1a** (1.8 mmol), **2b** (1.8 mmol), $Ni(cod)_2$ (0.027 mmol), dppf (0.054 mmol), MeOH (0.5 mL), in a sealed Schlenk tube. [b] Determined by GC.

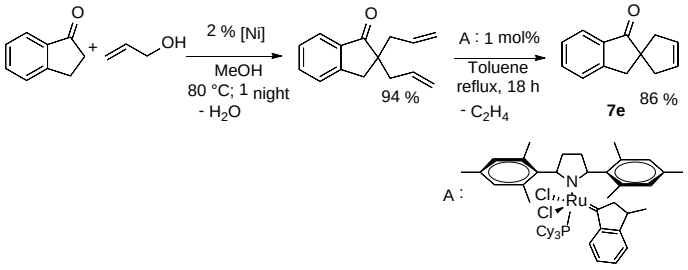
The proposed catalytic cycle of the reaction involves a dissociation step of dppf ligand followed by coordination of the allyl alcohol (Scheme 4).[22] The oxidative addition of allyl alcohol leads to the formation of a nickel (II) allyl complex. This step is probably a chemical equilibrium and is possibly favored by the presence of the protic solvent that activates the hydroxyl group of the substrate through hydrogen bonding.[23] Polar and protic solvents have also been shown to stabilise cationic nickel allylic complexes with an alkoxy group and it is likely that a similar behaviour is observed with a hydroxyl ligand.[24] The uncoordinated hydroxide anion acts as a suitable base in the self-etherification of allyl alcohol. This reaction is however clearly equilibrated and that's consistent with the possible use of diallyl ether as reagent for the α-allylation of ketones. The hydroxide anion can elsewhere deprotonate the ketone. The nucleophilic nickel enolate is further involved in a nucleophilic attack on the allyl moiety. This step is not reversible and thus drives the reaction toward the formation of the α-allylated ketone. The dissociation of the allylated ketone followed by the coordination of a new molecule of allyl alcohol allows a new catalytic cycle.



Scheme 4. Proposed mechanism for The Ni-catalysed allylation reaction of ketones.

The nickel catalyzed α-allylation of ketones with allyl alcohol is a clean synthetic protocol that opens the way to salt free more elaborated synthesis if combined with other suitable catalytic reactions. This is exemplified with an example of synthesis of spirocyclic structures that are particularly relevant in the field of drug design.[25] The synthesis involves the catalytic ketone α-allylation and olefin metathesis steps. This synthetic protocol has been exemplified with indanone as starting compound. Indanone was firstly quantitavely reacted according to the nickel catalyzed α-allylation protocol using the optimized reaction conditions. The product of reaction was further involved in a ruthenium catalyzed ring closing metathesis step that involves the two allyl moieties for the construction of the spirocyclic structure **7e** and yields ethylene as an easily removable side-product.[26]

Scheme 5. Salt free two step catalytic synthesis of spirocyclic derivatives



Conclusion

In summary, the first efficient nickel catalyzed α-allylation of ketones with allyl alcohol has been developed. The reaction is performed under neutral conditions without addition of any additive or base and water is the sole by-product. After optimization of reaction conditions, various allylic ketones have been synthesized. Acyclic as well as five and six membered cyclic ketones have been efficiently converted according to this salt free nickel catalysed protocol. Diallylether proved to be an alternative suitable reagent and beyond the synthetic interest, this reactivity shows that the self-etherification of allyl alcohol is not competing with the α-allylation of ketones. Finally, the nickel catalyzed α-allylation of ketone with allyl alcohol is a key step that opens the way to the synthesis of spirocyclic derivatives according to a two step protocol that involves salt free catalytic transformations.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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