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Graphical Abstract

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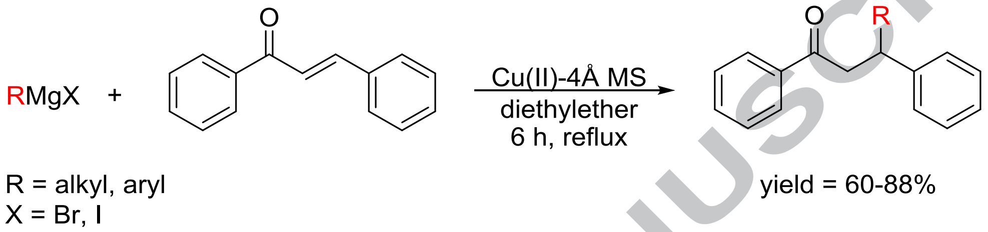

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Heterogeneous catalytic 1,4-addition of arylmagnesium compounds to chalcones

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ABSTRACT

Copper(II) on a 4Å molecular sieve support catalyses the chemoselective addition of alkyl- and arylmagnesium halides to chalcones. Only the 1,4-addition products were obtained in high yields.

1. Introduction

The addition of nucleophiles to electron-deficient conjugated systems is a widely used method for the formation of carbon-carbon bonds in synthetic organic chemistry. Generally, the reaction of α,β-unsaturated carbonyl compounds with organometallic reagents affords the corresponding 1,2-addition product. However, it was observed that the addition of a catalytic amount of a copper salt to the reaction mixture leads to conjugate addition.[1-4]

Kharasch and co-workers studied the reaction of α,β-unsaturated carbonyl compounds with methylmagnesium bromide. It was found that in the presence of a catalytic amount of metal salts 1,4-addition occurred, instead of 1,2-addition, yielding β-substituted carbonyl compounds (Fig. 1). Copper was found to be the most efficient metal to perform the conjugate addition.[5]

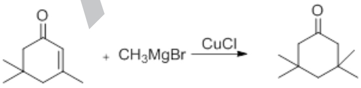

Figure 1. Conjugate addition of methylmagnesium bromide to isophorone

This reaction was extensively developed, and the catalytic activity of organocopper compounds[6] and the reactivity of α,β-unsaturated esters[7] have also been demonstrated. Most recently the stereochemistry of the reaction has been examined using chiral catalysts and/or ligands.[8]

The above mentioned methods are homogeneous catalytic processes. Homogeneous catalytic reactions have several disadvantages: the metal catalysts often require ligands, and during workup the separation of both the metal and the ligand can be tedious. The application of heterogeneous catalytic methods reduces some of these disadvantages, and thus the development of efficient heterogeneous catalytic processes represents an interesting area of research.

2. Results and Discussion

Recently our research group developed new heterogeneous copper-catalyzed methods for the preparation of propargylamines *via* A_3-coupling,[9] and for the Chan-Lam-coupling of amines and boronic acids.[10]

In continuation of our interest in the development of new heterogeneous catalytic methods, we examined the reaction of chalcones with Grignard compounds in the presence of copper(II) on a 4Å molecular sieve support [Cu(II)-4Å MS]. In the reaction of *trans*-chalcone (benzylideneacetophenone, **2a**) with ethylmagnesium iodide (**1a**), 3-ethyl-1,3-diphenyl-propan-1-one (**3a**) was formed in good yield (80%, Fig. 2). GC-MS examination of the reaction mixture showed that the 1,4-addition product was formed exclusively, and the 1,2-addition product (**4a**) was not observed. This was also confirmed by analysis of the ^{1}H and ^{13}C NMR spectra. It is well known that during the formation and reaction of Grignard compounds that homocoupling with formation of the corresponding dialkyl/diaryl compounds can occur. This side-reaction cannot be easily avoided, thus, based on our previous experience during the study of the Kumada-coupling, the halide derivatives were used in excess. The effect of different solvents was examined, where in case of tetrahydrofuran and diethyl ether no significant difference was found. When the reaction was carried out in methyl-*tert*-butyl-ether, no product was formed, and chalcone **2a** was recovered from the reaction mixture. Due to the simpler reaction workup, diethyl ether was chosen as for further reactions. The optimal reaction time was 6 h and longer reaction times did not result in improved yields (Table 1). In case of a 3 h reaction time,

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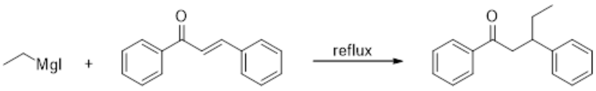
the chalcone could be still detected by TLC as well as in the ^{1}H NMR spectrum.

In order to demonstrate the need for the catalyst in this reaction a control experiment was carried out, where no catalyst was added. Upon analyzing the ^{1}H NMR spectrum of the reaction mixture a detectable amount of the 1,2-addition product as well as several unknown by-products could be identified. Therefore, it was proved that the selectivity of the reaction relies on the application of the Cu(II)-4Å MS catalyst (Table 1).

Table 1. Optimization of the reaction conditions



1a **2a** **3a**

Entry	Catalyst	Solvent	Time (h)	Yield[a] **3a** (%)
1	Cu(II)-4Å MS	Et_2O	6	80
2	-	Et_2O	6	65[b]
3	Cu(II)-4Å MS	Et_2O	3	55[b]
4	Cu(II)-4Å MS	Et_2O	12	79
5	Cu(II)-4Å MS	THF	6	80
6	Cu(II)-4Å MS	MTBE	6	0

[a] Based on GC-MS

[b] Based on ^{1}H NMR of the crude product

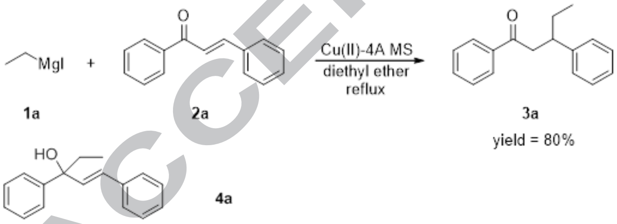
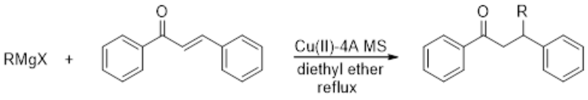


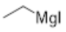
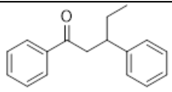
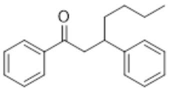
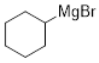
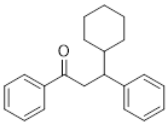
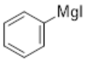
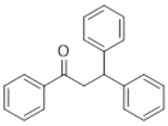
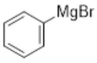
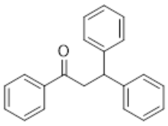
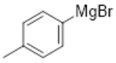
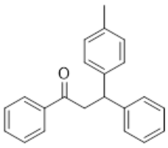
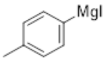
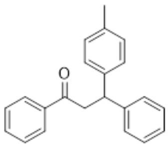
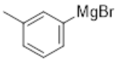
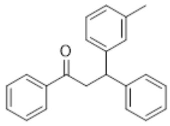
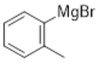
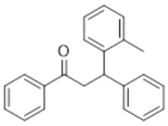
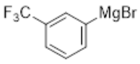
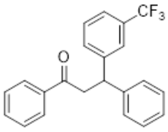
Figure 2. Reaction of ethylmagnesium iodide **1a** with chalcone **2a** in the presence of Cu(II)-4Å MS and the undesired product **4a**.

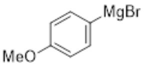
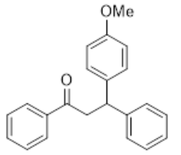
Under the optimized reaction conditions chalcone **2a** was reacted with different Grignard compounds (Table 2). In all cases the desired 1,4-addition products were obtained. As mentioned above due to the excess of the halide reactant, in the case of aromatic halides the corresponding biphenyl derivatives, arising from homocoupling of the Grignard compounds, were detected in the reaction mixture. Conversely, in the case of aliphatic Grignard compounds the highly volatile homocoupled dimers were removed from the reaction mixture either during the reaction, during the workup, or during solvent evaporation. The biphenyl derivatives could be separated from the products *via* chromatographic purification.

Table 2. Reaction of chalcone **2a** with Grignard compounds in the presence of Cu(II)-4Å MS[a]



1 **2a** **3**

Entry	RMgX		Product		Yield[b] **3** (%)
1		**1a**		**3a**	80
2		**1b**		**3b**	78
3		**1c**		**3c**	72
4		**1d**		**3d**	83
5		**1e**		**3d**	60
6		**1f**		**3e**	83
7		**1g**		**3e**	67
8		**1h**		**3f**	75
9		**1i**		**3g**	70
10		**1j**		**3h**	88

11	 1k	 3i	20

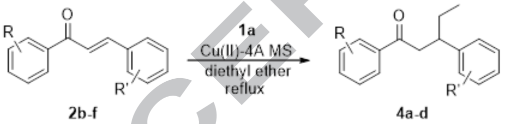
[a] Reagents and conditions: magnesium (2 mmol), alkyl/aryl halide (2.3 mmol), chalcone (1 mmol), catalyst (0.1 g, 9 mol% Cu), diethyl ether (9 mL), reflux, 6 h
[b] Based on GC-MS

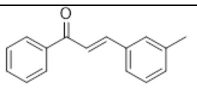
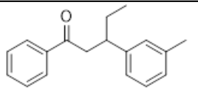
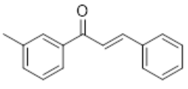
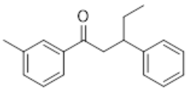
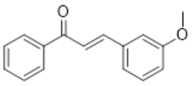
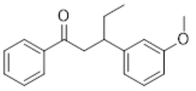
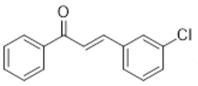
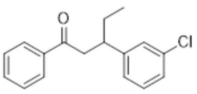
As shown in Table 2, good yields were obtained with both aliphatic and aromatic Grignard compounds and no significant steric effect was observed. Compound **1j**, containing a trifluoromethyl group also showed good activity. Because the reactivity of phenylmagnesium bromide **1e** toward chalcone is lower than the reactivity of phenylmagnesium iodide **1d**, the amount of biphenyl increased in the reaction of **1e**. This is the reason for the different yields attained in entries 4 and 5. As observed during our study of the Kumada coupling,[11] a methoxy substituent on the aryl halide may inhibit the Grignard reaction. This is the reason for the poor yield in entry 11. It was also observed, that the presence of a nitro group on the aryl halide decreases the solubility of the aryl halide in diethyl ether, thus no reaction occurred.

Next, we examined the reactivity of substituted chalcones (Table 3). In these cases no significant differences were observed in the reactivity of the different derivatives. The desired products were obtained in good yields.

The reusability or recyclability of the catalyst is an important advantage of heterogenous catalytic methods. Thus, the reusability of Cu(II)-4Å MS was tested in the reaction of ethylmagnesium iodide **1a** and chalcone **2a**. The catalyst was filtered from the reaction mixture, washed with acetone, and dried at 120 °C for 1 h, then a second experiment was carried out with the recovered catalyst The reusability was tested three times, and it was found that the catalyst can be reused without significant loss of activity (Table 4).

Table 3. Reaction of substituted chalcones **2b-e** with ethylmagnesium iodide **1a** in the presence of Cu(II)-4Å MS[a]



Entry	Chalcone	Product	Yield[b] (%)
1	 2b	 4a	80
2	 2c	 4b	88
3	 2d	 4c	85
4	 2e	 4d	89

[a] Reagents and conditions: magnesium (2 mmol), alkyl/aryl halide (2.3 mmol), chalcone (1 mmol), catalyst (0.1 g, 9 mol% Cu), diethyl ether (9 mL), reflux, 6 h
[b] Based on GC-MS

Table 4. Reusability of the Cu(II)-4Å MS catalyst

Entry	Number of uses	Yield[a] **3a** (%)
1	1	80
2	2	79
3	3	75
4	4	74

[a] Based on GC-MS

The method was also tested in the reaction of ethylmagnesium iodide with 2-cyclohex-1-one. In this case a complex reaction mixture was obtained, in which both the 1,2-addition product and the 1,4-addition product were detected together with undefined by-products in the ^{1}H NMR spectrum and the GC-MS chromatogram.

3. Conclusion

In conclusion, copper(II) on a 4Å molecular sieve support was demonstrated to be an efficient catalyst for the selective 1,4-addition of Grignard compounds to chalcones. The workup of the reaction mixture is straightforward, and the products were obtained in good yields. The preparation of the catalyst is simple, and after washing with acetone and drying can be reused multiple times without significant loss of activity.

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Highlights

- The method is simple and selective
- The workup of the reaction mixture is easy
- The catalyst can be simply prepared and can be reused without loss of activity