Transition Metal Catalyzed Preparation of Grignard Compounds**

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A multitude of organo halide compounds, in particular aromatic, heteroaromatic, and vinylic chloro compounds react slowly in low yield, if at all, with magnesium powder or turnings. In the course of our work on the so-called inorganic Grignard reagents [IGR, see Eq. (1)][1] we have developed efficient transition metal catalysts for the transformation of inactive organo chlorides into the corresponding Grignard compounds, commercial magnesium powder is used in this procedure.[2] Herein this method is introduced for several Grignard compounds that are considered to be difficult to prepare and the possible catalytic role of the IGR is discussed.

The catalysts for the preparation of Grignard compounds are produced through the reaction of transition metal halides, alcohols, or amides (precatalysts) in the presence of an excess of magnesium, and a Grignard or other organo magnesium compounds, usually in THF. The Grignard compound required for the preparation of the catalyst is preferably prepared in situ from an organo halide, such as ethyl bromide, and the excess magnesium present. To date Fe catalysts have been found to be the most active and the best cocatalysts are $MgCl_2$ and 9,10-diphenylanthracene (DPA).[2]

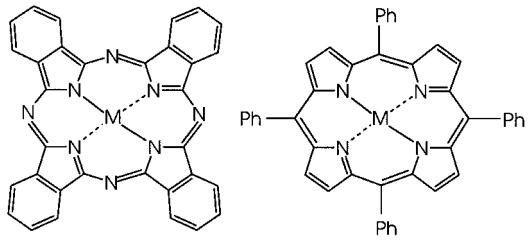
The influence that varying the precatalyst, the cocatalyst, and the reaction conditions has on the catalysis of the Grignard formation were investigated for, among others, 1-chloronaphthaline as the inactive organo chloride (Table 1). With the catalyst generated from Mg, EtBr, $FeCl_2$, and $MgCl_2$ the compound 1-naphthylmagnesium chloride (**1**) is formed in 76.7% yield in under 1 h (entry 1).[3] The best results are obtained when the drop-wise addition of the organo halide is rapid and is started within a few minutes of the addition of the transition metal component, this is because the catalytic activity decreases with time (entry 2). THF is the preferred solvent, but mono- (entry 4) and diglyme can also be used. As well as the iron compounds other compounds, in particular the corresponding manganese precatalysts, such as $MnCl_2$, can be considered (entry 5).

Table 1. Catalytic preparation of 1-naphthylmagnesium chloride **1** from 1-chloronaphthaline and Mg powder in THF.

Entry	EtBr[a] [mol%]	Precatalyst[a] (2.0 mol%)	$MgCl_2$[a] [mol%]	Aging[b] [min]	T [°C]	Yield [%][c] (t [h])[d]
1	1.1	$FeCl_2$	5.0	2	22 – b.p.	76.7 (1), 82.3 (18)
2	1.1	$FeCl_2$	5.0	70	22 – 26	16.7 (3), 35.2 (18)
3	1.1	$FeCl_2$	–	3	22 – b.p.	68.5 (1), 73.7 (20)
4[e]	0.5	$FeCl_2$	5.0	10	21 – b.p.	80.6 (1), 82.7 (4)
5	0.5	$MnCl_2$	5.0	30	23 – 62	62.2 (2), 66.5 (19)
6	1.1	**2a**	–	100	22 – b.p.	77.0 (1), 84.0 (6)
7	0.5	**2b**	–	40	22 – b.p.	87 (2)
8	0.5	**3a**	–	60	22 – b.p.	95 (2)
9	0.9	**3c**	–	45	22 – b.p.	69 (0.5)
10	0.9	**3d**	–	45	22 – b.p.	78 (4)

[a] Calculated from 1-chloronaphthaline. [b] Interval between the addition of the precatalyst and commencement of the 1-chloronaphthaline addition. [c] Determined by acidimetric titration. [d] After the end of the 1-chloronaphthaline addition. [e] Reaction in monoglyme; in addition to $MgCl_2$ in this experiment DPA[a] (2 mol%) was also used as cocatalyst.

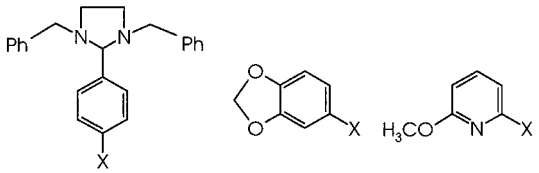
As precatalysts iron phthalocyanin (**2a**, **b**) or the porphine complexes of iron, manganese, cobalt, or copper (**3a**–**d**) can be used. With these compounds, and particularly in the case of



2a: M = Fe
2b: M = FeCl

3a: M = FeCl
3b: M = Mn
3c: M = Co
3d: M = Cu

the iron complexes (entries 6–8) highly active catalysts for Grignard formation are generated even without a cocatalyst ($MgCl_2$). The catalysts formed from these amides seem to be more stable in THF than the catalysts generated from transition metal halides such as $FeCl_2$. The aging of the catalysts before the start of the Grignard reaction (40–100 min) has in these cases no negative effect on the catalytic activity (entry 6–8). In general however, for every single organohalide substrate the optimal catalysts has to be identified. In most cases we use as first choice the catalytic system derived from Mg, EtBr, $FeCl_2$, and $MgCl_2$.[6] This system allows the conversion of the aminal-protected chlorbenzaldehyde **4a**,[7] the oxygen substituted chloroarene 5-chloro-1,3-benzodioxol **5a**, and the oxygen substituted chloroheteroarene 2-chloro-6-methoxypyridine **6a** into the corresponding Grignard compounds in high yield (Table 2). In the preparation of the Grignard compound **5b** the yield could be increased from 40 to 76% (after 2.5 h) by increasing the $EtMgBr/FeCl_2$ ratio from 0.2 to 2.0 (entries 2 and 3).[8] After hydrolysis and silation the corresponding benzodioxol and the



4a: X = Cl
4b: X = MgCl
4c: X = $Si(CH_3)_3$

5a: X = Cl
5b: X = MgCl
5c: X = $Si(CH_3)_3$

6a: X = Cl
6b: X = MgCl

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Table 2. Catalytic preparation of the Grignard compounds **4b**–**6b** from **4a**–**6a** and Mg powder.

Entry	$EtBr^{[a]}$ [mol %]	$FeCl_2^{[a]}$ [mol %]	$MgCl_2^{[a]}$ [mol %]	Aging[b] [min]	Substrate	T [°C]	Yield [%][c] (t [h])[d]
1	1.0	(2.1)	5.0	10–15	**4a**[7]	20–45	88 (10)[e,f]
2[g]	1.0	(5.1)	5.0	3	**5a**	21–36	40 (2.5)
3	10.9	(5.1)	5.0	3	**5a**	22–52	76 (2.5), 80.7 (8.5), 82.9 (23)[h,i]
4[j]	1.0	(5.1)	5.0	3	**6a**	22–33	37 (2.5), 52 (9)
5	10.9	(5.1)	5.0	3	**6a**	22–45	62 (2.5), 83 (9), 96 (23.5)[k]

[a] Calculated from the substrate. [b] Interval between the addition of $FeCl_2$ and commencement of the substrate addition. [c] Determined through acidmetric titration, unless otherwise stated. [d] After the end of the substrate addition. [e] Yield calculated from the amount of the trimethylsilyl derivative **4c**. [f] During the reaction the suspension was stirred with a paddle stirrer in the presence of glass sphere (i.d. = 5 mm; 5 mL) grinding elements. [g] Comparative experiment to entry 3. [h] Yield derived from the GC analysis of the benzodioxol formed by hydrolysis. [i] Comparative experiment without $FeCl_2$ and $MgCl_2$: 1.3 % yield after 38.5 h at 22 °C. [j] Comparative experiment to entry 5. [k] Comparative experiment without $FeCl_2$ and $MgCl_2$: 12.8 % yield after 30 h at 22 °C.

5-trimethylsilyl-1,3-benzodioxol **5c** were isolated in yields of 83 and 70 %, respectively. In the same manner the yield of the Grignard compound **6b** (entries 4 and 5) could be increased from 52 to 83 % (after 9 h). Without the Fe catalyst the Grignard compounds **4b**–**6b** could be prepared only in low yield, if at all.

To investigate the catalyst generation a catalyst solution, prepared with a Mg/*n*-$C_7H_{15}Br$/$FeCl_2$ ratio of 25/4/1, was analyzed. After a reaction time of 8.5 h the centrifuged catalyst solution contained an amount of magnesium and of bromine equivalent to the amount of *n*-heptyl bromide initially present and 95 and 89 % of the initial $FeCl_2$ as iron and chlorine, respectively. A GC analysis of the vacuum distillate of the catalyst solution showed 58.6 % of a 1-heptene/heptane mixture (calculated from heptyl bromide) was found by GC analysis.[9] From these results and based on the formation of Pd- and Pt-IGR from $PdCl_2$ and $PtCl_2$, respectively, and ethylmagnesium halides [Eq. (1)] or diethylmagnesium[1a,c] allows the formation of the catalyst to be described according to Eq. (2).

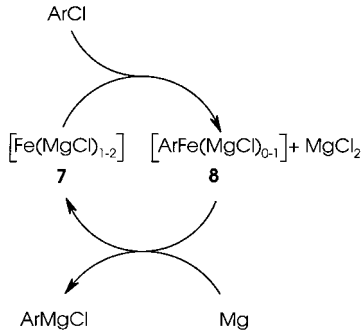
$$MCl_2 + 4\,C_2H_5MgX \longrightarrow [M(MgX)_2]^{[10]} + MgX_2 + 2\,(C_2H_4 + C_2H_6)\uparrow \quad (1)$$
M = Pd, Pt; X = Cl, Br

$$FeCl_2 + 4\,n\text{-}C_7H_{15}MgBr \longrightarrow [Fe(MgX)_2]^{[10]} + 2\,MgX_2 + 2\,(1\text{-}C_7H_{14} + C_7H_{16}) \quad (2)$$
X = Cl, Br

If in the generation of the catalyst the Grignard compound is not available in sufficient quantities for the reaction to proceed according to Eq. (2) then the known Fe-IGR [FeMgCl][1a] [Eq. (3)] can be formed from the $FeCl_2$ and the excess Mg powder. In the preparation of the Fe catalysts for the Grignard reaction Fe-IGR [$Fe(MgCl)_2$] [Eq. (1)] and [FeMgCl] [Eq. (3)] can be formed together.

$$FeCl_2 + 1.5\,Mg \longrightarrow [FeMgCl]^{[10]} + 0.5\,MgCl_2 \quad (3)$$

For the Fe-catalyzed Grignard formation (Scheme 1) we assume that the aryl iron intermediate **8** is formed from the mixture **7** and the chloroarene. This step is plausible bearing in mind the known high reactivity of IGR compared to perchlorovinyl and aryl compounds.[1e] In the next step of the catalysis the Grignard can be released from **8** by a Fe/Mg transmetalation[11, 12] with the excess Mg, this regenerates the catalytic species **7**. The cocatalytic function of $MgCl_2$ is probably to stabilize the catalytically active species, in particular **8**, by preventing the precipitation of Fe^0, the $MgCl_2$ is also necessary for the transmetalation step.



Scheme 1. Proposed mechanism for the iron-catalyzed preparation of Grignard compounds; Ar = aryl, heteroaryl.

With the transition metal catalyzed preparation of Grignard compounds the IGR species have demonstrated themselves to be useful homogenous catalysts, which extends the applications of the Grignard reaction to include inactive chloroarene compounds.[13]

Experimental Section

Typical procedure: The reactions were carried out under an argon atmosphere. THF was distilled over magnesium anthracene · 3 THF. Magnesium was used in the form of a commercially available (Eckart Werke, Fürth, Germany) powder (270 mesh). Anhydrous $MgCl_2$ was prepared from 1,2-dichloroethane and Mg powder in THF. The anhydrous $FeCl_2$ was obtained from Alfa. The organo chloride was dried over molecular sieves.

Mg powder (2.43 g; 100 mmol) in THF (30 mL) was treated with ethyl bromide (0.22 mL; 3 mmol to 0.56 mL 7.5 mmol depending upon the reactivity of the organo chloride to be used) and the mixture stirred for 1 h by using a magnetic stirrer bar. To mechanically activate the Mg surface, grinding elements (ca. 5 vol %), for example, glass spheres with a diameter of 5 mm can be added (Table 2, entry 1).[8] After the addition of $FeCl_2$ (0.19 g, 1.5 mmol to 0.48g, 3.8 mmol) and a solution of $MgCl_2$ (7.7 mL, 0.485 molar in THF, 3.7 mmol) the reaction mixture was then stirred for a total of 3 min during which time the solution turned dark brown. Immediately afterwards the organo chloride (75 mmol) was added drop wise over 30 min. In the course of the reaction the solution heated up, sometimes even reaching the boiling point of the solvent used. During the reaction samples were removed, and, after removal of the excess magnesium and hydrolysis, acidimetric titrated (Tables 1 and 2). To identify and quantify the reaction product an aliquot of the reaction solution was hydrolyzed and the organic phase examined by gas chromatography (Table 2, entry 3). When a sample of the Grignard reaction was treated with

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chlorotrimethylsilane, the corresponding organotrimethylsilane compound of the Grignard compound was obtained, which could be identified and quantified by GC/MS coupling (Table 2, entry 1).

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[3] According to the literature **1** is generated from 1-chloronaphthaline and Mg turnings in boiling THF in 40% yield (6 h)[4] and by the entrainment method [5] in boiling diethyl ether in 66% yield (12 h).

[4] H. E. Ramsden, A. E. Balint, W. R. Whitford, J. J. Walburn, R. Cserr, *J. Org. Chem.* **1957**, *22*, 1202 – 1206.

[5] D. A. Pearson, D. Cowan, J. D. Becker, *J. Org. Chem.* **1959**, *24*, 504 – 509.

[6] Grignard reactions, which proceed without a catalyst but first start after a long induction period can be initiated with this catalyst system.

[7] We thank the firm Bayer AG, Leverkusen, for providing a sample of **4a**.

[8] Patent registered.

[9] The rest is most likely to be the dimerization product $C_{14}H_{30}$.

[10] In light of EXAFS investigations (EXAFS = extended x-ray absorption fine structure), particularly of "$[Pt(MgCl)_2]$",[1c] we assume that the empirical formula $[M(MgCl)_m]_p(thf)_x$ ($m = 1,2,3$; $p \geq 2$) refers to the metal clusters M_p that are bound directly to the ligands MgCl(thf). The simplified form, such as "$[Fe(MgCl)_2]$" etc. denotes a fragment $1/p$ of this sort of cluster.

[11] C. Elschenbroich, A. Salzer, *Organometallchemie*, Teubner, Stuttgart, **1968**, p. 28.

[12] Y. Gao, F. Sato, *J. Chem. Soc. Chem. Commun.* **1995**, 659 – 660.

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Total Synthesis of Lankacyclinol**

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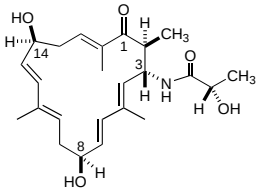
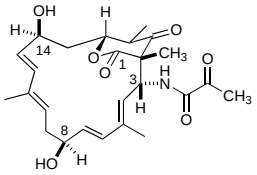
The lankacidins are a family of structurally unique antibiotics isolated from the fermentation broths of *Streptomyces griseofuscus*, *S. violaceoniger*, and *S. rochei var.*[1] These metabolites show strong antitumor activity against L1210 leukemia, B16 melanoma, and solid lymphosarcoma cells.[2] Lankacyclinol (**1**), which is also identified as T-2636 G,[3] is a rare example of a seventeen-membered carbocycle, and incorporates two independent pentadienyl alcohol systems as well as a novel β-amido ketone moiety. The assignments of relative



Lankacyclinol **1**

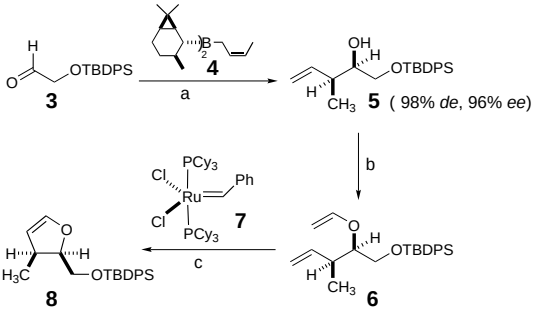


Lankacidin C **2**

stereochemistry at C3, C8, and C14, and the absolute configuration of **1** have been considered by comparison with lankacidin C (**2**) which was unambiguously characterized by X-ray crystallography.[4] Indeed, biosynthesis studies have suggested that enzymatic reduction of the 2′-oxopropionamide of **2** followed by base-induced decarboxylation provides lankacyclinol.[5]

However, the asymmetry at C2 of **1** has remained undefined in spite of substantial advancements leading to the synthesis of **2** by Kende and co-workers.[6] Our recent studies, stemming from 4,5-dihydrofurans, of tandem acyl nitrene insertions and Wittig reactions have demonstrated a stereocontrolled route to unique β-amido esters.[7] These results have provided the opportunity to address the challenges inherent in a proposed synthesis of **1**, particularly with regard to serious issues of acid and base instability and stereochemical concerns. In this communication, we describe the first enantioselective synthesis of (−)-lankacyclinol by a convergent pathway which establishes the relative and absolute configuration as illustrated in **1**.

An enantiocontrolled preparation of the C1 – C6 fragment was developed, which utilized *cis*-disubstituted dihydrofuran **8** and incorporated a ring-closing metathesis (RCM) strategy (Scheme 1). Addition of the (*Z*)-crotyl-di-(2-*iso*caranyl)borane **4**, as described by Brown and co-workers,[8] to aldehyde **3** gave the *syn*-homoallylic alcohol **5** as a single diastereomer.[9] Transetherification to afford the vinyl ether **6** was induced by treatment with ethyl vinyl ether in the presence of small amounts of mercuric trifluoroacetate.[10] Cyclization with the RCM protocol using the ruthenium Grubbs' catalyst **7**[11]



Scheme 1. a) **4**, $BF_3 \cdot Et_2O$, THF, −78 °C, 62%; b) $Hg(O_2CCF_3)_2$, ethyl vinyl ether, Et_3N, reflux, 60%; c) **7**, CH_2Cl_2, reflux, 48%. TBDPS = *tert*-butyldiphenylsilyl, Cy = cyclohexyl.

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