Nitrous Oxide

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Oxidative Coupling Reactions of Grignard Reagents with Nitrous Oxide**

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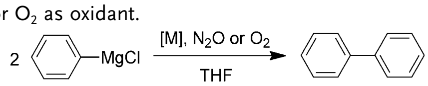
Nitrous oxide ("laughing gas", N_2O) is a potent oxidation agent, from a thermodynamic point of view.[1] Moreover, it is an environmentally benign oxidant, because the side product is dinitrogen. An obstacle in using N_2O in oxidation reactions is the inert nature of the gas. Heterogeneous catalysts have been used with good success for the activation of N_2O, but high temperatures and/or pressures are typically required to achieve acceptable reaction rates.[2] Thus far, N_2O-based oxidation reactions with homogeneous catalysts in solution have met with only limited success. Many transition-metal complexes are known to react with N_2O under mild conditions,[3] but catalytic turnover is difficult to achieve. Some polyoxometalates[4] and ruthenium complexes[5] were shown to catalyze oxidation reactions with N_2O, but the reactions require high temperatures (100–200°C) and often elevated pressures.[6] Furthermore, the reported turnover numbers are modest (≤ 100). Herein, we describe oxidative carbon–carbon coupling reactions with N_2O, which can be performed under mild conditions with good selectivity and unprecedented turnover numbers.

Oxidative homo- and cross-coupling reactions of Grignard reagents[7,8] in the presence of metal catalysts can be achieved with different oxidants, including 1,2-dihaloethanes[9] and dioxygen.[10] The reactions are believed to involve low-valent organometallic complexes.[7–10] We hypothesized that these low-valent, nucleophilic complexes might be susceptible to oxidation by N_2O. As a model reaction, we studied the homocoupling of phenylmagnesium chloride. The reactions were performed in THF at room temperature under an atmosphere of N_2O using different transition-metal salts as potential catalysts (Li_2CuCl_4, Li_2MnCl_4, $CoCl_2$, $FeCl_3$, $[Fe(acac)_3]$). To avoid reactions caused by traces of dioxygen, we have used N_2O of high purity (99.999%). Test reactions with metal salt (1 mol%) gave the oxidative coupling product biphenyl after 1 h in yields of 30–95% (Table 1, entries 1–5). The best results were found for $FeCl_3$ (94% yield), $[Fe(acac)_3]$ (94% yield) and $CoCl_2$ (95% yield). The latter two complexes were used for further studies.

First, we examined the efficiency of the reaction. Lowering the amount of catalyst from 1.0 mol% to 0.1 mol% had no effect on the yield. Further reduction to 0.01 mol% gave a poor yield in the case of $[Fe(acac)_3]$, even if the reaction time was prolonged. With $CoCl_2$, however, the catalyst loading could be reduced to 0.004 mol% and biphenyl was still obtained in 83% yield (Table 1, entry 7). Taking into account the small amount of product formed without catalyst (8% after 18 h), and assuming that one catalytic cycle produces one biphenyl molecule, we can calculate a turnover number of 9.4×10^3. This value greatly exceeds what has been reported thus far for metal-catalyzed oxidation reactions with N_2O in homogeneous solution.[4,5]

Table 1: Metal-catalyzed homocoupling of phenyl magnesium chloride with N_2O or O_2 as oxidant.



Entry	Catalyst (mol%)	Oxidant	*t* [h]	Yield [%][a]
1	Li_2CuCl_4 (1.0)	N_2O	1	30
2	Li_2MnCl_4 (1.0)	N_2O	1	32
3	$CoCl_2$ (1.0)	N_2O	1	95
4	$FeCl_3$ (1.0)	N_2O	1	94
5	$[Fe(acac)_3]$ (1.0)	N_2O	1	94
6	$[Fe(acac)_3]$ (0.1)	N_2O	1	94[b]
7	$CoCl_2$ (0.004)	N_2O	18	83
8	$[Fe(acac)_3]$ (0.1)	O_2	1	traces[c]
9	Li_2MnCl_4 (0.1)	O_2	1	9[d]

[a] Yields were determined by GC-MS analysis. [b] The the product was isolated in 92% yield. [c] A 41% yield of phenol was formed. [d] A 10% yield of phenol was formed.

The groups of Lei[10c] and Cahiez[10d] have shown that Fe complexes are able to catalyze the oxidative coupling of aryl Grignard reagents with O_2. In the case of 4-methylphenylmagnesium bromide, a yield of only 46% was reported for experiments using $[Fe(acac)_3]$ (5 mol%) under conditions related to our own (THF, room temperature).[10c] The difficulty in performing oxidative coupling reactions with O_2 is due to the reactivity of the Grignard reagent itself towards O_2. Consequently, the catalytic process has to be fast and high catalyst loadings are needed. This issue is illustrated by the attempted synthesis of biphenyl using O_2 and $[Fe(acac)_3]$ (0.1 mol%). Only traces of the desired coupling product were obtained and phenol was formed in 41% yield (Table 1, entry 8). Li_2MnCl_4 is another catalyst that is known to promote the coupling of Grignard reagents in the presence of O_2.[10b,d] Good yields for aryl–aryl coupling reactions were reported with Li_2MnCl_4 (5 mol%).[10d] When only a 0.1 mol% loading was used, however, this catalytic system failed to give an acceptable yield (Table 1, entry 9) and a 10% yield of phenol was obtained. These experiments reveal an intrinsic advantage of N_2O over O_2: as Grignard reagents are reluctant

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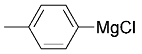
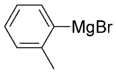
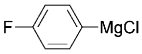
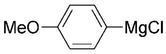
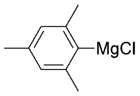
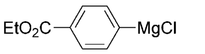
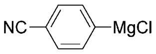
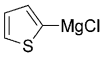
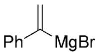
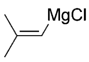
to react with N_2O,[1] metal-independent side reactions are less problematic.

Next, we examined the substrate scope. Aryl Grignard reagents containing different groups in the *para* position (CH_3, F, OMe) or a sterically congesting methyl group in the *ortho* position could be coupled cleanly with [Fe(acac)$_3$] (0.1 mol%; Table 2, entries 1–4) or $CoCl_2$ (Table S4). For reactions with $CoCl_2$, high turnover numbers of more than 10^3 could be achieved as well.

Table 2: Oxidative homocoupling of aryl and alkenyl Grignard reagents.[a]

$$2\ \mathrm{R{-}MgX} \xrightarrow[\mathrm{THF}]{[\mathrm{M}],\ \mathrm{N_2O}} \mathrm{R{-}R}$$

Entry	Catalyst (mol%)	*t* [h]	Substrate	Yield [%][b]
1	[Fe(acac)$_3$] (0.1)	1		93
2	[Fe(acac)$_3$] (0.1)	1		92
3	[Fe(acac)$_3$] (0.1)	1		92
4	[Fe(acac)$_3$] (0.1)	1		99 (96)[c]
5	$CoCl_2$ (5.0)	1.5		87[d]
6	$CoCl_2$ (5.0)	18		50[e]
7	[Fe(acac)$_3$] (5.0)	18		32[e]
8	[Fe(acac)$_3$] (1.0)	6		79
9	[Fe(acac)$_3$] (1.0)	1		77 (72)[c]
10	[Fe(acac)$_3$] (1.0)	1		77

[a] Unless noted otherwise, reactions were performed at RT. [b] Yields were determined by GC or GC-MS analysis. [c] Yields of isolated products are given in parentheses. [d] The reaction temperature was 50 °C and the Grignard reagent was slowly added to the catalyst solution with a syringe pump (over 1 h). [e] The Grignard reagents were prepared according to a literature procedure, the reaction was started at −20 °C and the mixture was then slowly warmed to RT.

Mesitylmagnesium bromide, a sterically very demanding substrate, provided bimesityl in 87% yield with $CoCl_2$ (5 mol%) after 1.5 h at 50 °C (Table 2, entry 5). The success of this reaction is in sharp contrast to what has been reported for reactions with dioxygen: the attempted coupling of mesitylmagnesium bromide gave only traces of product, despite the fact that a relatively large amount (20 mol%) of Li_2MnCl_4 catalyst was employed.[10b] The homocoupling of sterically demanding arylmagnesium halides is also not possible with the TEMPO-based method developed by the Studer group.[11b,c] Comparable yields for the homocoupling of mesitylmagnesium halides were only achieved when stoichiometric amounts of 1,2-dihaloethanes[9d,e] or 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone[11d] were used as oxidants.

Aryl Grignard reagents with reactive ester or cyano groups were found to be more challenging substrates for our N_2O based procedure. By increasing the catalyst loading to 5 mol%, it was possible to obtain the coupling products in 50% and 32% yield, respectively (Table 2, entries 6 and 7). Interestingly, $CoCl_2$ gave better results for the ester, whereas [Fe(acac)$_3$] gave superior results in the case of the cyano-containing substrate (Table S4). The substrate 2-thienylmagnesium chloride coupled to produce 2,2′-dithienyl in 79% yield after 6 h with only 1 mol% of [Fe(acac)$_3$] (Table 2, entry 8).

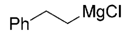
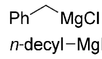
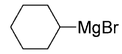
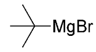
Alkenyl Grignard reagents also homodimerize readily: 2,5-dimethylhexa-2,4-diene and 2,3-diphenylbutadiene were both obtained from the corresponding Grignard reagents in 77% yield using [Fe(acac)$_3$] (1 mol%; Table 2, entries 9 and 10). For 2,3-diphenylbutadiene, $CoCl_2$ was significantly less effective than [Fe(acac)$_3$] (Table S4).

Attempts to homocouple sp-hybridized Grignard reagents failed, regardless of the catalyst employed (Table S2). Only low conversions were observed with $CoCl_2$, Li_2CuCl_4, or Li_2MnCl_4. Phenylethynylmagnesium bromide was consumed when iron(III) salts were present, but the yield of the homodimer was below 5%. The homocoupling of propynylmagnesium chloride was also not successful.

To date, there are few reports about the oxidative coupling of alkyl Grignard reagents.[9a,c,10d,11e,12] These substrates are problematic because they are prone to undergo side reactions (such as eliminations, isomerizations, or, in the case of O_2, reactions with the oxidant[9a]). When we screened different transition-metal salts for the catalytic oxidative homocoupling of phenethylmagnesium chloride with N_2O, we found that manganese, iron, and cobalt salts led to considerable amounts of styrene (Table S1). Phenethylmagnesium chloride is a "difficult" substrate, because β-hydride elimination of the corresponding transition metal alkyl complex is particularly easy. However, with Li_2CuCl_4 (1.0 mol%), an 84% yield of the homocoupling product 1,4-diphenylbutane was obtained (isolated in 80% yield) and only traces of styrene were observed (Table 3, entry 1). The catalyst loading could be lowered to 0.5 mol% without compromising the yield, but further reduction to 0.2 mol% gave a yield of only 57% (Table 3, entry 2) and an elevated amount of styrene

Table 3: Oxidative homocoupling of alkyl Grignard reagents.

$$2\ \mathrm{R{-}MgX} \xrightarrow[\mathrm{THF,\ RT}]{\mathrm{Li_2CuCl_4}\ (x\ \mathrm{mol\,\%}),\ \mathrm{N_2O\ or\ O_2}} \mathrm{R{-}R}$$

Entry	*x* [mol%]	Oxidant	substrate	Yield [%][a]
1	1.0	N_2O		84 (80)[b]
2	0.2	N_2O		57
3	1.0	O_2		17[c]
4	1.0	N_2O		85 (81)[b]
5	1.0	N_2O	*n*-decyl−MgBr	78
6	1.0	N_2O		79
7	1.0	N_2O		44

[a] Yields were determined by GC or GC-MS analysis. [b] Yields of isolated products are given in parentheses. [c] Other products: 2-phenylethanol (58%) and styrene (4%).

(10 %). As expected, it was not possible to replace N_2O by O_2: when the reaction was carried out with Li_2CuCl_4 (1 mol %) under an O_2 atmosphere, a 58 % yield of 2-phenylethanol was obtained, along with a 4 % yield of styrene and only a 17 % yield of the coupling product (Table 3, entry 3).

Using N_2O, other primary (benzyl, *n*-decyl) and secondary Grignard reagents (cyclohexyl) could be coupled in yields of 78–85 % (Table 3, entries 4–6). The sterically demanding *tert*-butylmagnesium bromide gave a lower yield, only 44 % (Table 3, entry 7). The success of copper as a catalyst for these reactions is in line with the well-known propensity of organocuprates to undergo C–C coupling reactions upon oxidation.[13,14] However, a stoichiometric amount of copper salts are typically used for these reactions.

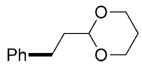
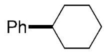
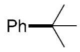
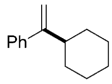
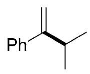
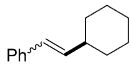
Having established that homocoupling reactions of Grignard reagents can be achieved with N_2O, we examined whether this method is also suitable for cross-coupling reactions. Cahiez et al. have reported oxidative cross-coupling reactions between sp- and sp^2-hybridized RMgX compounds with O_2 as oxidant and Li_2MnCl_4 (20 mol %) as catalyst.[10b] For some substrate combinations, they were able to achieve a good selectivity for the cross-coupling product.

First test reactions with two different sp^3-hybridized or two different sp^2-hybridized Grignard reagents yielded an almost statistic distribution of the possible coupling products. The formation of the mixed product could be favored by using a 1:2 ratio of the starting materials, but the final yield of the cross-coupling product was still below 50 %. A different behavior was observed for oxidative cross-coupling reactions between sp^2- and sp^3-hybridized Grignard reagents. The coupling of phenylmagnesium chloride with phenethylmagnesium chloride gave biphenyl, bibenzyl and diphenylbutane in the molar ratio 11:85:4, which is quite distinct from the statistical distribution of 1:2:1. Further optimization was achieved by lowering the reaction temperature to 0 °C and using a 1:2 ratio of the starting materials (Table S3). Under these conditions, it was possible to obtain the cross-coupling products of phenylmagnesium chloride and different primary (*n*-butyl, *n*-decyl, phenethyl) and secondary alkyl Grignard reagents (cyclohexyl) in yields of 59–83 % (Table 4, entries 1–4). In line with the low reactivity of *tert*-butylmagnesium bromide in the homocoupling reactions, the cross-coupling with phenylmagnesium chloride was not very efficient (Table 4, entry 5), whereas very good selectivities were obtained for oxidative alkenyl–alkyl cross-coupling reactions (Table 4, entries 6–8).

The results summarized in Tables 1–4 demonstrate that aryl, alkenyl and alkyl Grignard reagents (RMgX) can be efficiently coupled using N_2O as the oxidant and simple transition metal salts as catalysts. The mechanism of these reactions likely involves the formation of a diorganyl metal complex MR_2L_n, which undergoes a reductive elimination before or after oxidation by N_2O. The order of these two steps may depend on the substrate and the catalyst. In the case of iron-catalyzed cross-coupling reactions of Grignard reagents with electrophiles, catalytic cycles shuttling between Fe^{I}/Fe^{III}, Fe^{0}/Fe^{II} or Fe^{-II}/Fe^{0} have been proposed.[15] At the moment, we do not have experimental evidence in favor of a particular scenario. For the oxidation of organocuprates, it has been suggested that oxidation of a $[CuR_2]^-$ complex preceeds the reductive elimination,[13] and a similar mechanism can be proposed for our system. Whitesides et al. had observed that the oxidation of Li[CuPh(*n*Bu)] with O_2 gave a nearly statistical mixture of biphenyl, phenylbutane, and octane.[14a] Our catalytic cross-coupling reactions of aryl and alkyl Grignard reagents with N_2O, on the other hand, displayed good selectivity for the mixed product. Interestingly, we observed that the selectivity for the cross-coupling product was lower when higher catalyst loadings were employed (Table S3).

Table 4: Oxidative cross-coupling of Grignard reagents.

$$\underset{(1\ \text{equiv})}{\text{R–MgX}} + \underset{(2\ \text{equiv})}{\text{R'–MgX}} \xrightarrow[\text{THF}]{\text{Li}_2\text{CuCl}_4\ (1\ \text{mol}\ \%),\ \text{N}_2\text{O}} \underset{\textbf{A}}{\text{R–R}} + \underset{\textbf{B}}{\text{R–R'}} + \underset{\textbf{C}}{\text{R'–R'}}$$

Entry	*t* [h]	Product **B**	Yield **B** [%][a]	**A/B/C**
1	2	Ph—*n*Bu	59	8:84:8
2	2	Ph—*n*decyl	61	11:80:9
3[c]	18		67 (57)[b]	5:52:43
4	2		83	0:76:24
5	2		16	53:31:16
6	2		87	0:79:21
7	2		82 (76)[b]	0:100:–
8[d]	2		65	0:66:34

[a] Yields were determined by GC-MS analysis. [b] Yields of isolated products are given in parentheses. [c] The reaction was started at 0 °C and was then allowed to slowly warm to RT. [d] The *E*/*Z* ratio of the product (86:14) was similar to that of the starting material (89:11).

It is evident that N_2 is a likely side product for all N_2O reactions described above. To demonstrate that N_2O is indeed converted into N_2 during the catalytic cycle, we analyzed the gas headspace before, during, and after completion of the reaction of octylmagnesium bromide with Li_2CuCl_4 (1 mol %). The chromatograms clearly show the formation of N_2 (Figure S1). Along with N_2, one expects the formation of equal amounts of MgO (Scheme 1). The latter can aggregate

$$\text{RMgX} + \text{R'MgX} + \text{N}_2\text{O} \xrightarrow[\text{THF}]{\text{catalyst}} \text{R—R'} + \text{MgX}_2 + \text{MgO} + \text{N}_2$$

Scheme 1. General reaction of Grignard reagents with N_2O.

with MgX_2 to form magnesium oxohalide clusters, such as $[(MgO)(MgBr_2)_3(solv)_4]$ (solv = solvent), which are known oxidation products of Grignard reagents.[16]

In conclusion, we have shown that N_2O can be used as an oxidant for the oxidative coupling reactions of Grignard reagents with $[Fe(acac)_3]$, $CoCl_2$, or Li_2CuCl_4 as catalysts. For most reactions, catalyst loadings of 0.1–1.0 mol % were sufficient to obtain good yields. Some aryl–aryl coupling reactions could be performed with less than 0.01 mol% catalyst loading. The corresponding turnover numbers are unprecedented for solution-based oxidation reactions with N_2O. Compared to alternative procedures with O_2 as the oxidant, our new method offers some important advantages: 1) It is possible to use lower amounts of catalyst, as N_2O is less prone to undergo metal-independent side reactions. 2) Sterically demanding arylmagnesium halides can be used as substrates. 3) Reactive alkyl Grignard reagents can be employed as substrates. 4) Aryl–alkyl and alkenyl–alkyl cross-coupling reactions can be achieved with good selectivity. These features should be attractive for applications in organic synthesis. But the implications of our work are possibly broader. The N_2O method is apparently compatible with a variety of transition metals (Fe, Co, and Cu). Complexes of these metals are used as catalysts in many other oxidative coupling reactions of nucleophiles,[7] some of which are thought to involve low-valent organometallic species. It appears likely that N_2O can be used as oxidant for some of these reactions as well.

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