α-Keto Amides and 1,2-Diketones from *N,N'*-Dimethoxy-*N,N'*-dimethylethanediamide. A Synthetic and Mechanistic Investigation[1]

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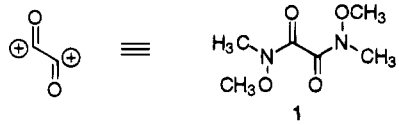
N,N'-Dimethoxy-*N,N'*-dimethylethanediamide (**1**), a 1,2-dicarbonyl synthon prepared from oxalyl chloride, undergoes nucleophilic displacements with Grignard reagents to provide α-keto amides **2–12** in 28–90% yields. The synthon also undergoes double nucleophilic displacements with organolithium reagents to furnish symmetrical 1,2-diketones **15–23** in 15–84% yields. A mechanism accounting for all the products from the reaction of **1** with nucleophiles has been proposed. Several control experiments were carried out to support the proposed mechanism.

Addition of organometallic reagents to carboxylic acid derivatives to provide ketones is a reaction which has received great scrutiny. This methodology suffers from side reactions in that reactive organometallic reagents (typically Grignard or organolithium) have a tendency to overadd to the substrates. Several routes to circumvent the overadditions have been described in the literature,[2] some of which require a carefully controlled low-temperature addition of 1 equiv or less of the organometallic reagent to an appropriate substrate. Nahm and Weinreb[3] reported that *N*-methoxy-*N*-methylamides function as carbonyl equivalents and react cleanly with both Grignard and organolithium reagents to form ketones. They showed that a variety of *N*-methoxy-*N*-methylamides undergo nucleophilic addition to produce ketones in good yields. These reactions do not require the stringent experimental conditions crucial to the success of many other methods. The utility of *N*-methoxy-*N*-methylamides in organic synthesis has been documented.[4]

The goal of this work was to find an efficient and convenient 1,2-dicarbonyl synthon, which could provide selectively both symmetrical and unsymmetrical 1,2-diketones and α-keto amides. The *N*-methoxy-*N*-methylamide **1**, derived from ethanedioic acid, was chosen as the 1,2-dicarbonyl synthon. This selection was based on



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the reactivity of *N*-methoxy-*N*-methylamides. The synthon **1** has two amide carbonyls, which can be manipulated individually either by changing the stoichiometry or by changing the nature of the nucleophile. With the addition of 1 equiv of the nucleophile to **1**, one can obtain α-keto amides. From 2 equiv, one can obtain symmetrical 1,2-diketones. And with the addition of 1 equiv of two different nucleophiles, one can obtain unsymmetrical 1,2-diketones.[5] In this paper, we report on the preparation of a variety of α-keto amides and symmetrical 1,2-diketones from **1**. Additionally, mechanistic details for organometallic addition to **1** and cleavage of the carbon–carbon bond during these reactions are also presented.

Results and Discussion

Synthesis of α-Keto Amides. Several methods have been reported in the literature for the preparation of α-keto amides.[6] Of these, nucleophilic addition to carboxylic acid derivatives has the best potential for the preparation of a wide variety of α-keto amides in a few simple synthetic operations. Adams *et al.*[6b–e] reported that the reaction of dimethyloxanilide with 4 equiv of ethylmagnesium bromide gave a 14% yield of the corresponding α-keto amide. Campaigne *et al.*[6a] investigated *N,N,N',N'*-tetramethylethanediamide as a 1,2-dicarbonyl equivalent and reported that reaction with 1 equiv of organolithium gave the corresponding keto amide in low to good yield.

Our approach to α-keto amides involved the treatment of **1** with a variety of nucleophiles. The initial task was the preparation of the starting material **1**. This diamide[7]

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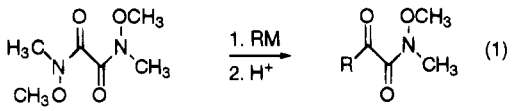
Table 1. Effect of Counterion and Solvent on α-Keto Amide Yields[a]

entry	RM[b]	solvent	temp, °C	yield,%
1	PhMgBr	ether	0	90
2	PhMgBr	THF	0	90
3	PhLi	THF	−78	65
4	2-thienylMgBr	THF	0 to rt	78
5	2-thienylLi	THF	0 to rt	42

[a] Yields are for column-purified materials. [b] 1.5 equiv of the reagent was used in each reaction.

was easily prepared from the reaction of oxalyl chloride with *N,O*-dimethylhydroxylamine hydrochloride in dichloromethane, with 2.2 equiv of pyridine as a proton scavenger, followed by aqueous acidic workup. The oxalyl amide was purified by simple recrystallization. The yield of the purified **1** was 95%. Compound **1** is a stable white crystalline material and does not require special storage.

Optimization of the reaction conditions for the formation of α-keto amides focused on the solvent, the reaction conditions, and the counterion of the nucleophile (eq 1).



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Several different solvents such as THF, DME, and ether were evaluated for their effectiveness. Solvent plays a minimal role in determining product yields (Table 1, entries 1 and 2). The effect of temperature on product yields depended on the nature of the counterion of the nucleophile. Two types of organometallic reagents, organolithiums and Grignard reagents, were investigated in this study. The organolithium reagents were more reactive than the corresponding Grignard reagents, and it was difficult to control the reaction to produce only the α-keto amide. In several reactions of **1** with 1−1.5 equiv of the organolithium reagent, we observed the formation of 1,2-diketones in minor amounts. These experiments indicated that the use of organolithiums as nucleophiles for the high-yield preparation of α-keto amide would be difficult. However, these results showed the potential for the use of organolithium reagents in the preparation of 1,2-diketones from **1**.

Under identical conditions, Grignard reagents gave significantly higher yields of the α-keto amides on reaction with **1** than the corresponding organolithium reagents (Table 1, entries 4 and 5). Thus, the optimized conditions for the formation of α-keto amides from **1** are treatment with 1−1.5 equiv of the Grignard reagent in THF at 0 °C for 1−4 h. In all of these reactions, we did not observe the formation of products from overaddition (tertiary alcohols) or 1,2-diketones from addition to both carbonyls. The selectivity observed in the preparation of α-keto amides can be attributed to the stable monochelated intermediate formed after nucleophilic addition.

The preparation of a variety of α-keto amides (eq 1), using these optimized reaction conditions, is shown in Table 2. The chemical yields range from moderate to excellent for a variety of substrates (52−90%) except in the case of **7** (28%). Nucleophiles containing primary and secondary aliphatic, aromatic, and heterocyclic functional groups react readily in this transformation. Unhindered aromatic nucleophiles gave the highest yields (compounds **2**−**6**). The presence of electron-donating or electron-withdrawing functional groups on the aromatic ring did not affect the chemical yields (compounds **3**−**5**). Steric hindrance has a large impact on the chemical yield. The reaction of **1** with the bulky (2,4,6-trimethylphenyl)-magnesium bromide provides **7** in only 28% yield. Similarly, the reaction of **1** with the more hindered (2-methoxyphenyl)magnesium bromide gave 70% of the keto amide **4**, whereas the reaction with the unhindered (4-methoxyphenyl)magnesium bromide gave 83% of the keto amide **3**.

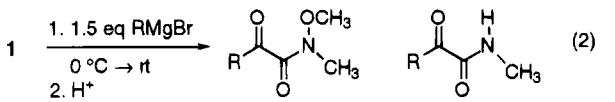
Table 2. Synthesis of α-Keto Amides[a]

compd	R	yield, %
2	Ph	90
3	4-MeOPh	83
4	2-MeOPh	70
5	4-ClPh	81
6	4-MePh	74
7	2,4,6-Me_3Ph	28
8	*n*-butyl	52
9	*n*-hexyl	64
10	cyclohexyl	64
11	2-thienyl	78
12	$PhCH_2$	60

[a] Yields are for column-purified materials.

Compared to other literature methods for the synthesis of α-keto amides, the present approach has the advantages of simplicity of the reaction procedure and ready availability of the starting materials. The methodology to prepare α-keto amides described here does not require stringent reaction conditions, temperature, and a large excess of nucleophile as reported by Campaigne *et al.*[6a] in their synthesis of α-keto amides. Additionally, Campaigne's methodology was limited to aromatic nucleophiles.

In the reaction of **1** with cyclohexylmagnesium bromide, a byproduct **13** was obtained in 11% yield in addition to the desired α-keto amide. This was identified as the α-keto *N*-methylamide, the product resulting from demethoxylation (eq 2).



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R = cyclohexyl **10** (64%) **13** (11%)
R = benzyl **12** (60%) **14** (17%)

A similar demethoxylation product was obtained in 17% yield from the reaction of **1** with benzylmagnesium bromide. This type of demethoxylation has been reported in the literature.[8] The mechanism of this demethoxylation has been postulated to involve an E_2 pathway.[9] The demethoxylation in this work appears to depend on the reactivity of the nucleophile. Other nucleophiles also gave minor amounts of the demethoxylated compounds.

Synthesis of Symmetrical 1,2-Diketones. In spite of the many reported methods for the preparation of 1,2-diketones,[10] direct nucleophilic additions to 1,2-dicarbonyl equivalents have been largely unexplored. The literature contains two reports on the synthesis of 1,2-diketones form 1,2-dicarbonyl equivalents. These are the reaction

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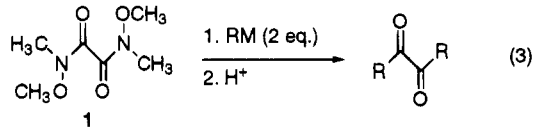
of 1,1'-oxalylimidazole[10m] and 1,4-dimethylpiperizine-2,3-dione[10n] with Grignard reagents. With the encouraging results from the use of **1** as an α-keto amide synthon, we set out to explore the utility of **1** as a precursor in the synthesis of 1,2-diketones (eq 3).



(3)

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To initiate this investigation, we chose benzil as our target molecule to optimize the reaction conditions. The optimization parameters included temperature, counterion of the nucleophile, solvent, and time. From our earlier experiments on nucleophiles with **1**, we surmised that the best starting point for the formation of 1,2-diketones would be at reflux temperature using Grignard reagents. Our attempts to prepare benzil by the reaction of phenylmagnesium bromide with **1** (nucleophile:**1** = 5:1) at room temperature and reflux (ether, at 35 °C or THF at 65 °C) were unsuccessful. A variety of products were formed under these reaction conditions (*vide infra*). Reaction of **1** with phenylmagnesium bromide at 0 °C or from −78 °C → rt showed minor amounts of benzil (TLC, GC analysis, and column chromatography).

For the next series of experiments, at different temperatures, phenyllithium was used as the nucleophile. Reaction of **1** with phenyllithium at 0 °C or higher gave minor amounts of the desired benzil. Lowering the reaction temperature to −20 °C gave benzil in 32% yield. The highest yield of benzil (75%) was obtained at −54 °C. Thus, the optimal condition for diketone formation was low temperature, with organolithium as the nucleophile. Product(s) from overaddition (tertiary alcohols) of the nucleophile were not observed when the reaction was carried out using phenyllithium and **1** at low temperatures (<−50 °C).

Failure of the reaction to produce 1,2-diketones from organometallics and **1** at 0 °C or above could be explained by the instability of the bis-chelated intermediate formed after the nucleophilic attack. The formation of diketones at lower temperatures indicates that the stability of the chelated intermediate increases as the temperature is lowered. Furthermore, the counterion also seems to play an important role in product formation. Unlike the preparation of α-keto amides in high yields with Grignard reagents, double addition to **1** requires the use of organolithium reagents. The higher reactivity of organolithiums as compared to Grignard reagents may be the critical factor in determining the formation of the 1,2-diketone product. However, these results are not indicative of the stability of the chelated intermediate with the two different counterions (Li^+ and Mg^{2+}).

Table 3. Synthesis of Symmetrical 1,2-Diketones[a]

entry	comp	R	yield, %
1	**15**	Ph	75
2	**16**	4-MeOPh	74
3	**17**	2-MeOPh	74
4	**18**	4-ClPh	64
5	**19**	4-MePh	73
6	**20**	4-FPh	84
7	**21**	2-furyl	73
8	**22**	2-thienyl	48
9	**23**	*n*-butyl	15

[a] Yields are for column-purified materials.

After establishing the optimal temperature for benzil formation, we then studied the effect of solvent on product formation. Several solvents were evaluated for their efficiency (THF, hexane, DME, ether, and THF–ether mixed systems). Among these, THF gave the best results. The starting material **1** has limited solubility in ether at low temperatures and is not suitable for reactions at low temperatures.

The next optimization parameter was reaction time, which plays a crucial role in this transformation. The product composition was analyzed by two methods: isolation of the pure compound by column chromatography and/or GC analysis with an internal standard. There were several minor byproducts in this reaction. With shorter reaction times (6.5 h), the reaction was only half complete (48% benzil), and GC analysis showed the presence of starting material. The optimum time was between 16 and 20 h. The reactions can be monitored by TLC and/or GC for complete consumption of the starting material. Longer reaction times decreased the amount of the desired diketone and increased the amounts of the byproducts. These results indicated that the chelated intermediate is not stable indefinitely at low temperatures and will undergo slow decomposition to furnish secondary products.

After completion of the optimization studies, we then investigated the scope of this reaction for the preparation of various 1,2-diketones (Table 3). The aryllithiums gave good to excellent yields of the desired diketones (entries 1–6). In contrast, heterocyclic nucleophiles gave moderate yields of the diketones (entries 7 and 8). The diketone formation from aliphatic nucleophiles was difficult and only produced the desired product in low yields (entry 9).

The present methodology compares favorably with the two reported methods[10m,n] for the preparation of 1,2-diketones from dicarbonyl equivalents and aromatic nucleophiles. This methodology is straightforward and provides moderate to good yields of the products. The limitations are the requirement for organolithiums as the nucleophiles and the stringent reaction conditions. Additionally, the reaction is suited for the preparation of aryl and heterocyclic 1,2-diketones only.

Mechanistic Studies. During our optimization studies for benzil preparation, we observed the formation of

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Scheme 1. Formation of Secondary Products during Diketone Synthesis

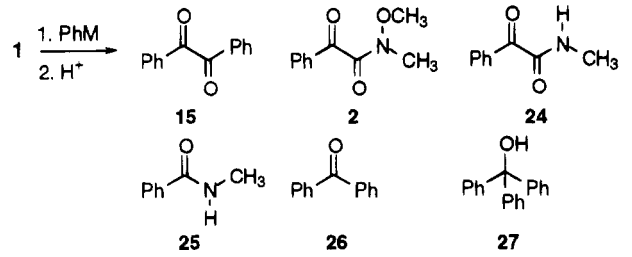

Table 4. Secondary Products during Diketone Synthesis[a]

entry	M	solvent	temp, °C	yield, % 15	2	24	25	26	27
1	Li	THF	−54	75	9	3	<5	–	–
2	Li	THF	0	1	5	5	36	21	–
3	Li	THF	rt	–	<1	<1	32	26	–
4	Li	ether	−62	53	12	1	11	3	–
5	MgBr	ether	−78 → rt	16	28	–	19	20	–
6	MgBr	ether	reflux	<1	2	<1	17	19	1
7	MgBr	ether:THF	reflux	–	–	–	26	22	–
8	MgBr	THF	reflux	–	<1	11	26	26	5

[a] Yields are for column-purified materials.

several minor products (Scheme 1). We surmised that a better understanding of the factors responsible for the formation of these compounds may help in delineating the optimal reaction conditions for diketone formation. Thus, a study was undertaken to investigate the reaction conditions under which the formation of secondary products could be controlled.

Phenyllithium and phenylmagnesium bromide were used as the nucleophiles, and the reactions were carried out under several conditions with variations in temperature, stoichiometry, and solvent. The results from these studies are presented in Table 4. The reactions were monitored by GC and TLC, and the products were isolated by column chromatography and their structures determined by spectroscopy (NMR and IR). The structures for these secondary products were further confirmed by comparison with authentic materials.

When the diketone synthesis was carried out under the optimal conditions (entry 1), the formation of three byproducts was observed. These were identified as α-keto *N*-methoxy-*N*-methylamide **2**, α-keto *N*-methylamide **24**, and *N*-methylbenzamide (**25**). Two additional products were also observed when the reaction was carried out using phenylmagnesium bromide in THF at reflux (entry 8). These were identified as benzophenone (**26**) and triphenylmethanol (**27**). The amount of these secondary products varied according to the reaction conditions.[11] The formation of the secondary products **25**–**27** requires carbon–carbon bond cleavage during the reaction, and experiments were designed to understand this process.

The cleavage of the carbonyl carbon–carbon bond of 1,2-dicarbonyls during nucleophilic additions has been reported in the literature. Adams and Weeks[12] reported the reaction of oxalyl chloride with alcohols in which primary alcohols gave oxalates smoothly, whereas secondary alcohols produced carbonates through a decarbonylative pathway. Staudinger *et al.*[13] reported similar decarbonylative reactions of oxalyl chloride with amine nucleophiles. Iida and Itaya[14] observed decarbonylations during their investigation of acylation of 1,2-glycols with oxalyl chloride. The product obtained from this reaction was a cyclic carbonate instead of the expected cyclic oxalate. From these studies, they proposed a mechanism for the reaction of 1 mol of oxalyl chloride with 2 mol of alcohol, in which the carbonyl carbon–carbon bond of the 1,2-dicarbonyl equivalent was cleaved. Tanner and Das[15] have also reported decarbonylation in their approach to the synthesis of pyruvyl and benzoyl formyl cyanides from the corresponding acyl chlorides with cuprous cyanide. Mueller-Westerhoff and Zhou have observed the formation of benzophenone and benzoylpiperidide in the reaction of oxalylpiperidide with excess phenyllithium.[16] Based on the above literature precedents and the reactions described in the previous sections, a comprehensive mechanism, which takes into account all the different reaction products from nucleophilic addition to **1**, was developed and is shown Scheme 2.

The formation of the secondary products **2** and **24** can be explained as arising from the addition of 1 equiv of the nucleophile to **1** through the intermediacy of a chelated intermediate **28**.[17] The formation of three other secondary products, *N*-methylbenzamide (**25**), benzophenone (**26**), and triphenylmethanol (**27**), requires the cleavage of the carbonyl carbon–carbon bond of a mono- or bis-adduct. Addition of excess nucleophile results in the formation of a bis-chelate **29**, which, on acidic treatment, yields the diketone **15**. This pathway dominates under the optimal reaction conditions for diketone formation. At elevated temperatures, the stability of **29** is lessened, allowing for fragmentation. This pathway involves the cleavage of the carbon–carbon bond through a six-membered transition state with loss of lithium or magnesium alkoxide and formation of fragments **30** and **31**. Fragment **30** undergoes further reaction with the excess nucleophile present in the reaction medium to give benzophenone (**26**), which can also undergo a subsequent nucleophilic addition to furnish triphenylmethanol (**27**). Fragment **31**, a stabilized anion, undergoes protonation during workup to give the benzamide **25**. It will be shown later that **25** is not a decarbonylation product of **24**.

The difference in reactivity between the Grignard and the organolithium reagents is quite striking. In the case of the Grignard reagents, the bis-chelate of type **29** is not present in any appreciable amount at 0 °C or higher since benzil is not isolated or detected (<1%, Table 4, entries 6, 7, and 8). Even at low temperatures, only a small amount of the bis-chelate **29** is formed from the Grignard reagent (Table 4, entry 5). However, the bis-chelate is readily formed from the organolithium at low temperatures (Table 4, entries 1 and 4). This difference in formation and/or stability of **29** with respect to the counterion may in part be due to the lower reactivity of

(11) According to the mechanism in Scheme 2, **25** and **26** should be formed in equal amounts. Small differences in the yields of these minor products as shown in Table 4 are artifacts of the workup procedure.

(12) Adams, R.; Weeks, L. F. *J. Am. Chem. Soc.* **1916**, *38*, 2514.

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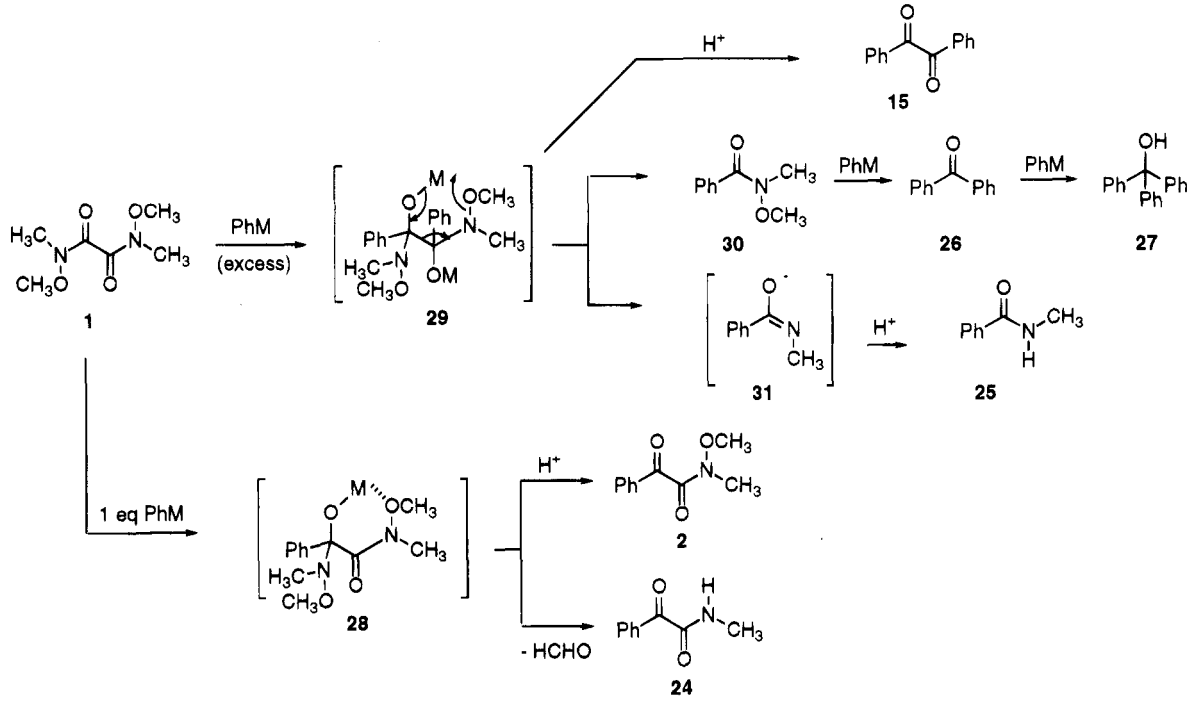
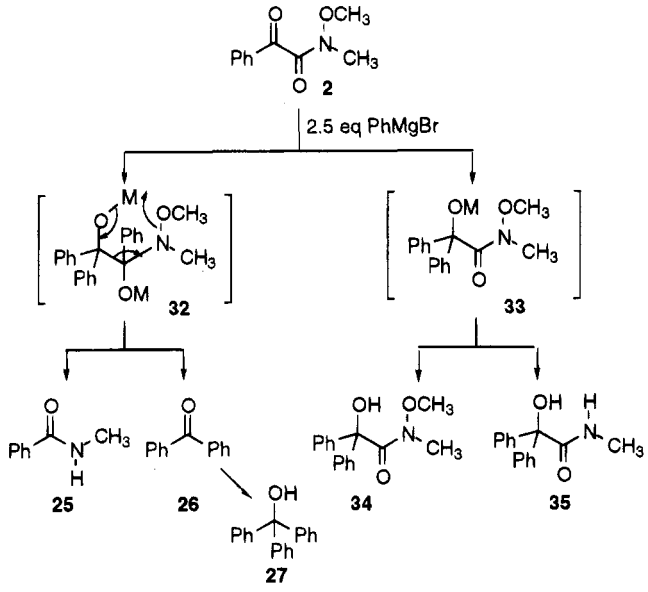
(16) See ref 6 in: Mueller-Westerhoff, U. T.; Zhou, M. *Tetrahedron Lett.* **1993**, *34*, 571.

(17) For all the chelated intermediates discussed in this section, the structures are written as the six-membered chelates for consistency and to explain some of the decomposition pathways. However, intermediates **28**, **29**, **32**, and **33** have multiple coordination sites, and the exact nature of the chelation (five-, six-, or seven-membered) is not known.

Scheme 2. Mechanism of Organometallic Additions to 1



Scheme 3. Reaction of PhMgBr with *N*-Methoxy-*N*-(methylbenzoyl)formamide

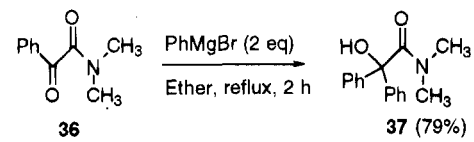


the Grignard reagent as compared to that of the corresponding organolithium reagent. The second factor which may contribute to this difference may have to do with the size of the ions. Intermediate **29** is a hexasubstituted ethane, and its formation could be difficult with the larger counterion, magnesium.

Several control experiments were undertaken to further corroborate the proposed mechanism. The first of these was to discern whether a bis-chelate, such as **29**, was needed for the fragmentation pathway. Additionally, this experiment would help in understanding whether the secondary products are formed from the α-keto amide. Thus, treatment of **2** with an excess of phenylmagnesium bromide at reflux with two different solvent systems gave multiple products (Scheme 3, Table 5).

Reaction of **2** with 1 equiv of phenylmagnesium bromide in ether at reflux for 2.5 h gave **34** in 74% yield along with 15% of recovered starting material (Table 5, entry 1).[18] Reaction of **2** with 2.5 equiv of phenylmagnesium bromide furnished several products (Table 5, entries 2 and 3). The formation of products **25** and triphenylmethanol (**27**) indicates that bis-adducts of the type **32** or **29** are most likely a requirement for fragmentation. Additionally, the formation of larger amounts of **25** and **27** in refluxing THF further supports the temperature dependence of chelate stability. Products **34** and **35** are not observed in the reaction of **1** with 1.5 equiv phenylmagnesium bromide at 0 °C, thus indicating that the mono-adduct **28** (Scheme 2) does not decompose to **2** during these reaction conditions.

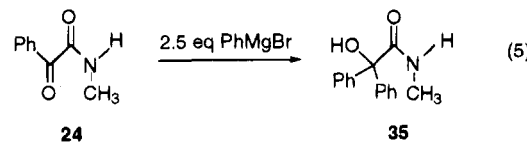
To ascertain whether the methoxy group of *N*-methoxy-*N*-methylamides is necessary for fragmentation, two separate experiments were carried out. The first experiment involved the treatment of *N*,*N*-(dimethylbenzoyl)-formamide **36** with phenylmagnesium bromide in ether at reflux (eq 4). The major product from this reaction



(4)

was the tertiary alcohol **37**.

The second experiment involved the treatment of *N*-(methylbenzoyl)formamide with excess phenylmagnesium bromide in three different solvent systems at reflux temperature (eq 5). Only a single product, the tertiary



(5)

alcohol **35** (ether, reflux, 80%; THF, reflux, 77%; ether: THF (1:1), reflux, 67%), was obtained in this reaction. This experiment shows that deprotonated secondary

Table 5. Reaction of PhMgBr with *N*-Methoxy-*N*-(methylbenzoyl)formamide[a,b]

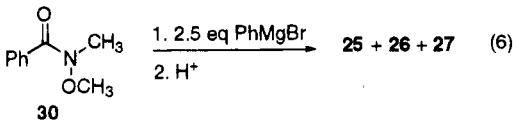
entry	PhMgBr, equiv	yield, % 34	35	25	27
1	1.0[c]	74	–	–	–
2	2.5[c]	56	3	6.5	8
3	2.5[d]	16	26	16	12

[a] Yields are for column-purified materials. [b] All reactions were carried out at reflux. [c] Ether was used as the solvent. [d] THF was used as the solvent.

amides do not undergo nucleophilic additions. The clean formation of **35** also indicates that **25** is not a decarbonylation product of **24**.

The above set of experiments indicates that the methoxy group of the *N*-methoxy-*N*-methylamide functionality is a requirement for fragmentation. These results also show that nucleophiles react chemoselectively with keto carbonyls in the presence of *N*-methoxy-*N*-methylamides.

To provide additional evidence for the proposed mechanism, we mimicked the conditions for the formation of triphenylmethanol from **30** (eq 6) by preparing an authentic sample of **30** and treating it with phenylmagnesium bromide.



30

In refluxing ether, benzophenone (**26**) (66%) and triphenylmethanol (**27**) (6%) were isolated after workup. A similar experiment with THF as the solvent gave benzophenone (65%) and triphenylmethanol (16%). These results demonstrate that triphenylmethanol is a product from the reaction between **30** and phenylmagnesium bromide. The formation of benzophenone in good yields under refluxing conditions indicates the high stability of the mono-chelate formed after addition of the Grignard reagent. This is in contrast to the fragmentation observed with the bis-chelate **29**. The evidence from the control experiments described above lends strong support to the postulated mechanism (Scheme 2). Hence, all of the products formed in our nucleophilic additions can be explained by a single mechanism. The product distribution in these reactions is governed by the stability of the chelated intermediate.

Conclusions

We have prepared a novel 1,2-dicarbonyl synthon form oxalyl chloride. This synthon has been successfully used in the preparation of a series of α-keto amides and symmetrical 1,2-diketones in good to excellent yields. A mechanism accounting for all of the products from the reaction of this dicarbonyl synthon with nucleophiles has been proposed. Several control experiments were performed to support the proposed mechanism. The extension of the present methodology to the synthesis of unsymmetrical 1,2-diketones, 1,*n*-diketones, and 1,2,3-tricarbonyl compounds is underway.

(18) The attack of the nucleophile at the amide carbonyl in preference to the keto carbonyl can be ruled out by the absence of benzil (or benzil derived) as one of the products. Product derived from quenching of **32** is also not observed, indicating that the intermediate **32** is unstable and undergoes fragmentation under the reaction conditions.

Experimental Section

All reagents were used as received from the supplier. Tetrahydrofuran, ether, and 1,2-dimethoxyethane were distilled from sodium benzophenone/ketyl prior to use. Chloroform, hexane, and methylene chloride were distilled from calcium hydride. Standard benchtop techniques were employed for handling air-sensitive reagents, and all reactions were carried out under nitrogen. Flash column chromatography was performed using Merck 60 silica gel, 230–400 mesh. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 and 65 MHz, respectively. Gas chromatography was performed on a DB-5 capillary column with a FID detector.

***N,N'*-Dimethoxy-*N,N'*-dimethylethanediamide (1).** To oxalyl chloride (15 mL, 172 mmol) was added 37.6 g (385 mmol) of *N,O*-dimethylhydroxylamine hydrochloride under N_2. The mixture was cooled to 0 °C using an ice bath, and 62.3 mL (770.6 mmol) of pyridine was added dropwise. After complete addition of the pyridine, the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with brine, and the organics were removed *in vacuo*. The aqueous solution was partitioned between brine and a 1:1 mixture of ether and CH_2Cl_2. The aqueous layer was reextracted twice with a 1:1 mixture of ether and CH_2Cl_2. The combined organics were washed with 3 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The product was crystallized from ethyl acetate–hexane to afford white crystals: mp 93–94 °C (lit.[7] mp 86 °C); ^1H NMR δ 3.66 (s, 3H), 3.16 (s, 3H); ^{13}C NMR δ 164.6, 61.8, 30.9.

General Procedure for the Preparation of α-Keto Amides. To **1** (1 mmol) in 3 mL of freshly distilled THF under N_2 was added dropwise 1.1–1.5 mmol of Grignard reagent. Upon complete consumption of starting material (0.5–4 h, TLC), the reaction was quenched with 3 M HCl and the THF was removed *in vacuo*. The resulting aqueous solution was extracted with EtOAc (20 mL), and the layers were separated. The aqueous layer was reextracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of solvent and purification by flash column chromatography (EtOAc–hexane) gave products.

***N*-Methoxy-*N*-methyl-α-oxobenzeneacetamide (2):** mp 65–66 °C; ^1H NMR δ 7.92 (d, J = 7.3 Hz, 2H), 7.64 (m, 1H), 7.52 (m, 2H), 3.66 (s, 3H), 3.37 (s, 3H); ^{13}C NMR δ 190.6, 166.8, 134.2, 132.4, 128.9, 128.5, 61.6. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.94; H, 5.69; N, 7.31.

***N*-Methoxy-*N*-methyl-α-oxo-4'-methoxybenzeneacetamide (3):** mp 47–48 °C; ^1H NMR δ 7.88 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 3.35 (s, 3H); ^{13}C NMR δ 189.3, 167.4, 131.5, 125.6, 114.0, 61.8, 55.4, 31.1. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.23; H, 5.89; N, 6.21.

***N*-Methoxy-*N*-methyl-α-oxo-2'-methoxybenzeneacetamide (4):** mp 48–49 °C; ^1H NMR δ 7.73 (dd, J = 8.1 Hz, 1H), 7.51 (dt, J = 7.3 Hz, 1H), 6.93–7.04 (m, 2H), 3.84 (s, 3H), 3.58 (s, 3H), 3.23 (s, 3H); ^{13}C NMR δ 188.8, 159.9, 159.5, 135.7, 129.5, 122.0, 120.5, 112.0, 60.9, 56.0, 31.6. Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.34; H, 5.92; N, 6.29.

***N*-Methoxy-*N*-methyl-α-oxo-4'-chlorobenzeneacetamide (5):** mp 73–74 °C; ^1H NMR δ 7.86 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 3.66 (s, 3H), 3.36 (s, 3H); ^{13}C NMR δ 189.4, 166.6, 141.0, 131.1, 130.5, 129.2, 62.0, 31.2; IR ($CHCl_3$) 1691, 1665 cm^{-1}. Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.93; H, 4.53; N, 6.15.

***N*-Methoxy-*N*-methyl-α-oxo-4'-methylbenzeneacetamide (6):** mp 115–117 °C; ^1H NMR δ 7.80 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 3.65 (s, 3H), 3.35 (s, 3H), 2.43 (s, 3H); ^{13}C NMR δ 190.4, 167.4, 145.6, 129.5, 129.4, 61.9, 31.2, 21.7. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.78. Found: C, 63.80; H, 6.30; N, 6.73.

***N*-Methoxy-*N*-methyl-α-oxo-2',4',6'-trimethylbenzeneacetamide (7):** ^1H NMR δ 6.88 (s, 2H), 3.66 (s, 3H), 3.25 (s, 3H), 2.36 (s, 6H), 2.28 (s, 3H); ^{13}C NMR δ 194.0, 169.0, 141.6, 138.2, 132.1, 129.6, 61.7, 32.5, 21.2, 20.2. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.24; H, 7.51; N, 5.85.

***N*-Methoxy-*N*-methyl-α-oxohexaneamide (8):** ^{1}H NMR δ 3.66 (s, 3H), 3.20 (s, 3H), 2.67 (t, J = 7.33 Hz, 2H), 1.62 (m, 2H), 1.34 (m, 2H), 0.91 (t, 3H); ^{13}C NMR δ 200.0, 167.5, 61.4, 38.5, 30.6, 23.9, 21.4, 13.0. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.21; H, 9.00; N, 8.01.

***N*-Methoxy-*N*-methyl-α-oxooctaneamide (9):** ^{1}H NMR δ 3.59 (s, 3H), 3.10 (s, 3H), 2.59 (t, J = 7.3 Hz, 2H), 1.24–1.57 (m, 8H), 0.79 (t, 3H); ^{13}C NMR δ 200.2, 167.8, 61.6, 39.0, 31.0, 30.8, 28.17, 21.9, 13.4. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.80; H, 9.28; N, 6.80.

***N*-Methyl-*N*-methoxy-α-oxocyclohexaneacetamide (10):** ^{1}H NMR δ 3.48 (s, 3H), 3.03 (s, 3H), 2.51–2.54 (d, J = 6.6 Hz, 1H), 1.51–1.79 (m, 4H), 1.07–1.23 (m, 6H); ^{13}C NMR δ 202.7, 167.8, 61.4, 46.3, 30.6, 26.5, 25.2, 24.7; IR ($CHCl_3$) 1659, 1714 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.70; H, 8.60; N, 7.07. Found: C, 61.00; H, 8.42; N, 7.25.

***N*-Methoxy-*N*-methyl-α-oxo-2-thienylacetamide (11):** mp 68–69 °C; ^{1}H NMR δ 7.76 (dd, J = 3.7 Hz, 2H), 7.18 (t, J = 4.4 Hz, 1H), 3.71 (s, 3H), 3.34 (s, 3H); ^{13}C NMR δ 182.6, 166.0, 139.6, 135.9, 135.7, 128.4, 62.1, 31.4. Anal. Calcd for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.19; H, 4.75; N, 7.00.

***N*-Methoxy-*N*-methyl-α-oxobenzenepropanamide (12):** mp 93–94 °C; ^{1}H NMR δ 7.29–7.38 (m, 5H), 4.01 (s, 2H), 3.62 (s, 3H), 3.15 (s, 3H); ^{13}C NMR δ 197.3, 167.3, 131.5, 129.7, 128.4, 127.1, 62.0, 46.1, 31.2. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.56; H, 6.56; N, 6.51.

***N*-Methyl-α-oxocyclohexaneacetamide (13):** mp 53–54 °C; ^{1}H NMR δ 4.72 (m, 1H), 2.86 (d, J = 5.1 Hz, 3H), 0.98–2.40 (m, 11H); ^{13}C NMR δ 201.4, 160.6, 43.3, 28.0, 25.8, 25.7, 25.3. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.87; H, 8.93; N, 8.27. Found: C, 63.94; H, 8.79; N, 8.10.

***N*-Methyl-α-oxo-3-phenylpropanamide (14):** ^{1}H NMR δ 7.29 (m, 5H), 4.22 (s, 2H), 2.87 (d, J = 5.1 Hz, 3H); ^{13}C NMR δ 195.2, 160.1, 132.1, 129.1, 128.0, 126.5, 42.4, 25.3. Correct combustion analysis could not be obtained due to the slow decomposition of this compound.

General Procedure for the Preparation of 1,2-Diketones. To **1** (1 mmol) in 4 mL of freshly distilled THF cooled to −55 °C under N_2 was added the organolithium reagent at a rate of 0.21 mL/min *via* a syringe pump. Upon complete consumption of starting material (~16 h, TLC), the reaction was quenched with 4 mL of 3 M HCl and the mixture warmed to rt. The organic solvent was removed *in vacuo* and the resulting aqueous solution extracted with EtOAc (20 mL). The aqueous portion was reextracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of solvent and purification by flash column chromatography (EtOAc–hexane) gave the products.

1,2-Diphenylethanedione (benzil) (15):[19] mp 93–94 °C (lit. mp 94–95 °C); ^{1}H NMR δ 7.96–7.99 (m, 4H), 7.63–7.69 (m, 2H), 7.49–7.54 (m, 4H); ^{13}C NMR δ 194.5, 134.8, 132.9, 129.8, 128.9. The structure for the compound was confirmed by comparison of the spectral and analytical data with that of an authentic sample.

Bis(4-methoxyphenyl)ethanedione (4,4′-dimethoxybenzil) (16):[20] mp 128–129 °C (lit. mp 132–134 °C); ^{1}H NMR δ 7.94 (d, J = 6.6 Hz, 4H), 6.96 (d, J = 6.6 Hz, 4H), 3.88 (s, 6H); ^{13}C NMR δ 193.4, 164.8, 132.3, 126.2, 114.2, 55.5.

Bis(2-methoxyphenyl)ethanedione (2,2′-dimethoxybenzil) (17):[21] mp 126–127 °C (lit. mp 127–128 °C); ^{1}H NMR δ 8.08 (d, J = 6.3 Hz, 2H), 7.54–7.60 (m, 2H), 7.09–7.26 (m, 2H), 6.95 (d, J = 7.1 Hz, 2H), 3.59 (s, 6H); ^{13}C NMR δ 192.4, 160.2, 135.5, 130.3, 123.3, 121.2, 112.4, 55.8.

Bis(4-chlorophenyl)ethanedione (4,4′-dichlorobenzil) (18):[22] mp 195–196 °C (lit. mp 199 °C); ^{1}H NMR δ 7.92 (d, J = 8.1 Hz, 4H), 7.50 (d, J = 8.1 Hz, 4H); ^{13}C NMR δ 192.3, 141.8, 131.2, 131.1, 129.4.

Bis(4-methylphenyl)ethanedione (4,4′-dimethylbenzil) (19):[19] mp 99–100 °C (lit. mp 102–104 °C); ^{1}H NMR δ 7.86 (d, J = 8.1 Hz, 4H), 7.29 (d, J = 8.1 Hz, 4H), 2.44 (s, 6H); ^{13}C NMR δ 194.4, 146.0, 130.1, 129.9, 129.6, 21.9.

Bis(4-fluorophenyl)ethanedione (4,4′-difluorobenzil) (20):[19] mp 119–120 °C (lit. mp 120–122 °C); ^{1}H NMR δ 8.05 (m, 2H), 7.20 (m, 2H); ^{13}C NMR δ 192.31, 168.7 and 164.9 (J_{C-F} = 258 Hz), 132.7, 116.6, 116.2.

2,2′-Difurylethanedione (furil) (21):[19] mp 160–161°C (lit. mp 163–165 °C); ^{1}H NMR δ 7.79 (s, 2H), 7.65 (d, J = 3.7 Hz, 2H), 6.64 (d, J = 3.7 Hz, 2H); ^{13}C NMR δ 176.8, 149.3, 124.6, 113.0.

2,2′-Dithienylethanedione (22):[23] mp 79–80 °C (lit. mp 82–84 °C); ^{1}H NMR δ 8.07 (d, J = 4.1 Hz, 2H), 7.85 (d, J = 5.9 Hz, 2H), 7.19–7.26 (m, 2H); ^{13}C NMR δ 182.3, 138.5, 137.4, 137.2, 128.6.

5,6-Decanedione (23):[24] ^{1}H NMR δ 2.83–2.95 (m, 4H), 1.53–1.62 (m, 4H), 1.29–1.40 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H); ^{13}C NMR δ 199.1, 36.4, 25.2, 22.1, 13.7.

Mechanistic Studies. Formation of Secondary Products During Diketone Synthesis. (Table 4, Entry 8). To **1** (0.352 g, 2.0 mmol) in 15 mL of freshly distilled THF was added dropwise 10 mL (10.0 mmol) of freshly prepared phenylmagnesium bromide. The solution was refluxed for 18 h and the reaction monitored by TLC. The reaction mixture was cooled to 0 °C in an ice bath and the reaction quenched with 4 mL of 3 M HCl. The THF was removed *in vacuo*, the resulting aqueous solution was extracted with EtOAc (20 mL), and the layers were separated. The aqueous layer was reextracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of solvent and separation of the products by flash column chromatography (EtOAc–hexane) gave **2** (<1%), **24** (11%), **25** (26%), **26** (26%), and **27** (5%).

***N*-Methyl-α-oxobenzeneacetamide (24):** mp 70–71 °C; ^{1}H NMR δ 8.34 (dd, J = 8.1 Hz, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.48 (dd, J = 8.3 Hz, 2H), 2.99 (s, 3H), 2.97 (s, 3H); ^{13}C NMR δ 187.6, 162.6, 134.0, 133.01, 130.7, 128.1, 25.7. Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.43; H, 5.71; N, 8.61.

***N*-Methylbenzamide (25):**[19] mp 76–78 °C (lit. mp 76–78 °C); ^{1}H NMR δ 7.74–7.77 (m, 2H), 7.38–7.52 (m, 3H), 3.01 (d, J = 4.4 Hz, 3H); ^{13}C NMR δ 168.2, 134.5, 131.2, 128.4, 126.8, 26.7. The structure for the compound was confirmed by comparison of the spectral and analytical data with that of an authentic sample.

Benzophenone (26):[19] mp 48–49 °C (lit. mp 49–51 °C); ^{1}H NMR δ 7.46–7.51 (m, 4H), 7.57–7.63 (m, 2H), 7.79–7.83 (m, 4H); ^{13}C NMR δ 196.5, 137.5, 132.3, 129.9, 128.1. The structure for the compound was confirmed by comparison of the spectral and analytical data with that of an authentic sample.

Triphenylmethanol (27):[19] mp 161–162 °C (lit. mp 160–163 °C); ^{1}H NMR δ 7.30 (s, 15H), 2.80 (s, 1H); ^{13}C NMR δ 146.7, 127.8, 127.7, 127.1, 81.9. The structure for the compound was confirmed by comparison of the spectral and analytical data with that of an authentic sample.

***N*-Methoxy-*N*-methylbenzamide (30).** The compound was prepared from benzoyl chloride and *N,O*-dimethylhydroxylamine: ^{1}H NMR δ 7.66 (dd, J = 8.1, 1.49 Hz, 2H), 7.43–7.39 (m, 3H), 3.55 (s, 3H), 3.35 (s, 3H); ^{13}C NMR δ 169.5, 130.1, 127.7, 127.6, 60.6, 33.3. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.51; H, 6.80; N, 8.45.

Reaction of Phenylmagnesium Bromide with *N*-Methoxy-*N*-methyl-α-oxobenzeneacetamide (Table 5, Entry 3). To **2** (0.0981 g, 0.51 mmol) in 15 mL of THF under N_2 was added dropwise 2.5 mL (2.54 mmol) of freshly prepared phenylmagnesium bromide. The solution was refluxed for 18 h and the reaction monitored by TLC. The reaction mixture was cooled to 0 °C by an ice bath and the reaction quenched with 4 mL of 3 M HCl. The solvent was removed *in vacuo*, the resulting aqueous solution was extracted with EtOAc (10

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(24) Bloch, H.; Lehr, H.; Erlenmeyer, H. *Helv. Chim. Acta* **1945**, *28*, 1406.

mL), and the layers were separated. The aqueous layer was reextracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of solvent and purification by flash column chromatography (EtOAc–hexane) gave **25** (16%), **27** (12%), **34** (16%), and **35** (26%).

2,2-Diphenyl-2-hydroxy-*N*-methoxy-*N*-methylacetamide (34): mp 73–74 °C; ^{1}H NMR δ 7.37 (m, 10H), 6.01 (s, 1H), 3.12 (s, 3H), 2.55 (s, 3H); ^{13}C NMR δ 174.5, 142.4, 128.0, 127.8, 127.6, 81.3, 59.1, 33.7. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 71.00; H, 6.27; N, 4.93.

2,2-Diphenyl-2-hydroxy-*N*-methylacetamide (35): mp 148–149 °C; ^{1}H NMR δ 7.32–7.43 (m, 10H), 6.34 (b, 1H), 3.94 (s, 1H), 2.87 (d, J = 5.1 Hz, 3H); ^{13}C NMR δ 173.8, 142.8, 128.3, 128.1, 127.4, 81.4, 26.6. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.26; N, 5.80. Found: C, 74.00; H, 6.91; N, 5.63.

***N,N*-Dimethyl-α-oxobenzeneacetamide (36).**[25] The compound was prepared from benzoyl formyl chloride and dimethylamine: ^{1}H NMR δ 7.94 (d, J = 8.1 Hz, 2H), 7.61–7.67 (m, 1H), 7.48–7.53 (m, 2H), 3.11 (s, 3H), 2.95 (s, 3H); ^{13}C NMR δ 191.5, 166.7, 134.4, 132.6, 129.1, 128.6, 36.5, 33.5. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.61; H, 6.17; N, 7.86.

Reaction of Phenylmagnesium Bromide with *N,N*-Dimethyl-α-oxobenzeneacetamide. To **36** (0.109 g, 0.56 mmol) in 8 mL of ether under N_2 was added dropwise 1.12 mL (1.12 mmol) of freshly prepared phenylmagnesium bromide. The solution was refluxed for 2 h and the reaction monitored by TLC. The reaction mixture was cooled to 0 °C in an ice bath and the reaction quenched with 4 mL of 3 M HCl. The ether was removed *in vacuo*, the resulting aqueous solution was extracted with EtOAc (20 mL), and the layers were separated. The aqueous layer was reextracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of solvent and purification by flash column chromatography (EtOAc–hexane) gave **37** (79%).

2,2-Diphenyl-2-hydroxy-*N,N*-dimethylacetamide (37):[26] mp 130–131 °C (lit. mp 131–132 °C); ^{1}H NMR δ 7.38–7.29 (m, 10H), 3.05 (s, 3H), 2.82 (s, 3H); ^{13}C NMR δ 169.1, 141.2, 128.3, 128.2, 128.1, 75.6, 39.8, 37.8.

Reaction of Phenylmagnesium Bromide with *N*-Methyl-α-oxobenzeneacetamide. To **24** (0.0829 g, 0.51 mmol) in 8 mL of ether under N_2 was added dropwise 2.54 mL (2.54 mmol) of freshly prepared phenylmagnesium bromide. The solution was refluxed for 18 h and the reaction monitored by TLC. The reaction mixture was cooled to 0 °C in an ice bath and the reaction quenched with 4 mL of 3 M HCl. The ether was removed *in vacuo*, the resulting aqueous solution was extracted with EtOAc (10 mL), and the layers were separated. The aqueous layer was reextracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of solvent and purification by flash column chromatography (EtOAc–hexane) gave **35** (80%).

Reaction of Phenylmagnesium Bromide with *N*-Methoxy-*N*-methylbenzamide. To **30** (0.1651 g, 1.0 mmol) in 8 mL of freshly distilled THF under N_2 dropwise was added 5.0 mL (5.0 mmol) of freshly prepared phenylmagnesium bromide. The solution was refluxed for 18 h and the reaction monitored by TLC. The reaction mixture was cooled to 0 °C in an ice bath and the reaction quenched with 4 mL of 3 M HCl. The THF was removed *in vacuo*, the resulting aqueous solution was extracted with EtOAc (20 mL), and the layers were separated. The aqueous layer was reextracted with EtOAc (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of solvent and purification by flash column chromatography (EtOAc–hexane) gave benzophenone (**26**) (65%) and triphenylmethanol (**27**) (16%).

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