

Copper-Free Alternatives to Access Ketone Building Blocks from Grignard Reagents

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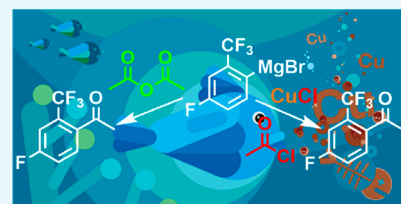


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ABSTRACT: Grignard reactions are an efficient way to form carbon–carbon bonds with widespread applications in large-scale processes. Classically, the electrophiles of choice to form ketones from Grignard reagents are acid chlorides. The reactions are typically catalyzed by additives such as CuCl to increase selectivity and yields. This work was focused on the use of acetic anhydride as an alternative to acetic chloride in the synthesis of 4-fluoro-2-(trifluoromethyl)acetophenone (**3**), a useful intermediate for the synthesis of active agricultural ingredients. The use of acetic anhydride as an electrophile not only equals but also surpasses acetic chloride in yield and selectivity, while also being more tolerable toward higher reaction temperatures. Furthermore, the reaction was performed in the absence of any additive, making it a highly attractive process for large-scale production. Computational mechanistic studies suggest that this advantageous behavior can be ascribed to the superior complexation of carboxylic acid anhydrides in the transition state.



1. INTRODUCTION

Grignard reactions are highly versatile, offering a comparable cheap access to active carbon nucleophiles to form carbon–carbon bonds.^{1–3} In recent years, different upgraded procedures for Grignard reactions were developed which apply various additives or catalysts, ranging from alkali salts such as lithium chloride to transition-metal salts like copper(I) chloride and iron(III) chloride.^{4–8} These catalysts usually increase the reactivity of the Grignard reagent (also referred to as “turbo-Grignard”), allowing milder reaction conditions and thereby widening the scope of Grignard reactions to substrates bearing various functional groups like ester, cyano, or nitro.^{9–11} Their higher reactivity is ascribed to the breakup of the otherwise characteristic aggregates and solvent complexes formed by Grignard reagents in ethers like Et₂O and tetrahydrofuran (THF).¹² In these solvents, the different active species are described by the Schlenk equilibrium.^{13,14} Recent theoretical studies on the reaction mechanism suggest that the energetic differences between these solvated species are minor, and the Grignard reaction should be considered as an ensemble of transformations that can occur simultaneously.¹⁵ However, catalyst addition not only increases the complexity of the reaction mechanism but also raises raw material costs. More importantly, for large-scale industrial processes, they significantly increase the intricacy and expenses for the waste stream treatment and disposal. Notably, copper salts are of major concern due to their high toxicity to aquatic life with long-lasting effects.¹⁶ Limits for wastewater outlets as well as for drinking water are congruously extremely low.¹⁷

2. RESULTS AND DISCUSSION

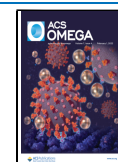
In Scheme 1 two synthetic pathways toward 4-fluoro-2-(trifluoromethyl)acetophenone (**3**) are presented, starting from the corresponding Grignard reagent (**1**) (4-fluoro-2-(trifluoromethyl)phenyl)magnesium bromide). The classical access to ketones proceeds using Grignard reagents and acid chlorides due to their high reactivity.^{18–20}

As depicted in Scheme 1a, the use of acetyl chloride (**2**) yields the target compound (**3**) as expected. However, to access (**3**) in high yields, Cu(I) salts in catalytic quantities and low temperatures of –5 to –10 °C are required.^{21,22} In the absence of CuCl, the reaction is known to proceed significantly slower and less selective, resulting in lower yields due to both side product formation and the required extended workup and purification steps. The role of copper in such catalyzed Grignard reactions was studied in the past. Most proposed reaction mechanisms involve a transmetalation from magnesium to copper and the formation of organocuprates as the active species in the actual C–C-bond formation.^{23,24} A similar catalytic cycle can be formulated for the aryl Grignard reaction with acetyl chloride and acetic anhydride in the presence of copper(I) (Scheme 2). Yet, for large-scale industrial processes, the use of CuCl has a series of disadvantages. The salts have low solubility under typical Grignard reaction conditions, forming a suspension in the reactor that tends to develop solid

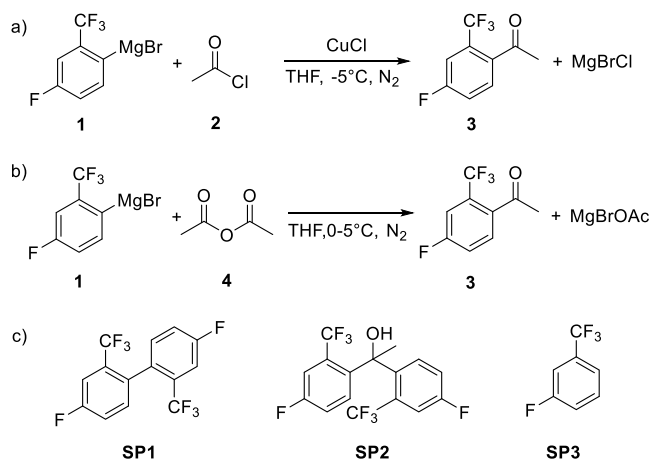
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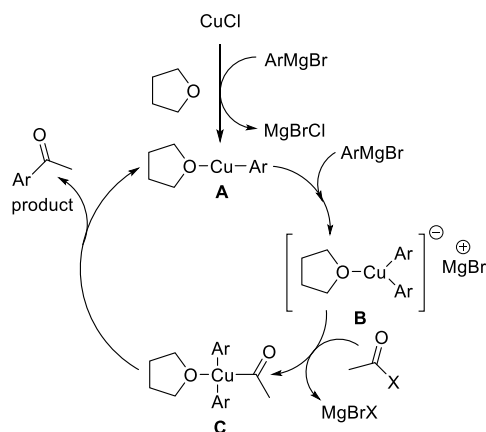
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Scheme 1. Reaction Pathways to Access 4-Fluoro-2-(trifluoromethyl)acetophenone (3); (a) Copper(I) Chloride-Catalyzed Grignard Reaction of (1) with Acetyl Chloride (2), (b) Grignard Reaction of (1) with Acetic Anhydride (4), and (c) Chemical Structures of the Main Side Products (SP1), (SP2), and (SP3)



Scheme 2. Proposed Catalytic Cycle for the Copper(I)-Catalyzed Grignard Reaction (X = Cl; OAc)



deposits on reactor walls and pipes, thus deteriorating heat exchange and promoting blockages in transfer pipes. Furthermore, copper ions form a variety of complexes, including those with THF.²⁵ These complexes hinder the solvent recovery by significantly increasing the reaction mixture's boiling point and causing problems in an alternative aqueous workup by hampering phase separations with increasing amounts of copper(I). The most significant disadvantage, however, is the high ecotoxicity of copper toward aqueous life. Consequently, the presence of copper salts in a chemical process inevitably requires an extensive and therewith expensive wastewater treatment to remove copper ions from the waste stream for a conscientious and sustainable chemical operation.²⁶ In our search for an efficient and more ecological synthetic access to our target compound (3), we found that simply replacing acetyl chloride with acetic anhydride (Scheme 1b and Table 1) outperforms the copper-catalyzed acetyl chloride variant.

An overview of the results is given in Table 1. While the copper-catalyzed variant with acetyl chloride gives appreciable high yields (above 90%), we did not succeed in increasing them above 95% (entry 1 in Table 1). Similar results were

Table 1. Overview of the Reaction conditions^a and Experimental Results for the Grignard Reaction of (1) with AcCl (2) and Ac₂O (4)

electrophile (equiv)	catalyst (equiv)	T ₁ [°C]	yield [%] ^b	SP1 [a %] ^c	others [a %] ^c
AcCl (1.2)	CuCl (0.03)	-5	93–95	0.5–1.5	~5
Ac ₂ O (1.05)	CuCl (0.03)	-5	93.5	0.5	6
Ac ₂ O (1.05)		-5	98.5	0.01	1.49
Ac ₂ O (1.05)		0	99.7 ^d	n/a ^e	0.3
Ac ₂ O (1.05)		5	99	n/a ^e	1
Ac ₂ O (1.05)		25	70	n/a ^e	30
Ac ₂ O (1.05)		50	35	n/a ^e	65

^aReactions were performed in semibatch mode by parallel dosage of (1) and the respective electrophile. Detailed experimental description is given in the Supporting Information. ^bIsolated yield after distillation. ^cCalculated based on GC analyses. ^dAveraged yield over five runs. ^en/a = compound was not detected in GC analysis.

achieved when acetic anhydride was used as an electrophile instead of acetyl chloride in the presence of copper(I) chloride (entry 2 in Table 1). Notably, the same side product distribution was found with the homocoupling product (SP1) as the largest single impurity formed in quantities of 0.5–1.5 a % by gas chromatography (GC) analysis (entries 1 and 2 in Table 1). These results indicate that the reaction proceeds according to the same reaction mechanism in the presence of copper(I) salts, regardless of the electrophile used. This is supported by the nearly identical reaction rates observed. In both cases, the reaction progress is dosage-controlled without significant accumulation of the reagents at a dosage speed of 1/3 mol/(kg h).

However, unlike acetyl chloride, the reaction with acetic anhydride proceeds smoothly in the absence of copper ions or any other catalysts. The reaction initiates immediately after starting the parallel dosage of the Grignard reagent and of acetic anhydride, leading to an almost quantitative conversion of the Grignard reagent to the target compound (3). Additionally, full conversion of (1) is achieved with a reduced excess of the electrophile (Table 1, entries 3–5). Best results with acetic anhydride were achieved within the range of 1.02–1.07 equiv compared to 1.2 equiv for acetyl chloride. A higher excess of acetic anhydride is not necessary, reducing the undesired formation of the 4-bromobutylacetate side product from the ring opening of THF in the presence of magnesium and bromide ions. Reducing the electrophile equivalents below 1.02 equiv resulted in slightly lower yields, which can be ascribed to the incomplete conversion of (1), forming (SP3) as the reaction product of (1) with water during workup (for details, see the Supporting Information). Interestingly, the formation of the homocoupled species (SP1) significantly decreased and can be suppressed below detectable limits in the absence of copper. This could be explained by the absence of cuprate species B and C in Scheme 2, which prevents a homocoupling of the Grignard compounds by an Ullmann-type reaction. In the absence of these species, a homocoupling could require a radical mechanism to form SP1. However, this mechanism appears to be suppressed at moderately elevated temperatures (<+5 °C). Hence, in the absence of a copper catalyst in the range of -5 to +5 °C, the acetylation of the Grignard reagent (1) with acetic anhydride afforded nearly quantitative yields (Table 1, entries 3–5). A further increase of the reaction temperature to 25 and 50 °C (Table 1, entries 6 and 7) resulted in a rapid decrease of the yield. This reduction

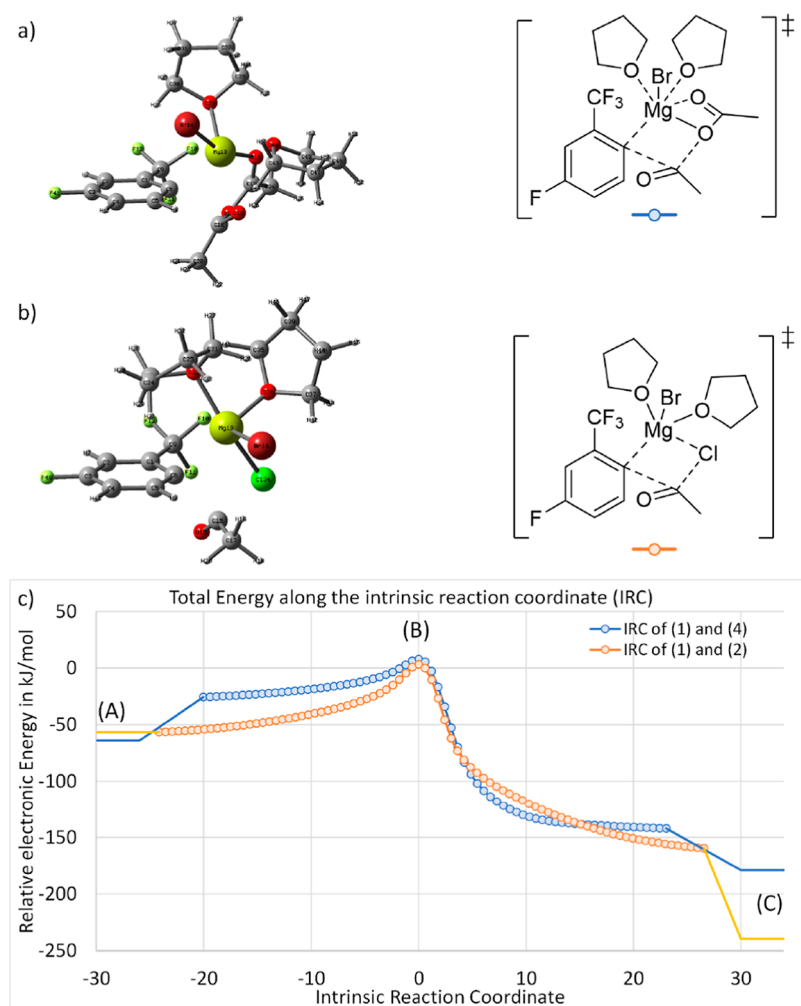


Figure 1. Calculated transition states for the Grignard reactions with acetic anhydride (**4**) and acetyl chloride (**2**) with an IRC calculation (calculated at PM7, with the SMD-THF solvation model, using Gaussian 16). 3D structure of the transition state (a) in the reaction of (**1**) with acetic anhydride (**4**) with a single imaginary frequency of -341 cm^{-1} and an activation energy of 56 kJ/mol and (b) in the reaction of (**1**) with acetyl chloride (**2**) with a single imaginary frequency of -406 cm^{-1} and an activation energy of 60 kJ/mol. (c) Graphical representation of the total energy along the IRC for the reaction of (**1**) with (**4**) and (**1**) with (**2**), respectively. The stations (A) represent the energy of the geometry-optimized adduct of the Grignard reagent (**1**) and acetic anhydride (**4**) or acetyl chloride (**2**), respectively; stations (B) represent the transition-state energies and (C) the geometry-optimized products. The relative energies are related to the energy of the isolated Grignard reagent (**1**) as well as the electrophile acetic anhydride (**4**) or acetyl chloride (**2**), respectively.

was related to subsequent reactions of the formed ketone product (**3**) with the Grignard reagent (**1**) to form (SP2) or other aldol-type condensation reactions, resulting in a variety of side products, such as acetoacetylated products or aldol dimers. The temperature tolerance and the nearly quantitative yields are rather remarkable, as most reported Grignard reactions with anhydrides only exhibited moderate-to-low yields and were run at extremely low temperatures (e.g., $-76\text{ }^{\circ}\text{C}$).^{27,28}

Explaining the observed differences in terms of Grignard reaction mechanisms is not straightforward, as mechanistic studies are still subject to scientific debates.¹⁵ A striking observation, for example, is the absence of the impurity (SP1) in reactions without the addition of copper(I)chloride. We interpret this peculiarity to a possible Ullmann-type cross-coupling reaction. However, the remaining concentration of 2-bromo-5-fluorobenzotrifluoride ($<0.3\%$ in the Grignard reagent solution; see the Supporting Information) from the preparation of the Grignard reagent is not sufficient to fully explain the observed amounts of the impurity (SP1) in excess

of 1%. We, therefore, suppose that a reductive elimination from species (C) in Scheme 2 might also be a pathway for SP1 formation.¹⁵ In the absence of copper, the experimental results are in agreement with a polar Grignard reaction mechanism. In the reaction of the Grignard reagent with the two electrophiles acetyl chloride (**2**) and acetic anhydride (**4**), in the absence of a copper catalyst, an unusual difference in selectivity was observed. To gain a deeper insight into these unusual reactivity differences of the two electrophiles AcCl (**2**) and Ac₂O (**4**), a computational mechanistic study was conducted using Gaussian 16 on a PM7 level using the SMD solvation model with THF parameters. Figure 1 shows the structures and energies for the calculated transition states corresponding to the reactions of (**1**) with (**4**) (Figure 1a) and of (**1**) with (**2**), respectively (Figure 1b). The progress of the reactions is illustrated using the intrinsic reaction coordinate (IRC) calculations for the proposed polar mechanisms in the absence of copper (Figure 1c).

In the transition-state complex (TSC) of the reaction of (**1**) with acetyl chloride (**2**) (Figure 1b), the magnesium center is

coordinated to the chloride atom still partially bonded to the acetyl group, which is already interacting with the aromatic ring. The transition-state structure of acetic anhydride (**4**) with the Grignard reagent (**1**) is dominated by the chelating properties of the acyl oxygens. The initial Grignard reagent forms an adduct (situation (A) in Figure 1c) with the electrophiles (acetic anhydride or acetyl chloride, respectively). These adducts form true energetic minima. While the acetic anhydride–Grignard adduct requires a relatively large conformational rearrangement to enter a rather flat IRC pathway to the transition state (situation (B) in Figure 1c), the acetyl chloride–Grignard adduct is geometrically already closely aligned to the IRC pathway. Nevertheless, the pathways proceed rather similar with similar activation energies of 56 and 60 kJ/mol for the acetic anhydride and acetyl chloride pathways, respectively. The similarity of the activation energy corresponds nicely to the experimental minor differences in reaction kinetics. The biggest difference between the two reaction pathways in Figure 1c is the higher energy released (61 kJ/mol) in the reaction with acetyl chloride compared to the reaction with acetic anhydride. According to Hammond's postulate, the transition state of the acetic anhydride reaction should therefore be structurally closer to the final product compared to the transition state of the reaction with acetyl chloride.²⁹ According to this postulate, a more exothermic reaction has a lower selectivity. Thus, the larger amount of released energy using acetyl chloride can explain the higher selectivity of using acetic anhydride compared to acetyl chloride.

3. CONCLUSIONS

Concluding, acetic anhydride can be used as a highly selective electrophile in Grignard reactions. Our studies show that, in contrast to acetyl chloride, high selectivity and yields were achieved without catalyst addition. We attribute this superior performance to the acetic anhydride ability to complex to the magnesium center, forming a more favorable transition state, which is closer to the product compared to acetyl chloride. This complexation not only facilitates the carbon–carbon bond formation but also promotes the dissociation of the TSC, resulting in a highly selective reaction with almost quantitative yields. Our results confirm that a rigorous parameter control during the reaction course, especially of the temperature and of the reagent ratio, is essential to achieve the best results. Yet, a stringent control of the dosage regime is important for both the studied electrophiles, acetic chloride (**2**) and acetic anhydride (**4**), as an excess of the Grignard reagent results in the formation of (SP2), while an excess of the electrophile triggers the formation of 4-halogenobutylacetates as side products. Our initial studies further suggest that the above-described strategy is not only limited to the above Grignard reagent but also suitable for the electron-richer Grignard species (see Supporting Information, procedure 4). We hope this work will help to raise awareness of the implications of using heavy-metal catalysts in large-scale chemical processes. Catalysts are valuable tools for the development of efficient organic synthesis and processes; however, especially in large-volume processes, the disposal of heavy metals must also be considered, and a heavy-metal-free alternative then brings great advantages.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c06202>.

Experimental procedures, analytical methods, and details related to the computational methods used (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

THF, tetrahydrofuran; Et, ethyl; IRC, intrinsic reaction coordinate; Ac, acetyl; T_i , internal reaction temperature; GC, gas chromatography; TS, transition state; TSC, transition-state complex; a %, area percent; PM7, parameterized model 7; SMD, solvation model based on density

■ REFERENCES

- (1) Grignard, V. Sur quelques nouvelles combinaisons organo-métalliques du magnésium et leur application à des synthèses d'alcools et d'hydrocarbures (On some new organometallic compounds of magnesium and their application to syntheses of alcohols and hydrocarbons). *C. R. Seances Acad. Sci., Ser. C* **1900**, *130*, 1322–1325.
- (2) Yamamoto, Y.; Asao, N. Selective reactions using allylic metals. *Chem. Rev.* **1993**, *93*, 2207–2293.
- (3) Yus, M.; González-Gómez, J. C.; Foubelo, F. Diastereoselective allylation of carbonyl compounds and imines: application to the synthesis of natural products. *Chem. Rev.* **2013**, *113*, 5595–5698.
- (4) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. Einfache Herstellung funktionalisierter Arylmagnesium-reagentien unter Verwendung von Magnesium in Gegenwart von LiCl. *Angew. Chem.* **2008**, *120*, 6907–6911; *Angew. Chem. Int. Ed.* **2008**, *47*, 6802–6806.
- (5) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. On the mechanism of the copper-catalyzed Enantioselective 1,4-addition of Grignard reagents to α,β -unsaturated carbonyl compounds. *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.

- (6) López, F.; Minnaard, A. J.; Feringa, B. L. Catalytic enantioselective conjugate addition with Grignard reagents. *Acc. Chem. Res.* **2007**, *40*, 179–188.
- (7) Ackermann, L. Air- and moisture-stable secondary phosphine oxides as preligands in catalysis. *Synthesis* **2006**, 1557–1571.
- (8) Hatakeyama, T.; Nakamura, M. Iron-catalyzed selective biaryl coupling: Remarkable Suppression of Homocoupling by the Fluoride Anion. *J. Am. Chem. Soc.* **2007**, *129*, 9844–9845.
- (9) Ziegler, D. S.; Wei, B.; Knochel, P. Improving the halogen–magnesium exchange by using new turbo-Grignard reagents. *Chem.—Eur. J.* **2018**, *25*, 2695–2703.
- (10) Robertson, S. D.; Uzelac, M.; Mulvey, R. E. Alkali-metal-mediated synergistic effects in polar main group organometallic chemistry. *Chem. Rev.* **2019**, *119*, 8332–8405.
- (11) Colas, K.; dos Santos, A. C. V. D.; Mendoza, A. *i*-Pr₂NMgCl·LiCl enables the synthesis of ketones by direct addition of Grignard reagents to carboxylate anions. *Org. Lett.* **2019**, *21*, 7908–7913.
- (12) Krasovskiy, A.; Straub, B. F.; Knochel, P. Hocheffiziente Reagentien für den Brom-Magnesium-Austausch. *Angew. Chem.* **2005**, *118*, 165–169; *Angew. Chem. Int. Ed.* **2005**, *45*, 159–162.
- (13) Schlenk, W.; Schlenk, W. Über die Konstitution der Grignardschen Magnesiumverbindungen. *Ber. Dtsch. Chem. Ges. B* **1929**, *62*, 920–924.
- (14) Tammiku-Taul, J.; Burk, P.; Tuulmets, A. Theoretical study of magnesium compounds: The Schlenk equilibrium in the gas phase and in the presence of Et₂O and THF molecules. *J. Phys. Chem. A* **2004**, *108*, 133–139.
- (15) Peltzer, R. M.; Gauss, J.; Eisenstein, O.; Cascella, M. The Grignard reaction – unraveling a chemical puzzle. *J. Am. Chem. Soc.* **2020**, *142*, 2984–2994.
- (16) <https://www.epa.gov/wqc/aquatic-life-criteria-copper> (accessed on 21.10.2021).
- (17) <https://www.epa.gov/dwreginfo/lead-and-copper-rule> (accessed on 21.10.2021).
- (18) Gilman, H.; Nelson, J. F. Relative reactivities of organometallic compounds. IX. cadmium. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 518–530.
- (19) Amri, H.; Villieras, J. Alkylation d'acetates de cyclenols fonctionnels (5 et 6 chainons) par les reactifs de grignard et les enolates lithiens catalysee (ou non) par les sels de cuivre (I). Synthese rapide de la (±) mitsugashiwalactone. *Tetrahedron Lett.* **1987**, *28*, 5521–5524.
- (20) Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. Addition of Grignard reagents to aryl acid chlorides: an efficient synthesis of aryl ketones. *Org. Lett.* **2005**, *7*, 5593–5595.
- (21) Gebhardt, J.; Saelinger, D.; Ehresmann, M.; Goetz, R. Process for the preparation of substituted phenyl ketones. WO 2016202807 A1. 2016.
- (22) Vogelbacher, U. J.; Gebhardt, J.; Rack, M.; Götz, R.; Fülster, S. Process for the preparation of substituted phenoxyphenyl ketones. WO 2015091045 A1, 2015.
- (23) Ouali, A.; Taillefer, M. Grignard reagents and Copper. *Phys. Sci. Rev.* **2016**, *1*, 244.
- (24) Yoshikai, N.; Nakamura, E. Mechanisms of Nucleophilic Organocopper(I) Reactions. *Chem. Rev.* **2012**, *112*, 2339.
- (25) Halvagar, M. R.; Tolman, W. B. Isolation of a 2-hydroxytetrahydrofuran complex from copper-promoted hydroxylation of THF. *Inorg. Chem.* **2013**, *52*, 8306–8308.
- (26) Al-Saydeh, S. A.; El-Naas, M. H.; Zaidi, S. J. Copper removal from industrial wastewater: A comprehensive review. *J. Ind. Eng. Chem.* **2017**, *56*, 35–44.
- (27) Kammann, K. P. J. Mixed carboxylic anhydrides in the Grignard reaction. LSU Historical Dissertations and Theses, Louisiana State University and Agricultural and Mechanical College, 1962.
- (28) Urch, C. J. Trimethylacetyl Chloride. *Encycl. Reagents Org. Synth.* **2001**, *1*. DOI: 10.1002/047084289x.rt264
- (29) Hammond, G. S. A Correlation of Reaction Rates. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.