Kinetically-Controlled, Highly Chemoselective Acylation of Functionalized Grignard Reagents with Amides by N–C Cleavage

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Abstract: *The direct transition-metal-free acylation of amides with functionalized Grignard reagents by highly chemoselective N–C cleavage under kinetic control has been accomplished. The method offers rapid and convergent access to functionalized biaryl ketones via transient tetrahedral intermediates. The direct access to functionalized Grignard reagents via in situ halogen-magnesium exchange promoted by the versatile turbo-Grignard reagent (i-PrMgCl·LiCl) permits for excellent substrate scope with respect to both the amide and Grignard coupling partners. These reactions enable facile, operationally-simple and chemoselective access to tetrahedral intermediates from amides under significantly milder conditions than chelation-controlled intermediates. This novel direct two-component coupling sets the stage for using amides as acylating reagents in an alternative paradigm to the metal-chelated approach and acyl-metals.*

The carbonyl group represents one of the most important functional groups in organic synthesis.[1] Biaryl ketones are found in a plethora of bioactive architectures,[2] and importantly serve as versatile intermediates for the installation of various functional groups by the direct *ipso* C=O functionalization.[3] The classic way of synthesizing ketones involves nucleophilic addition of organometallic reagents to N-methoxy-N-methylamides[4] that capitalize on the formation of kinetically-stable, yet unreactive, metal-chelated intermediates (Figure 1A).[5] In this context, the discovery that amide functionalization can be accomplished by the direct insertion of a transition-metal to give the acyl-metal intermediate from historically unreactive amide bonds ($n_N \rightarrow \pi^*_{C=O}$ delocalization) was an important achievement that enabled the construction of important motifs for chemical synthesis (Figure 1B).[6,7] Continuing this theme, herein, we report the third mode of reactivity of amide bonds, wherein the direct, highly chemoselective, transition-metal-free acylation of amides with functionalized Grignard reagents[8] is accomplished by transient tetrahedral intermediates under kinetic control (Figure 1C).[9,10] The reaction enables the construction of a wide variety functionalized ketones with excellent functional group tolerance, including ester, cyano, nitro, chloro, bromo, thiomethyl, tosyl, amino, and trifluoromethyl ether, and sets the stage for using amides as acylating reagents in an alternative paradigm to the metal-chelated approach[4,5] and acyl-metals.[6,7]

As shown in Figure 1C, we postulated that the highly electrophilic nature of N,N-Boc$_2$-amides[11] would permit for the direct nucleophilic addition of an organometallic reagent to the N–C(O) bond to generate a transient acyl-metal-intermediate. If the rate of the nucleophilic addition of organometallic to the

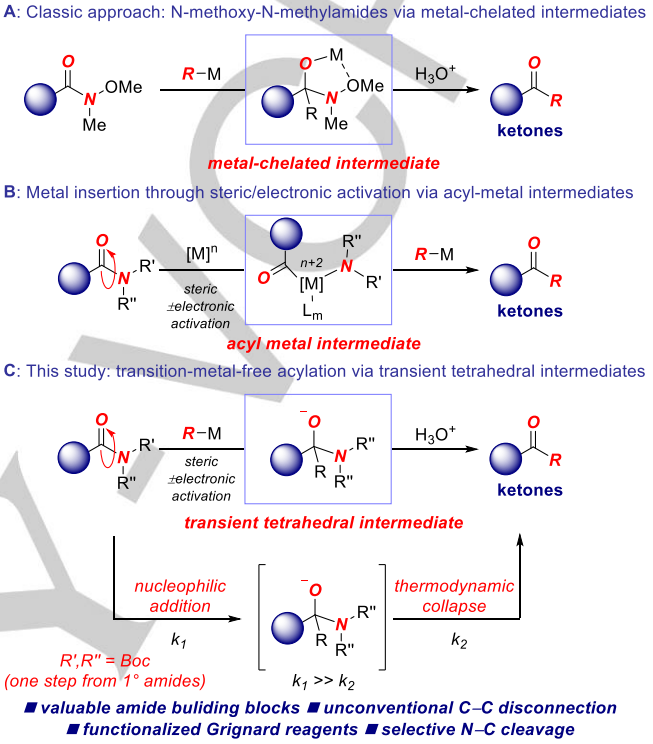

Figure 1. Amide bond cleavage in organic synthesis.

amide bond (k_1) is faster than the rate of the collapse of tetrahedral intermediate (k_2), a highly chemoselective reaction could ensue. In this scenario, the formation of overaddition products (k_3), a process that plagues direct acyl substitution reactions,[4,5] could be avoided by tuning the reactivity of the amide leaving group and organometallic reagent. A central design in this strategy is the fact that N,N-Boc$_2$-amides unlike N-methoxy-N-methylamides[4] can be readily prepared either from 1° benzamides by double N-selective *tert*-butoxycarbonylation or from carboxylic acid derivatives,[11] thus providing new avenues for unconventional C–C bond disconnection. In general, amides are the least reactive carboxylic acid derivatives due to high kinetic barrier for nucleophilic addition. In the present case, the resonance is minimized (ER = 6.3 kcal/mol). Second, the collapse must be thermodynamically favored. Third, overaddition must be controlled to prevent the formation of alcohols.[10e,f]

Although our initial studies were conducted using 4-tolylmagnesium bromide, from the outset we were attracted to the use of a versatile turbo-Grignard reagent platform (*i*-PrMgCl·LiCl) introduced by Knochel and co-workers.[12–15] The facile halogen magnesium exchange using *i*-PrMgCl·LiCl permits for a high yielding preparation of a broad range of functionalized organomagnesium reagents for the production of high value motifs in organic synthesis.

Our investigation started with an examination of the addition of 4-TolMgBr to N,N-Boc$_2$-benzamide (Table 1). Two other representative N-Boc-benzamides, namely N-Boc/Ph and

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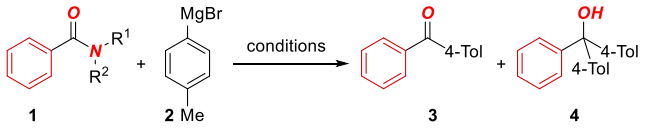
Table 1. Optimization of the reaction conditions[a]



1 2 3 4

Entry	Starting material / Conditions	$R^1 = R^2 = Boc$		$R^1 = Ph$ $R^2 = Boc$		$R^1 = Me$ $R^2 = Boc$		$R^1 = Me$ $R^2 = OMe$	
		3	**4**	**3**	**4**	**3**	**4**	**3**	**4**
1	Standard conditions	90%	<5%	78%	<5%	65%	<5%	66%	0%
2	**2** added over 20 s	75%	15%	60%	4%	60%	4%	64%	0%
3	**2**, 3.0 equiv	trace	94%	0%	88%	0%	66%	98%	0%
4	**1**, 1.1 equiv	94%	trace	80%	trace	67%	trace	55%	0%
5	THF (1.0 M)	85%	5%	60%	3%	40%	18%	63%	0%
6	Room temperature	50%	44%	61%	3%	50%	10%	67%	0%
7	Reaction time 5 min	90%	<5%	75%	<5%	63%	<5%	4%	0%
8	Reaction time 5 s	85%	0%	80%	0%	66%	0%	3%	0%
9	- 78 °C	0%	0%	0%	0%	0%	0%	0%	0%
10	PhMgCl 1.0 equiv	88%	trace	75%	trace	64%	trace	68%	0%
11	Et_2O	70%	14%	46%	15%	56%	10%	70%	0%
12	PhLi 1.0 equiv	<5%	37%	<5%	40%	<5%	40%	>98%	0%

[a]Standard conditions: **1** (1.0 equiv), **2** (1.0 equiv), THF (0.25 M), 0 °C, 30 min.

N-Boc/Me benzamides,[16] and the classic N-methoxy-N-methyl-benzamide[4] were screened at the same time. We anticipated that the difference in amidic resonance[10] and leaving group aptitude would influence the reactivity and provide insight into the reaction pathway. The desired ketone was produced in excellent 90% yield using 4-TolMgBr (fast addition, 1.0 equiv) in THF at 0 °C (entry 1). *Under these conditions, the non-selective N-Boc scission and overaddition to give the ketone were not observed, consistent with (1) the high electrophilicity of the N–C(O) amide bond, and (2) a rapid collapse of the tetrahedral intermediate.*

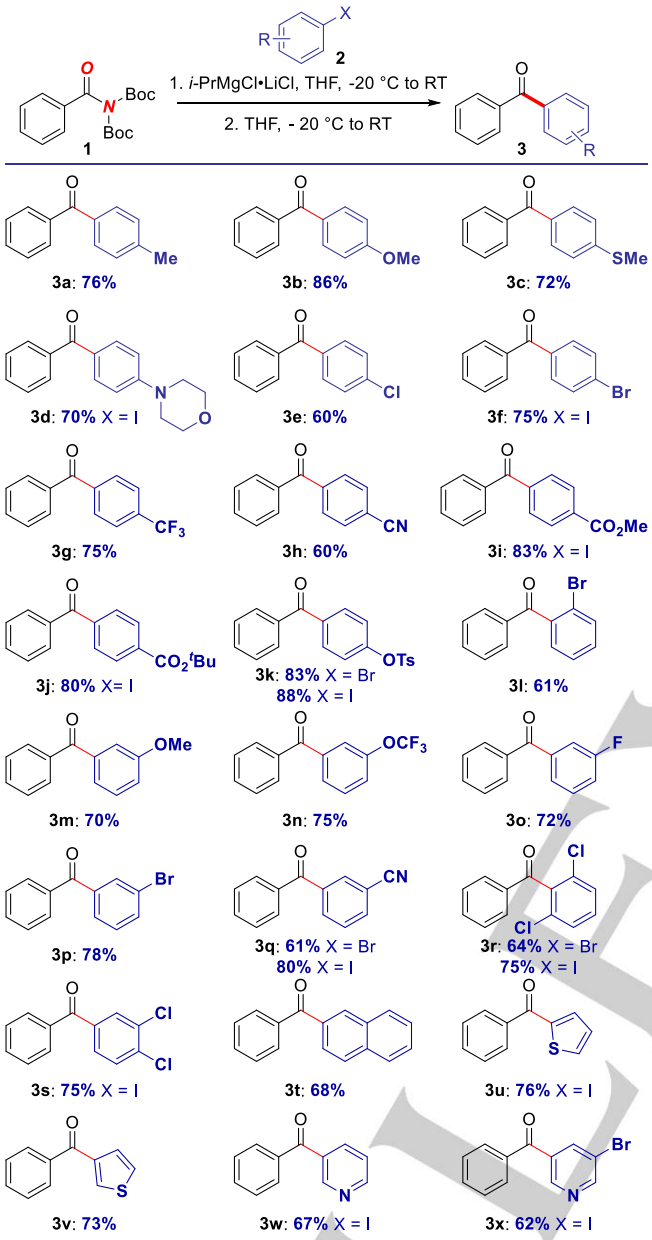
Several optimization experiments are worth noting. (1) The slow dropwise addition of the Grignard reagent resulted in a non-selective process (entry 2). (2) Likewise, the use of an excess of the Grignard reagent furnished a clean conversion to the alcohol product (entry 3). (3) A slight excess of amide (1.1 equiv) was found to be optimal (entry 4). (4) Changes in the reaction concentration and higher reaction temperature resulted in lower reaction selectivity (entries 5-6). (5) The reaction was found to be remarkably fast (i.e. close to full conversion *on the order of the time required for reagent mixing at 0 °C*); however, no reaction was observed at -78 °C (entries 7-9). (6) ArMgCl was found to be a competent nucleophile, while lower selectivity was observed in Et_2O as a solvent (entries 10-11). (7) As expected, ArLi led to a non-selective process,[11] resulting in a full conversion to the tertiary alcohol (entry 12).

The optimization data highlight key differences between N,N-Boc_2-amides and N-methoxy-N-methylamides as acylating reagents: (a) N,N-Boc_2-amides[11] are significantly more reactive than the present state-of-the-art N-methoxy-N-methylamides[4] (*vide infra*); (b) N,N-Boc_2-amides[11] react through transient tetrahedral intermediates vs. metal-chelated intermediates from N-methoxy-N-methylamides.[4] Furthermore, the optimization data demonstrate that a selective nucleophilic addition to N-Ar/Boc and N-alkyl/Boc amides that are readily prepared from either from 2° benzamides or from carboxylic acid derivatives[10] is also feasible through the same type of transient tetrahedral intermediates. Full Table 1, including unselective N–Boc scission, is presented in the SI.

With the optimized conditions in hand, the scope of the direct nucleophilic addition to N,N-Boc_2 amides was examined. To emphasize the utility of *i*-PrMgCl·LiCl enabling highly chemoselective preparation of functionalized organomagnesium reagents,[12–15] all Grignard reagents used in the substrate scope examination were prepared by *in situ* halogen-magnesium exchange promoted by *i*-PrMgCl·LiCl. As shown in Table 2, the reaction furnishes the desired ketones with an excellent efficiency and striking functional group tolerance. Electron-donating alkyl (**3a**), alkoxy (**3b**), thioether (**3c**) and amine (**3d**) functional groups can be readily incorporated. This direct nucleophilic acylation is compatible with electron-withdrawing groups, such as chloro (**3e**), bromo (**3f**), trifluoromethyl (**3g**), cyano (**3h**), methyl ester (**3i**), *tert*-butyl ester (**3j**) and OTs (**3k**), furnishing the desired ketones with excellent levels of selectivity and providing handles for further functionalization. Ortho-substitution with a sterically-demanding 2-arylbromide that is selectively prepared from 1,2-dibromobenzene is compatible (**3l**).[12a] Various electronically-differentiated substituents at the meta-position, such as methoxy (**3m**), trifluoromethylether (**3n**), fluoro (**3o**), bromo (**3p**) and cyano (**3q**) provided the desired ketone products in good to excellent yields. Furthermore, poly-chlorinated arenes, including sterically-hindered 2,6-dichloro (**3r**), and 3,4-dichloro (**3s**) formed the products in good yields. Finally, we were pleased to find that the reaction is compatible with polyaromatic arenes, such as naphthalene (**3t**) and heterocycles such as electron-rich thiophenes (**3u-3v**) and electron-deficient pyridines (**3w-3x**). Overall, the reaction shows superior scope to all other acyl-substitution reactions of amides by acyl-metal intermediates[6,7] or using N-methoxy-N-methylamides.[4]

The compatibility with various N,N-Boc_2 amides was also striking (Table 3). These reactions were performed using representative functionalized organomagnesium reagents[12.13] containing ester, ether, cyano, heterocycle and bromo functional groups, resulting in a rapid synthesis of complex ketones. As shown in Table 3, electron-withdrawing fluoro (**3y**) and nitro (**3z**), electron-rich thiophene (**3aa**) and cyano (**3ab**) groups were compatible on the amide coupling partner. Furthermore, ortho-sterically hindered (**3ac**) and polyaromatic (**3ad**) amides were well-tolerated. Sensitive functional groups, such as bromo (**3ae**) and ester (**3af**) as well as various electronically-differentiated substituents (**3ag-3ai**) provided the desired ketones in high yields. It is worthwhile to note that 3-pyridyl ketone (**3aj**) is derived directly from nicotinamide, thus illustrating the potential of this method in drug derivatization.[7e] Finally, we were pleased to find that the method could achieve the synthesis of challenging

Table 2. Chemoselective acylation of amides with functionalized Grignard reagents: scope of Grignard reagents.[a]



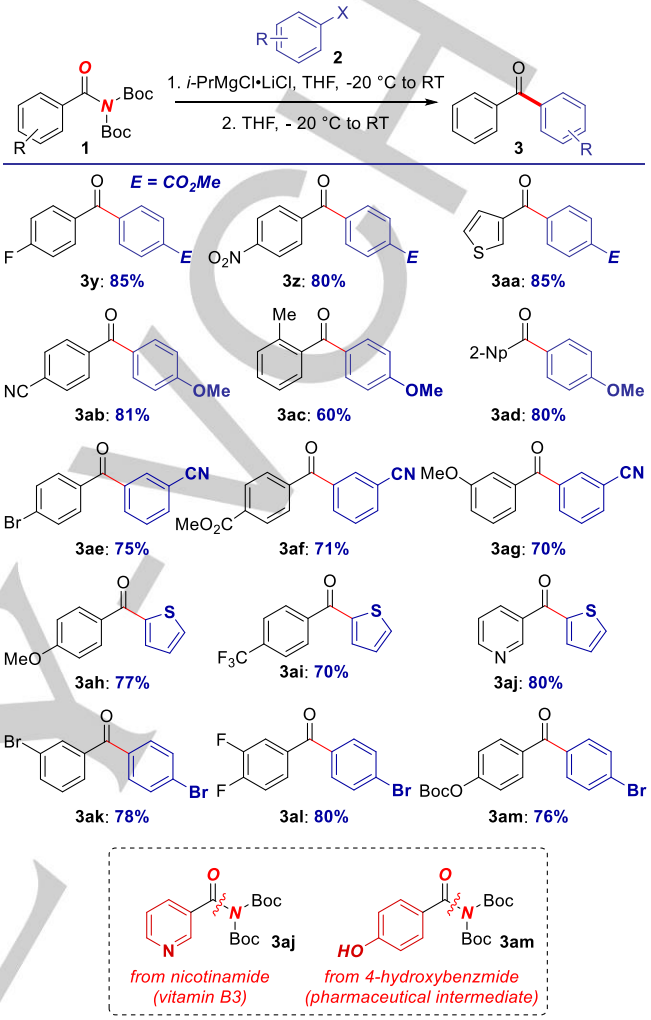
[a]Standard conditions, Br/Mg or I/Mg exchange using *i*-PrMgCl·LiCl: ArX (1.0 equiv), *i*-PrMgCl·LiCl (1.05 equiv), THF, -20 °C to RT, **1** (1.0 equiv), -20 °C to RT. See SI for details. X = Br unless stated otherwise.

unsymmetrical bromo-substituted (**3ak**), polyfluorinated ketones (**3al**) and Boc protected phenols (**3am**).

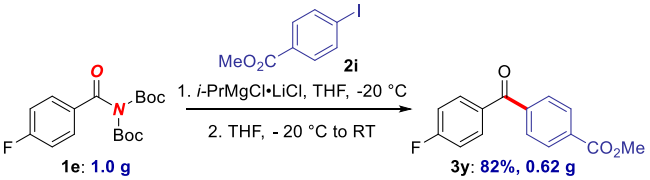
To illustrate the scalability of the method, the reaction was performed on a gram scale using an ester-containing Grignard reagent, furnishing the desired ketone in 82% yield (Scheme 1), clearly demonstrating the potential of this method in acylation reactions of amides by N–C cleavage.

Finally, we also sought to evaluate this acylation method in using more complex Grignard reagents. We were pleased to find that the bis-functional aryl-Grignard reagent containing both the

Table 3. Chemoselective acylation of amides with functionalized Grignard reagents: scope of amides.[a]



[a]Standard conditions, Br/Mg or I/Mg exchange using *i*-PrMgCl·LiCl: ArX (1.0 equiv), *i*-PrMgCl·LiCl (1.05 equiv), THF, -20 °C to RT, **1** (1.0 equiv), -20 °C to RT. See SI for details.

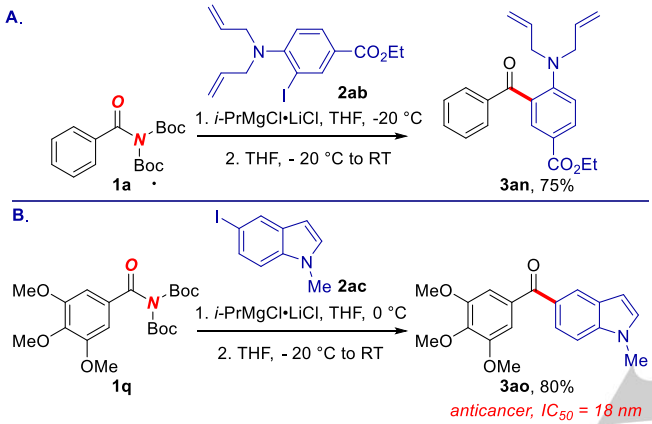


Scheme 1. Gram-scale acylation.

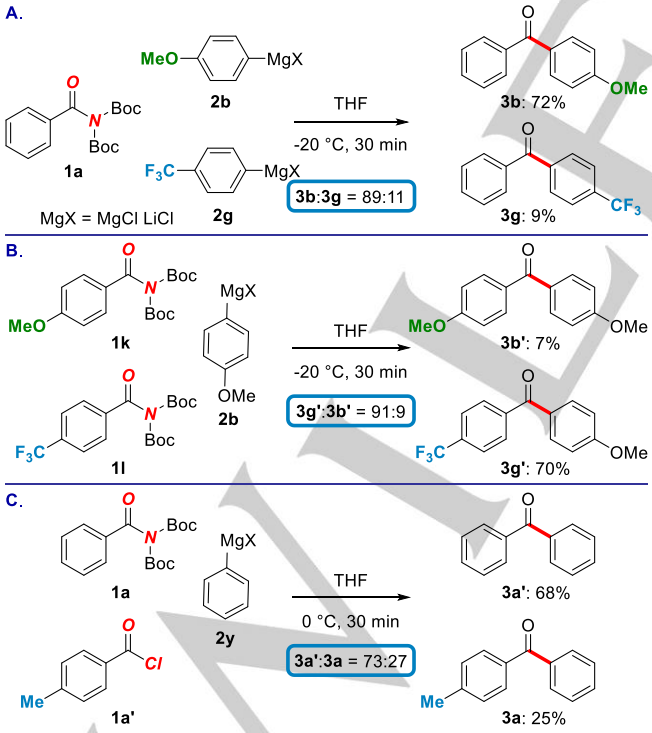
nucleophilic and electrophilic handle[17] leads to highly selective acylation (**3an**, Scheme 2A). Perhaps more importantly, the synthesis of a potent anticancer 5-indol-yl-functionalized biaryl ketone **3ao** (Scheme 2B)[18] demonstrates the potential of this N–C acylation in the synthesis of medicinally-relevant compounds.

We also conducted intermolecular competition studies to gain preliminary insight into the reaction mechanism (Scheme 3). The studies highlight that the observed reactivity is consistent with the nucleophilicity of the organomagnesium reagent (Scheme 3A) and electrophilic properties of the amide bond (Scheme 3B).[9a] *Remarkably, the competition experiments*

established a higher order of reactivity of N,N-Boc$_2$ amides than aroyl chlorides. This unexpected finding suggests a significant potential of N,N-Boc$_2$ amides as highly reactive acylating reagents in organic synthesis in a non-conventional C–C bond disconnection by N–C cleavage. It is interesting to note that the chelation with N-Boc is less effective in this case (six-membered chelate) than with the classic Weinreb amides (five-membered chelates). The collapse is thermodynamically favored due to expulsion of the non-nucleophilic NBoc$_2$ moiety. As expected, the ketone products react under the reaction conditions at much higher rate than the amide starting materials. At the present stage of reaction development, alkyl Grignard reagents are not tolerated. Future studies will focus on expanding the substrate scope to alkyl Grignard reagents.



Scheme 2. Bis-functional Grignard reagents and application in medicinal chemistry.



Scheme 3. Competition experiments.

In conclusion, we have reported a transition-metal-free direct acylation of amides with functionalized Grignard reagents. The reaction proceeds by a highly chemoselective N–C cleavage and operates under kinetic control via transient tetrahedral intermediates. The reaction conditions are exceedingly mild, operationally-simple and tolerate a wide range of functional groups. The reaction capitalizes on the use of *i*-PrMgCl·LiCl to enable highly effective halogen-metal exchange, providing rapid access to functionalized ketones by an unconventional amide bond acylation. Taken together, our findings represent an important advance that demonstrates amides as highly reactive acylating reagents in an alternative paradigm to metal-chelation and acyl-metals. Studies directed at better understanding of the mechanism by computation methods as well elucidation of the nature of the Grignard reagent are currently underway. We expect that the scope of this protocol will be expanded to other broadly useful methods by N–C functionalization.

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Keywords: functionalized Grignard reagents • acylation • transition-metal-free • N–C activation • amides

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[16] Note that amidic resonance of N,N-Boc_2 amides (RE = 6.3 kcal/mol) is significantly reduced as compared with planar amides (e.g. DMAC, RE = 18.3 kcal/mol).[11]

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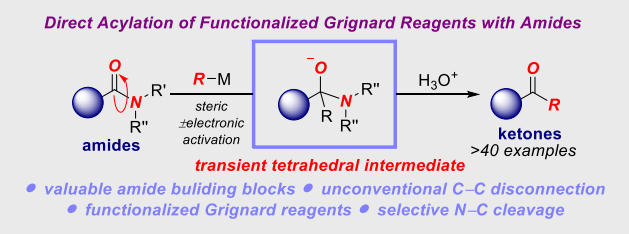

We report a direct transition-metal-free acylation of amides with functionalized Grignard reagents by highly chemoselective N–C cleavage under kinetic control. The method operates under exceedingly mild conditions. This novel direct two-component coupling sets the stage for using amides as acylating reagents in an alternative paradigm to the metal-chelated approach and acyl-metals.

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Kinetically-Controlled, Highly Chemoselective Acylation of Functionalized Grignard Reagents with Amides by N–C Cleavage