

# Organic & Biomolecular Chemistry

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# Synthesis of Biaryl Ketones by Arylation of Weinreb Amides with Functionalized Grignard Reagents under Thermodynamic Control vs. Kinetic Control of N,N-Boc<sub>2</sub>-Amides

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A highly efficient method for chemoselective synthesis of biaryl ketones by arylation of Weinreb amides (N-methoxy-N-methylamides) with functionalized Grignard reagents is reported. This protocol offers rapid entry to functionalized biaryl ketones after Mg/halide exchange with *i*-PrMgCl·LiCl under operationally-simple and practical reaction conditions. The scope of the method is highlighted in >40 examples, including bioactive compounds and pharmaceutical derivatives. Collectively, this transition-metal-free approach offers a major advantage over the recently established cross-coupling of amides by oxidative addition of N–C(O) bonds. Considering the utility of amide acylation reactions in modern synthesis, we expect that this method will be of broad interest.

Beyond doubt, Weinreb amides (N-methoxy-N-methylamides) are among the most successful and important amide derivatives developed to date in organic synthesis.<sup>1–3</sup> The overwhelming utility of N-methoxy-N-methylamides arises from the formation of well-defined, five-membered, metal-chelated intermediates in direct nucleophilic addition of organolithium and organomagnesium reagents, resulting in their numerous applications in natural product synthesis, drug discovery and materials science.<sup>4–6</sup>

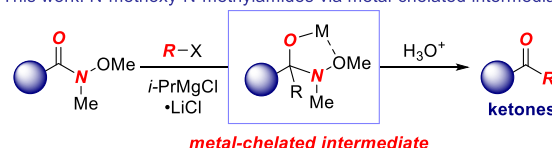
On the other hand, the recent years have witnessed the emergence of amide bond cross-coupling reactions, wherein activation of the amide bond is achieved by oxidative addition of the N–C(O) amid bond to generate an acyl-metal complex.<sup>7,8</sup> This mode of amide bond activation has already been extended to decarbonylative processes to furnish aryl-metal electrophiles<sup>9</sup> and holds promise as a new general cross-coupling manifold in organic synthesis.<sup>10</sup>

Simultaneously, remarkable progress has been achieved in transition-metal-free activation of amides, wherein direct nucleophilic addition to ground-state-destabilized amides provides acyl addition products under kinetic control of tetrahedral intermediates.<sup>11</sup> From the practical standpoint, transition-metal-free methods are vastly preferred because they obviate the removal of toxic transition-metal impurities.

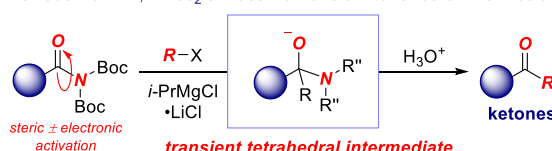
In this context, recently our laboratory established arylation of N,N-Boc<sub>2</sub> amides with functionalized Grignard reagents,<sup>12</sup> wherein (1) N,N-Boc<sub>2</sub> amides are prepared from 1° amides by selective double N-*tert*-butoxycarbonylation,<sup>8</sup> thus enabling to use common benzamides as arylation precursors; (2) the reaction proceeds under kinetic control of the tetrahedral intermediate, whereas the use of excess Grignard reagents leads to the overaddition to give alcohol products (Fig. 1). We questioned whether functionalized Grignard reagents prepared by Mg/halide exchange with *i*-PrMgCl·LiCl could be broadly employed as nucleophiles in the arylation<sup>13</sup> of Weinreb amides for the synthesis of biaryl ketones.

As a critical design element, we envisioned the use of versatile turbo-Grignard (*i*-PrMgCl·LiCl) elegantly pioneered by Knochel.<sup>14–16</sup> We recognized that the highly chemoselective Mg/halide exchange with *i*-PrMgCl·LiCl could enable practical, operationally-simple and highly functional group tolerant synthesis of biaryl ketones by exploiting straightforward access to functionalized organomagnesium reagents under thermodynamic control of five-membered chelates.

A: This work: N-methoxy-N-methylamides via metal-chelated intermediates



B: Previous work: N,N-Boc<sub>2</sub> amides via transient tetrahedral intermediates



C: Amides as acylating reagents (R–M = functionalized Grignard reagents)

Weinreb amides	N,N-Boc <sub>2</sub> amides
<ul style="list-style-type: none"> <li>• classic amides in organic synthesis</li> <li>• prepared from carboxylic acids / aryl chlorides</li> <li>• metal-chelated intermediates</li> <li>• less reactive/more stable</li> </ul>	<ul style="list-style-type: none"> <li>• emerging novel acyclic twisted amides</li> <li>• prepared from 1° amides</li> <li>• transient intermediates</li> <li>• more reactive/less stable</li> </ul>

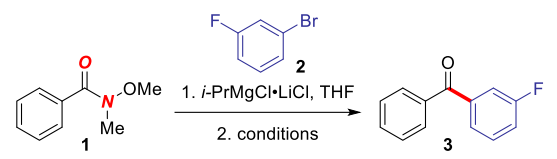
**Fig. 1** Context of this work: synthesis of functionalized ketones via selective arylation of unreactive amide bonds.

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**Table 1** Optimization of the Reaction Conditions<sup>a</sup>


entry	1 (equiv)	solvent	T (°C)	yield (%) <sup>b</sup>
1	1.0	THF	23	66
2	1.0	CH <sub>2</sub> Cl <sub>2</sub>	23	40
3	1.0	CH <sub>3</sub> CN	23	85
4	1.0	Et <sub>2</sub> O	23	62
5	1.0	toluene	23	71
6	1.2	toluene	23	74
7	1.5	toluene	23	74
8	3.0	toluene	23	70
9	1.2	toluene	0	60
10	1.2	toluene	60	63

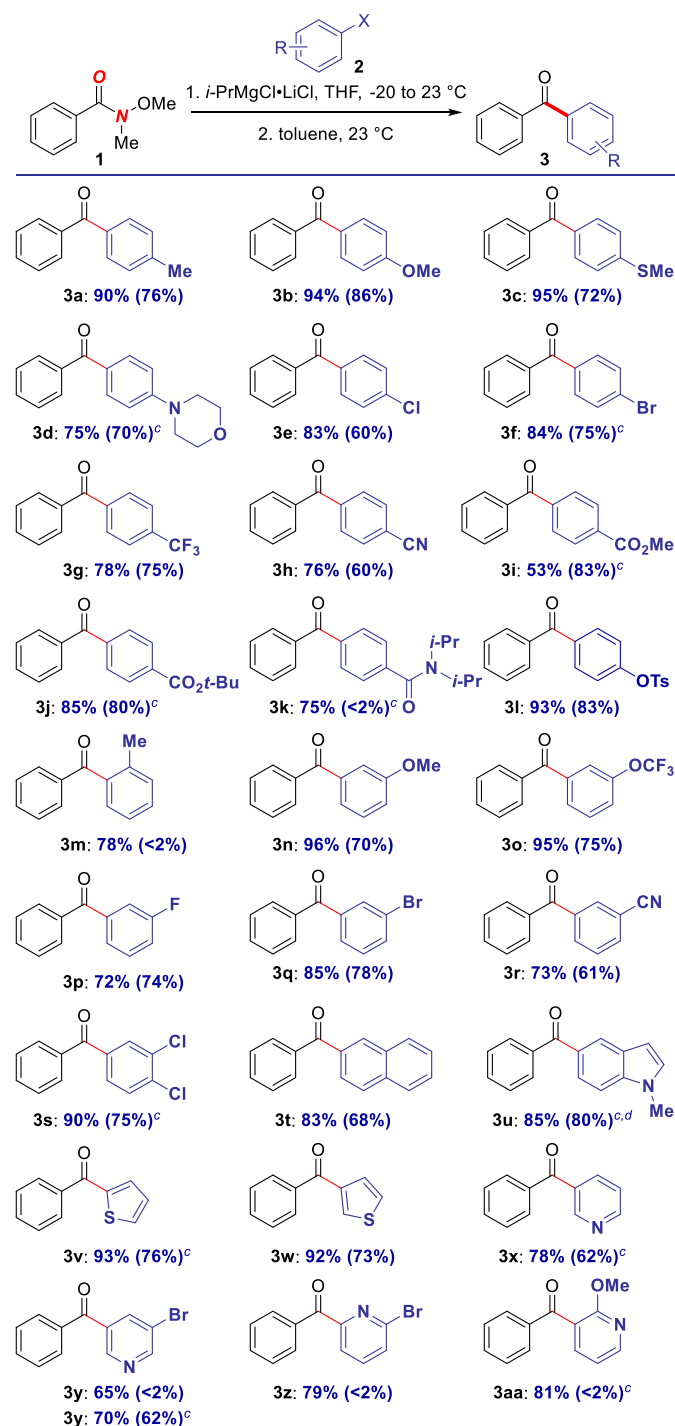
<sup>a</sup>Conditions: X/Mg exchange using *i*-PrMgCl·LiCl: ArX (1.0 equiv), *i*-PrMgCl·LiCl (1.20 equiv), THF, -20 °C to 23 °C, **1** (1.0 equiv), T, solvent. See ESI for details. <sup>b</sup>Determined by <sup>1</sup>H NMR and GC/MS.

Several points should be noted. (1) Despite the importance of Weinreb amides in organic synthesis, few methods for the synthesis of biaryl ketones using functionalized Grignard reagents containing sensitive electrophilic groups are available. Electrophilic functional groups are defined as those that contain reactive C=O groups and equivalents (e.g., esters, amides, nitriles) and sensitive halides (e.g. Br) that are not easily compatible with the traditional generation of Grignard reagents.<sup>17</sup> (2) Furthermore, it should be pointed out that the synthesis of organomagnesium reagents using the turbo Grignard approach represents a major synthetic improvement over established methods,<sup>14–16</sup> while no investigation of the selective nucleophilic addition of ArMgCl·LiCl reagents to yield important biaryl ketones has been reported.<sup>1–16</sup> (3) Biaryl ketones are among the most prevalent ketones in organic synthesis, wherein they represent the target building blocks or versatile C=O electrophiles for functionalization by ipso-substitution to yield an array of functional groups.<sup>18</sup>

Herein, we describe the successful development of this reaction and report a highly efficient method for chemoselective synthesis of biaryl ketones by arylation of Weinreb amides with functionalized Grignard reagents without the need for transition-metals. The reaction tolerates excess of reagents owing to the stability of the five-membered metal chelate (cf. N,N-Boc<sub>2</sub> amides). This method is contrasted with the arylation of N,N-Boc<sub>2</sub> amides by kinetic control.<sup>12</sup> Collectively, this approach offers a major advantage over the recently established cross-coupling of amides by oxidative addition of N–C(O) electrophiles.<sup>7–10,19,20</sup> Considering the utility of amide acylation reactions in modern organic synthesis, we expect that this approach will be of broad synthetic interest.

We believe that the organic community will benefit from a comparative study on acylation reactions using functionalized organomagnesium reagents and various classes of amides.<sup>1,7–13</sup>

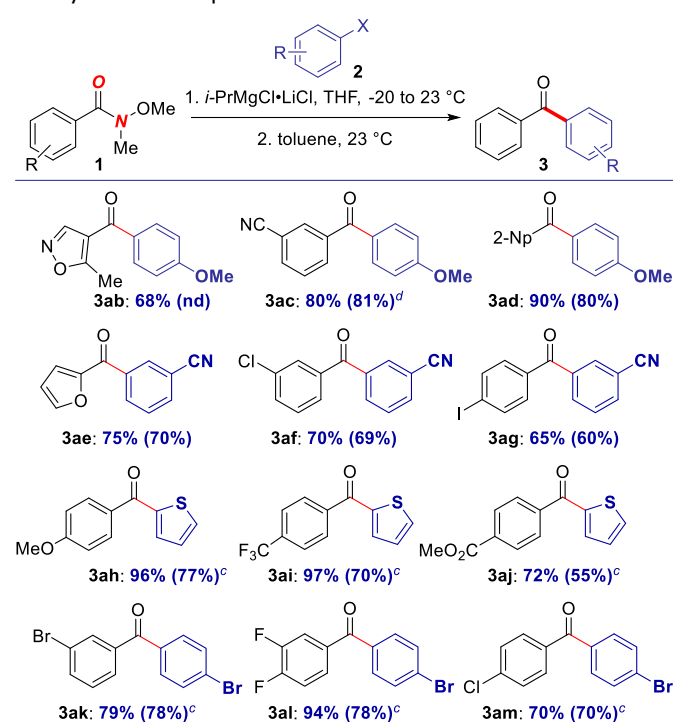
Our studies started with the addition of 3-fluorophenylmagnesium chloride, prepared by Mg/halide

**Scheme 1** Chemoselective Arylation of N-Methoxy-N-Methylamides: Scope of Functionalized Grignard Reagents<sup>a</sup>

<sup>a</sup>Conditions: Br/Mg exchange using *i*-PrMgCl·LiCl: ArX (1.0 equiv), *i*-PrMgCl·LiCl (1.2 equiv), THF, -20 °C to 23 °C, **1** (1.0 equiv), toluene, 23 °C. See SI for details. <sup>b</sup>Isolated yields. <sup>c</sup>I/Mg exchange. <sup>d</sup>N,N-Boc<sub>2</sub>-3,4,5-trimethoxybenzamide. Yields obtained using N,N-Boc<sub>2</sub> amides are shown in brackets. See ESI for details.

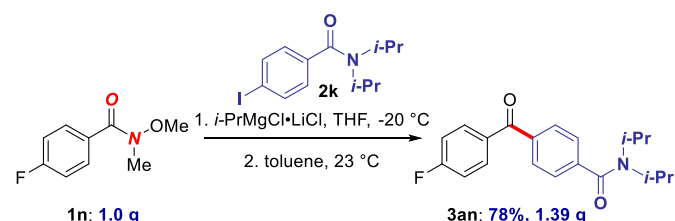
exchange with *i*-PrMgCl·LiCl, to N-methoxy-N-methylbenzamide (Table 1). It should be noted that typical acylation using functionalized organomagnesium reagents requires the use of aroyl chlorides and transmetalation with CuCN.<sup>14a</sup> Likewise, our study with N,N-Boc<sub>2</sub> amides requires

### Scheme 2 Chemoselective Arylation of N-Methoxy-N-Methylamides: Scope of Amides<sup>a,b</sup>



<sup>a-c</sup>See Scheme 1. <sup>d</sup>N,N-Boc-2-cyanobenzamide. See ESI for details. Yields obtained using N,N-Boc<sub>2</sub> amides are shown in brackets.

### Scheme 3 Gram Scale Arylation

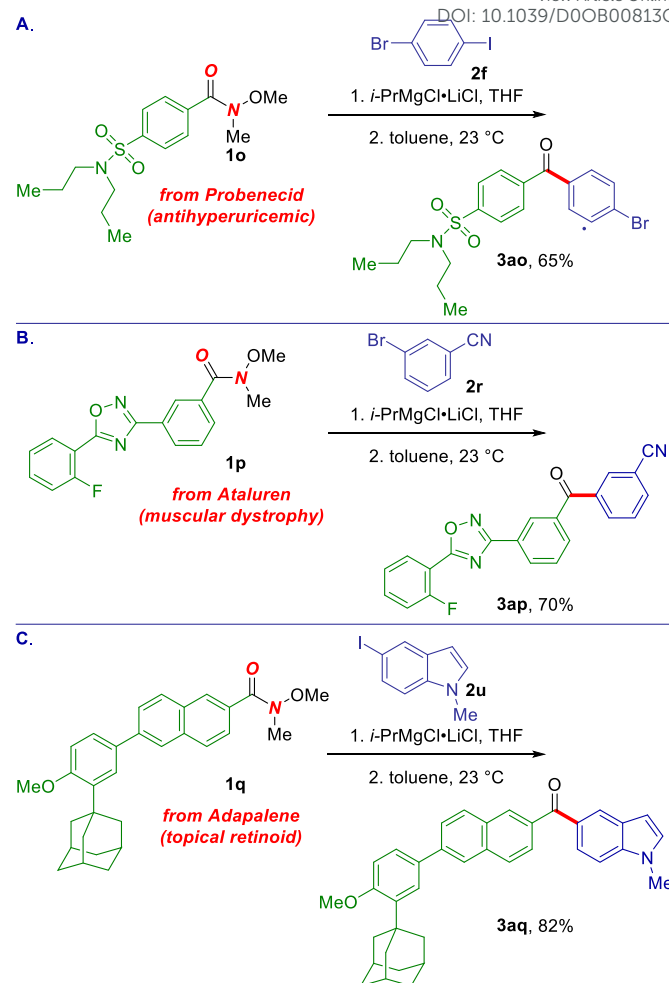


careful control of the reagent stoichiometry due to rapid collapse of the tetrahedral intermediate.<sup>12</sup> Experiments indicated that several solvents, such as THF, CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN, Et<sub>2</sub>O, toluene, could be used for the arylation of N-methoxy-N-methylbenzamide with 3-fluorophenylmagnesium chloride (Table 1, entries 1-5), with CH<sub>3</sub>CN and toluene proving to be the most efficient. Further, the reaction readily tolerates an excess of Grignard reagent (Table 1, entries 6-8). Importantly, the reaction was also successful at higher temperature (Table 1, entry 10), thus indicating a high stability of the metal-chelated intermediate, while arylation of the more reactive N,N-Boc<sub>2</sub> amides leads to the formation of alcohol products upon heating.<sup>12</sup> The optimized conditions involve preparation of functionalized Grignard by Mg/halide exchange according to the procedure by Knochel and co-workers,<sup>14a</sup> followed by the addition to N-methoxy-N-methylamide.

With optimized conditions in hand, we evaluated the scope of the reaction (Schemes 1-2). For comparison, the yields obtained using N,N-Boc<sub>2</sub> amides are presented in brackets. We were delighted to find that the scope of the reaction is very broad and accommodates a broad range of N-methoxy-N-methylamides and functionalized Grignard reagents, including

### Scheme 4 Derivatization of Pharmaceuticals

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a vast array of sensitive functional groups (Scheme 1). As such, alkyl, methoxy, thioether, amine, chloro, bromo, trifluoromethyl, cyano, methyl ester, *tert*-butyl ester, amide, and sulfonyl ester were all tolerated, providing the desired ketones in high to excellent yields (**3a-3l**). Furthermore, steric hindrance, meta-substitution, polyaromatic and heterocyclic substrates, such as indole, thiophene and pyridine rapidly underwent arylation to give the product ketones in high yields (**3m-3aa**). It is worth noting that (1) the yields are generally slightly higher than with N,N-Boc<sub>2</sub> amides, likely due to lower stability of tetrahedral intermediates derived from N,N-Boc<sub>2</sub> amides (see also Fig. 2); (2) the formation of overaddition products was not observed, resulting in a broadly useful process that complements the reaction of N,N-Boc<sub>2</sub> amides and expands the cross-coupling approach.

Similarly, we found that the scope of N-methoxy-N-methylamides is also very broad and accommodates various functional groups (Scheme 2). As such, sensitive heterocycles, such as isoxazoles, nitriles, polyaromatic substrates, electron-rich heterocycles, such as furans, chlorides and iodides were excellent substrates for the reaction (**3ab-3ag**). High reaction efficiency was observed with both electron-rich and electron-withdrawing substituents on the amide component (**3ah-3aj**). Furthermore, functional handles such as ester, bromides, fluorides and chlorides were well-tolerated and produced the



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desired ketones in high yields (**3aj-3am**). The reactivity of N-methoxy-N-methylamides in the amide scope compares well to N,N-Boc<sub>2</sub>,<sup>12</sup> and it should be noted that the methods are complementary since N,N-Boc<sub>2</sub> amides are typically obtained by N-*tert*-butoxycarboxylation of 1° amides<sup>8</sup> (cf. N,N-MeO/Me amides from aroyl chlorides or carboxylic acids).

We were pleased to find that the reaction is scalable to deliver the product on a gram scale in 78% yield (Scheme 3). *This reaction highlights distinct reactivity of two amide bonds, wherein the more reactive N-methoxy-N-methylamide reacts chemoselectivity in the presence of N,N-dialkylbenzamide* (see also Fig 2).<sup>8</sup>

The synthetic utility of the method is highlighted in the direct arylation of pharmaceutical derivatives (Scheme 4, **3ao-3aq**). As such, arylation of N-methoxy-N-methylamide derived from probenecid, an antihyperuricemic drug, delivered the desired ketone product containing a functional bromide handle in 65% yield, arylation of N-methoxy-N-methylamide of ataluren, a drug for muscular dystrophy treatment furnished the biaryl ketone with cyano functional handle in 70% yield, while arylation of N-methoxy-N-methylamide of adapalene, a topical retinoid for the treatment of acne, furnished the heterocyclic ketone in 82% yield.

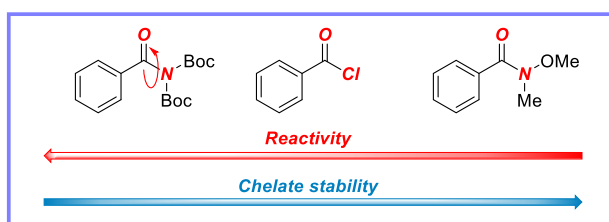


Fig. 2 Relative reactivity of N,N-Boc<sub>2</sub> and N,N-MeO/Me amides.

To gain preliminary insight into the reaction, we conducted intermolecular competition experiments (see ESI). *The following order of reactivity in acyl addition reactions: N,N-Boc<sub>2</sub> amides > aroyl chlorides > N-methoxy-N-methylamides is opposite to the capacity of amides to stabilize the tetrahedral intermediate by chelation* (Fig. 2).<sup>8</sup>

In summary, we have developed a highly efficient method for chemoselective synthesis of biaryl ketones by arylation of N-methoxy-N-methylamides with functionalized Grignard reagents prepared by Mg/halide exchange with *i*-PrMgCl-LiCl. This method complements and significantly extends the flourishing amide bond activation manifold by direct metal insertion into the N–C(O) bond. The utility has been demonstrated in excellent functional group tolerance, including in the direct functionalization of pharmaceutical derivatives. Considering the great utility of amide acylations in modern organic chemistry, we anticipate that the method will be of broad synthetic interest. Further studies on amide bond activation are ongoing and will be reported shortly.

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support.

## Notes and references

- For a comprehensive review on organometallic addition to amides, see: V. Pace, W. Holzer and B. Olofsson, *Adv. Synth. Catal.*, 2014, **356**, 3697.

- For a recent excellent review of mechanistic studies on amide bond activation, see: H. Wang, S. Q. Zhang and X. Hong, *Chem. Commun.*, 2019, **55**, 11330.
- For selected monographs, see: (a) B. M. Trost and I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, 1991; (b) M. B. Smith and J. March, *Advanced Organic Chemistry*, Wiley, 2007; (c) A. Greenberg, C. M. Breneman and J. F. Liebman, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, Wiley, 2003.
- (a) For a study on isolation of tetrahedral intermediates from Weinreb amides, see: L. Castoldi, W. Holzer, T. Langer and V. Pace, *Chem. Commun.*, 2017, **53**, 9498; (b) For a review on tetrahedral intermediates, see: M. Adler, S. Adler and G. Boche, *J. Phys. Org. Chem.*, 2005, **18**, 193.
- For selected examples of acylation reactions of amides, see: (a) D. A. Evans, G. Borg and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2002, **41**, 3188; (b) S. T. Heller, J. N. Newton and R. Sarpong, *Angew. Chem. Int. Ed.*, 2015, **54**, 9839; (c) C. Liu, M. Achtenhagen and M. Szostak, *Org. Lett.*, 2016, **18**, 2375; (d) J. Nugent and B. D. Schwartz, *Org. Lett.*, 2016, **18**, 3834.
- For a recent excellent progress in carbenoid addition to Weinreb amides, see: (a) M. Miele, A. Citarella, N. Micale, W. Holzer and V. Pace, *Org. Lett.*, 2019, **21**, 8261; (b) R. Senatore, L. Castoldi, L. Ielo, W. Holzer and V. Pace, *Org. Lett.*, 2018, **20**, 2685; (c) R. Senatore, L. Ielo, E. Urban, W. Holzer and V. Pace, *Eur. J. Org. Chem.*, 2018, 2466; (d) V. Pace, I. Murgia, S. Westermayer, T. Langer and W. Holzer, *Chem. Commun.*, 2016, **52**, 7584; For a review, see: (e) R. Senatore, L. Ielo, S. Monticelli, L. Castoldi and V. Pace, *Synthesis*, 2019, **51**, 2792; See also: (f) V. Pace, L. Castoldi and W. Holzer, *J. Org. Chem.*, 2013, **78**, 7764; (g) S. Monticelli, W. Holzer, T. Langer, A. Roller, B. Olofsson and V. Pace, *ChemSusChem*, 2019, **12**, 1147.
- For reviews on N–C functionalization, see: (a) S. Shi, S. P. Nolan and M. Szostak, *Acc. Chem. Res.*, 2018, **51**, 2589; (b) C. Liu and M. Szostak, *Chem. Eur. J.*, 2017, **23**, 7157; (c) Y. Bourne-Branchu, C. Gosmini and G. Danoun, *Chem. Eur. J.*, 2019, **25**, 2663; (d) M. B. Chaudhari and B. Gnanaprakasam, *Chem. Asian J.*, 2019, **14**, 76.
- For a pertinent study on amide bond destabilization, see: G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, *J. Am. Chem. Soc.*, 2018, **140**, 727, and references cited therein.
- C. Liu and M. Szostak, *Org. Biomol. Chem.*, 2018, **16**, 7998.
- For selected examples, see: (a) L. Xiong, R. Deng, T. Liu, Z. Luo, Z. Wang, X. F. Zhu, H. Wang and Z. Zeng, *Adv. Synth. Catal.*, 2019, **361**, 5383; (b) Z. Luo, L. Xiong, T. Liu, Y. Zhang, S. Lu, Y. Chen, W. Guo, Y. Zhu and Z. Zeng, *J. Org. Chem.*, 2019, **84**, 10559; (c) Z. Luo, H. Wu, Y. Li, Y. Chen, J. Nie, S. Lu, Y. Zhu and Z. Zeng, *Adv. Synth. Catal.*, 2019, **361**, 4117; (d) H. Wu, T. Liu, M. Cui, Y. Li, J. Jian, H. Wang and Z. Zeng, *Org. Biomol. Chem.*, 2017, **15**, 536; (e) M. Cui, H. Wu, J. Jian, H. Wang, C. Liu, D. Stelck and Z. Zeng, *Chem. Commun.*, 2016, **52**, 12076, and references cited therein.
- For a review, see: (a) G. Li and M. Szostak, *Chem. Rec.*, 2019, doi: 10.1002/tcr.201900072. For selected examples, see: (b) G. Li and M. Szostak, *Nat. Commun.*, 2018, **9**, 4165; (c) D. Ye, Z. Liu, H. Chen, J. L. Sessler and C. Lei, *Org. Lett.*, 2019, **21**, 6888; (d) T. Ghosh, S. Jana and J. Dash, *Org. Lett.*, 2019, **21**, 6690; (e) H. Wu, W. Guo, D. Stelck, C. Liu and Z. Zeng, *Chem. Eur. J.*, 2018, **24**, 3444; (f) W. Guo, J. Huang, H. Wu, T. Liu, Z. Luo, J. Jian and Z. Zeng, *Org. Chem. Front.*, 2018, **5**, 2950.
- G. Li and M. Szostak, *Chem. Eur. J.*, 2020, **26**, 611.
- For reviews on acylation reactions, see: (a) R. K. Dieter, *Tetrahedron*, 1999, **55**, 4177; (b) J. Buchspies and M. Szostak, *Catalysts*, 2019, **9**, 53.
- (a) A. Krasovskiy and P. Knochel, *Angew. Chem. Int. Ed.*, 2004, **43**, 3333; (b) A. Krasovskiy, B. F. Straub and P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 159; (c) H. Ren, A. Krasovskiy and P. Knochel, *Org. Lett.*, 2004, **6**, 4215; (d) H. Ren, A. Krasovskiy and P. Knochel, *Chem. Commun.*, 2005, 543; (e) C. Y. Liu and P. Knochel, *Org. Lett.*, 2005, **7**, 2543; (f) H. Ren and P. Knochel, *Chem. Commun.*, 2006, 726; (g) C. Y. Liu, H.

- Ren and P. Knochel, *Org. Lett.*, 2006, **8**, 617; (h) A. H. Stoll, A. Krasovskiy and P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 606; (i) F. Kopp, S. Wunderlich and P. Knochel, *Chem. Commun.*, 2007, 2075; (j) L. Melzig, C. B. Rauhut and P. Knochel, *Chem. Commun.*, 2009, 3536; (k) C. Despotopoulou, R. C. Bauer, A. Krasovskiy, P. Mayer, J. M. Stryker and P. Knochel, *Chem. Eur. J.*, 2008, **14**, 2499; (l) F. M. Piller, P. Appukkattan, A. Gavryushin, M. Helm and P. Knochel, *Angew. Chem. Int. Ed.*, 2008, **47**, 6802.
- 15 For reviews, see: (a) D. S. Ziegler, B. Wei and P. Knochel, *Chem. Eur. J.*, 2019, **25**, 2695; (b) R. L. Y. Bao, R. Zhao and L. Shi, *Chem. Commun.*, 2015, **51**, 6884; (c) N. M. Barl, V. Werner, C. Sämann and P. Knochel, *Heterocycles*, 2014, **88**, 827; (d) T. Klatt, J. T. Markiewicz, C. Sämann and P. Knochel, *J. Org. Chem.*, 2014, **79**, 4253; (e) H. Ila, O. Baron, A. J. Wagner and P. Knochel, *Chem. Commun.*, 2006, 583; (f) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem. Int. Ed.*, 2003, **22**, 4302.
- 16 For selected applications, see: (a) S. Yamada, A. Gavryushin and P. Knochel, *Angew. Chem. Int. Ed.*, 2010, **49**, 2215; (b) P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2010, **49**, 2219; (c) P. Anbarasan, H. Neumann and M. Beller, *Chem. Eur. J.*, 2010, **16**, 4725; (d) P. Anbarasan, H. Neumann and M. Beller, *Chem. Eur. J.*, 2011, **17**, 4217. For monographs on organomagnesium compounds, see: (e) P. Knochel, *Handbook of Functionalized Organometallics*, Wiley, 2005; (f) Z. Rappoport and I. Marek, *The Chemistry of Organomagnesium Compounds*, Wiley, 2008.
- 17 A comprehensive Scifinder search (April 18, 2020) indicated very few examples of the addition of functionalized Grignard reagents to amides to yield biaryl ketones using turbo Grignard reagent (*i*-PrMgCl-LiCl). This is consistent with a higher reactivity of  $\alpha$ -alkyl N-methoxy-N-methylamides in the direct acylation reactions (cf. aryl amides to yield biaryl ketones). See: (a) 3-MeO-C<sub>6</sub>H<sub>4</sub>-MgCl-LiCl: J. Debnath, S. Siricilla, B. Wan, D. C. Crick, A. J. Lenaerts, S. G. Franzblau and M. Kurosu, *J. Med. Chem.*, 2012, **55**, 3739; (b) 6-Br-C<sub>5</sub>H<sub>3</sub>N-MgCl-LiCl: T. Nakajima, M. Sugawara, S. I. Uchida, T. Ohno, Y. Nomoto, N. Uesaka and Y. Nakasato, EP1700856, Sep 13, **2006**. For a further example of alkyl amides, see: (c) K. Conrad, Y. Hsiao and R. A. Miller, *Tetrahedron Lett.*, 2005, **46**, 8587.
- 18 For selected references on biaryl ketones, see: (a) I. Jabeen, K. Pleban, U. Rinner, P. Chiba and G. F. Ecker, *J. Med. Chem.*, 2012, **55**, 3261; (b) K. Maeyama, K. Yamashita, H. Saito, S. Aikawa and Y. Yoshida, *Polym. J.*, 2012, **44**, 315; (c) W. Sharmoukh, K. C. Kol, C. Noh, J. Y. Lee and S. U. Son, *J. Org. Chem.*, 2010, **75**, 6708; (d) S. K. Vooturi, C. M. Cheung, M. J. Rybak and S. M. Firestine, *J. Med. Chem.*, 2009, **52**, 5020; (e) M. P. Leze, M. Le Borgne, P. Pinson, A. Paluszczak, M. Duflos, G. Le Baut and R. W. Hartmann, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1134; (f) M. H. Keylor, B. S. Matsuura and C. R. J. Stephenson, *Chem. Rev.*, 2015, **115**, 8976; (g) L. Brunton, B. Chabner and B. Knollman, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw Hill, **2010**.
- 19 For additional selected studies, see: (a) B. Suchand and G. Satyanarayana, *J. Org. Chem.*, 2016, **81**, 6409; (b) S. Balasubramaniam and I. S. Aidhen, *Synthesis*, 2008, **23**, 3707.
- 20 For studies on the synthesis of amides from nitriles under mild conditions, see: (a) T. Kanda, A. Naraoka and H. Naka, *J. Am. Chem. Soc.*, 2019, **131**, 825; For a review, see: (b) H. Naka and A. Naraoka, *Tetrahedron Lett.*, 2020, **61**, 151557.