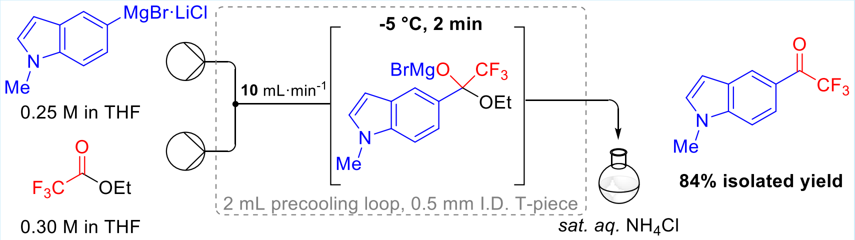
OL Organic Letters
Letter
Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow

Benjamin Heinz,[‡] Dimitrije Djukanovic,[‡] Maximilian A. Ganiek,[†] Benjamin Martin,[†] Berthold Schenkel,[†] and Paul Knochel*

Department of Chemistry, Ludwig-Maximilians-Universität, Butenandtstr. 5-13, 81377 Munich, Germany

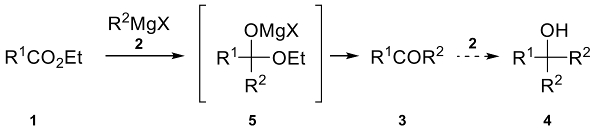
Supporting Information



ABSTRACT: A selective acylation of readily accessible organomagnesium reagents with commercially available esters proceeds at convenient temperatures and short residence times in continuous flow. Flow conditions allow us to prevent premature collapse of the hemiacetal intermediates despite noncryogenic conditions, thus furnishing ketones in good yields. Throughout, the coordinating ability of the ester and/or Grignard was crucial for the reaction outcome. This was leveraged by the obtention of several bisaryl ketones using 2-hydroxy ester derivatives as substrates.

The preparation of polyfunctional ketones using the selective acylation of Grignard reagents with acid chlorides, Weinreb amides, and related activated carbonyl groups is well established.[1,2] A drawback of such acylations can be the moderate stability as well as the poor commercial availability of activated acyl derivatives. In contrast, ethyl esters of type **1** are readily available and are stable under a wide range of conditions. However, their acylation with organomagnesium reagents R^2MgX (**2**) is often complicated by a facile secondary reaction of the produced ketones **3** with the Grignard reagent present in solution, leading to undesired tertiary alcohols of type **4** (Scheme 1).[3]

Scheme 1. General Reaction of Organomagnesium Reagents of Type 2 with Ethyl Esters of Type 1



The performance of organometallic reactions in continuous flow may have considerable advantages since it allows us to control the generation of organometallic intermediates more accurately.[4] For the above shown acylation, it may allow the generation and consumption of the tetrahedral magnesiated hemiacetal of type **5** in a controlled manner and therefore avoid the imminent formation of the tertiary alcohol **4**. Also, such a setup would allow us to avoid low temperatures which are required in batch reactions for controlling the reaction selectivity.[5]

Yoshida showed that functionalized ketones can be prepared in continuous flow by the reaction of strongly activated acid chlorides with organolithium reagents using extremely fast micromixing.[6] Also lithium organometallics react with dialkyl oxalates to selectively produce *α*-keto-esters in continuous flow.[7]

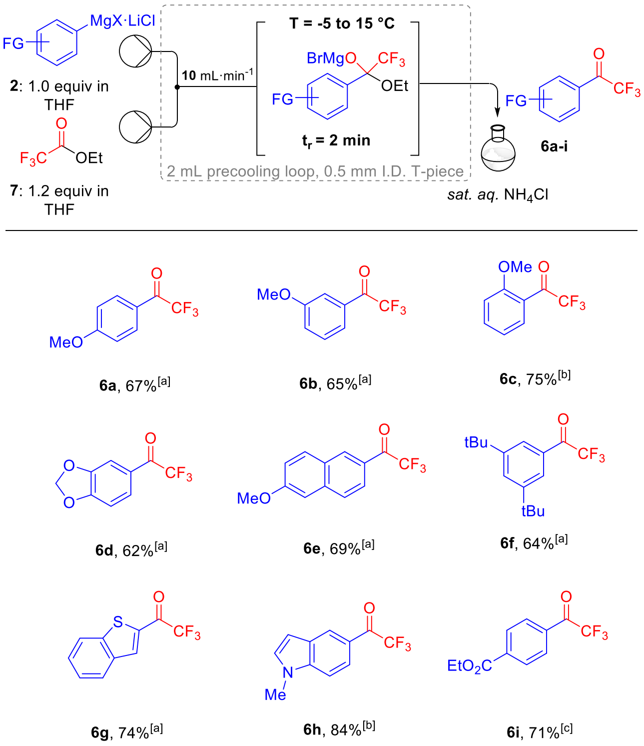
Herein, we report a selective acylation of various classes of esters with Grignard reagents at convenient temperatures (−5 to 25 °C). In preliminary experiments, we have examined the preparation of *p*-anisyl trifluoromethyl ketone **6a** by the reaction of ethyl trifluoroacetate (**7**) with *p*-anisylmagnesium bromide (**2a**) (Scheme 2). Performing this reaction in batch by slowly adding the Grignard reagent **2a** to ethyl trifluoroacetate (**7**, 1.0 equiv in THF) at −78 °C within 1 min, followed by a reaction time of 2 min, provides the desired ketone **6a** in 50% calibrated GC yield as well as 10% of the tertiary alcohol **8** (Table 1, entry 1). Extending the reaction time (3 h) increased the conversion only to a small extent, improving the GC yield of **6a** to 66% (entry 2). Performing the reaction in batch at −5 °C led to an improved conversion but produced a mixture of **6a** and **8**, showing clearly the limitation of the batch process at elevated temperatures (entry 3).

Next, we investigated the reaction performance in a commercial flow setup. After optimization of several reaction conditions such as residence time (t_r), reaction temperature,

Received: November 26, 2019

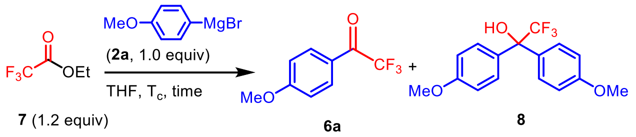
DOI: 10.1021/acs.orglett.9b04254

Scheme 2. Synthesis of Trifluoro Ketones 6a−i Using Ethyl Trifluoroacetate (7) and Grignard Reagents



[a]−5 °C reaction temperature. [b]0 °C reaction temperature. [c]15 °C reaction temperature.

Table 1. Batch/Flow Comparison for the Formation of *p*-Anisyl Trifluoromethyl Ketone 6a and the Undesired Tertiary Alcohol 8



entry	setup	[°C][a]	[min][b]	conversion [%][c]	yield 6a [%][d]	yield 8 [%][d]
1	batch[e]	−78	2	71	50	10
2	batch[e]	−78	180	83	66	9
3	batch[e]	−5	2	92	37	27
4	flow[f]	−5	2	90	72	8

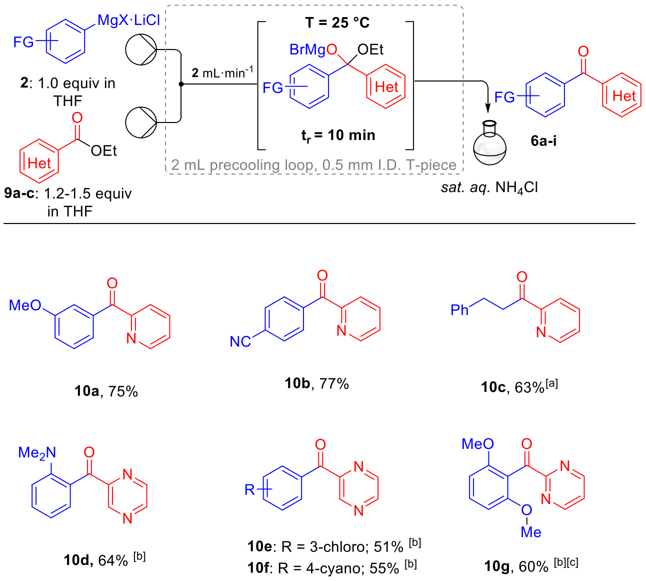
[a]Reaction temperature. [b]Reaction time. [c]Conversion of **2a** determined by GC analysis of anisole compared to an internal standard. [d]Calibrated GC yield of **6a** and **8** using tetradecane as the internal standard. [e]Batch reactions were carried out in a 0.5 mmol scale, and the Grignard reagent **2a** was added dropwise over 1 min. [f]For optimization of the continuous flow procedure, see the Supporting Information.

and stoichiometry,[8] a conversion of 90% was achieved, and the desired ketone **6a** was obtained in 72% GC yield accompanied by only 8% of **8** (entry 4).

With these optimized conditions in hand, a range of valuable trifluoromethyl ketones were prepared.[9] Thus, the reaction of *m*- and *p*-anisylmagnesium bromide with ethyl trifluoroacetate (**7**) was complete after a residence time (t_r) of 2 min at −5 °C in THF using an overall flow rate of 10 mL·min^{-1}, producing the anisyl trifluoromethyl ketones **6a−b** in 65−69% isolated yield (Scheme 2). Interestingly, the use of *o*-anisylmagnesium bromide furnished **6c** in a higher yield of 75%, presumably due to a chelating effect of the methoxy group, which leads to a further stabilization of the tetrahedral intermediate of type **5**. Other Grignard reagents bearing various electron-donating groups were also converted into the corresponding ketones **6d−f** in 62−69% yield. Additionally, reaction of heteroarylmagnesium bromide prepared from 2-bromobenzothiophene via magnesium insertion reaction led to the heteroaryl ketone **6g** in 74% yield. The indolyl ketone **6h** was obtained in 84% yield, using a temperature of 0 °C. Moreover, an organomagnesium reagent containing a sensitive ester group was also a suitable substrate and gave the polyfunctional ketone **6i** in 71% yield. The stabilization of the tetrahedral intermediate **5** by the electron-poor ester group allowed the use of a higher reaction temperature of 15 °C.

In order to extend the scope of esters substrates for such acylation reactions in continuous flow, N-heterocyclic esters of type **9** were examined. These esters were especially selected for providing a stabilizing coordinating effect on the tetrahedral intermediate **5**. Thus, *m*-anisylmagnesium bromide was mixed with ethyl 2-picolinate (**9a**) in continuous flow at room temperature for 10 min using an overall flow rate of 2 mL·min^{-1}, yielding the 2-pyridyl ketone **10a** in 75% yield (Scheme 3). Reaction of the ester **9a** with the electron-poor *p*-cyanophenylmagnesium bromide furnished the corresponding ketone **10b** in 77% yield. Even despite their destabilizing effect on the intermediate **5**, alkylmagnesium bromides were good substrates in the reaction with ethyl 2-picolinate (**9a**) under flow conditions, leading to alkylpyridyl ketone **10c** in 63% yield. Pyrazine esters like methyl 2-pyrazinecarboxylate (**9b**) were also suitable substrates for this acylation procedure. Several organomagnesium reagents reacted well with the pyrazine ester **9b**, producing the desired heteroaryl ketones **10d−f** in 51−64% yield. Additionally, pyrimidinyl ketone **10g** was obtained in 60% yield using methyl pyrimidine-2-

Scheme 3. Synthesis of Heteroaryl Ketones 10a−g Using N-Heterocyclic Esters of Type 9 and Grignard Reagents[a]

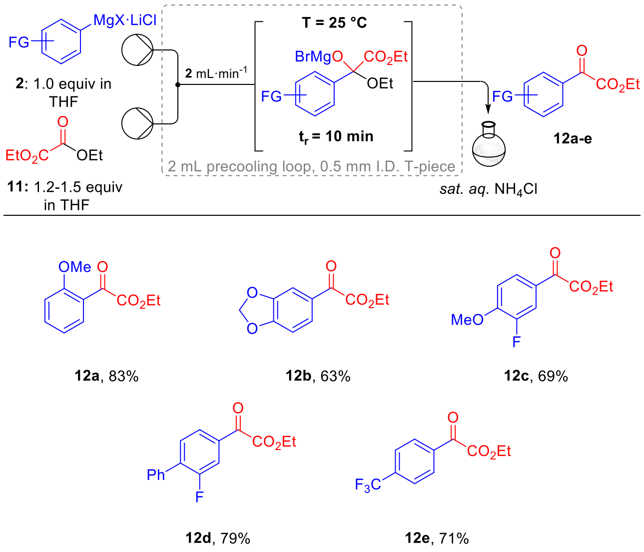


[a]0 °C reaction temperature. [b]Methyl ester was used instead of ethyl ester. [c]40 min residence time.

carboxylate (**9c**) and the corresponding Grignard reagent and an extended residence time of 40 min.

Having the utility of α-keto esters in organic synthesis in mind,[10] we included diethyl oxalate **11** in our scope of electrophiles. Thus, various α-keto esters were obtained at room temperature within 10 min using an overall flow rate of 2 mL·min^{-1} (Scheme 4). Thus, the use of electron-rich Grignard reagents led to the desired α-keto esters **12a–b** in 63–83% yield. Also, fluorine-containing compounds **12c–d** were produced in 69–79% yield. Furthermore, a trifluoromethyl-substituted organomagnesium reagent was used, affording the α-keto ester **12e** in 65% yield.

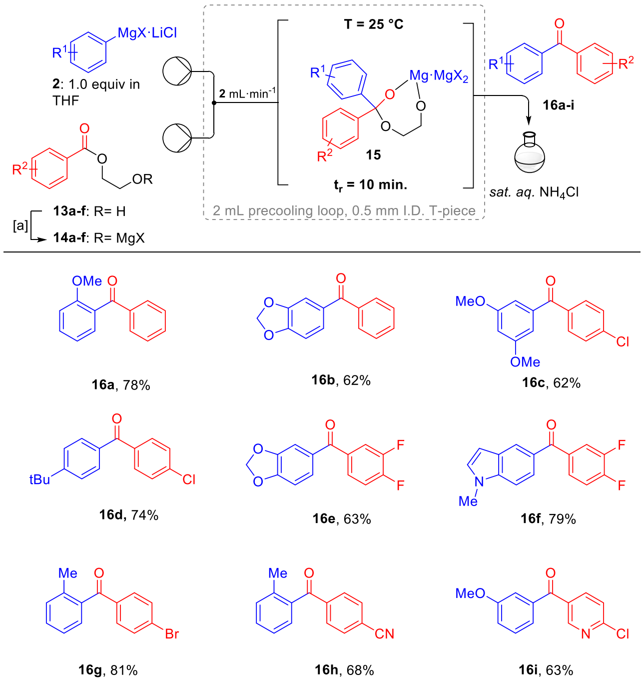
Scheme 4. Synthesis of α-Keto Esters 12a–e Using Diethyl Oxalate (11) and Grignard Reagents



Notably, the coordinating effect proved beneficial for the stabilization of the tetrahedral intermediate **5** and hence for selective ketone formation.[1a,c,h,k] After extensive experimentations, it was found that 2-hydroxyethyl esters of type **13**, bearing an alkoxy group for coordination in an intermediate of type **15**, are useful reagents for the otherwise elusive formation of bisaryl ketones (Scheme 5). The alkoxy group was generated by mixing *i*PrMgCl·LiCl (1.05 equiv)[11] and the corresponding ethylene glycol monoester at 0 °C in THF for 5 min in batch. Thus, reaction of Grignard reagents of type **2** with these new ester electrophiles in flow enabled a selective reaction producing bisaryl ketones **16a–b** in 62–78% yield. For comparison, using ethyl benzoate for the reaction with *o*-anisylmagnesium bromide in continuous flow provides only 10% of the desired product **16a** and a large amount of double addition. Furthermore, halogenated alkoxybenzoates (**14b–d**) were suitable substrates for this acylation protocol, leading to chloro-substituted aryl ketones **16c–d** in 62–74% yield, difluoroaryl ketones **16e–f** in 63–79% yield, and the bromoaryl ketone **16g** in 81% yield. Moreover, the cyano-substituted ester in reaction with *o*-tolylmagnesium bromide provides the bis-substituted ketone **16h** in 68% yield. Interestingly, the 3-pyridyl ketone **16i** was afforded in 63% yield by using the 3-pyridyl ester derivatives of type **14**, which was not possible using the regular ethyl nicotinate of type **9**.

In summary, a selective acylation in continuous flow at convenient temperatures (−5 to 25 °C) and short reaction times was developed using commercially available ester starting materials and readily accessible organomagnesium reagents. This procedure is applicable to ethyl trifluoroacetate, diethyl oxalates, and N-heterocyclic esters, leading to various functionalized ketones. Moreover, bisaryl ketones were obtained in satisfactory yields from esters without an ortho-stabilization heteroatom by using magnesiated derivaties of 2-hydroxyethyl esters.

Scheme 5. Synthesis of Bisaryl Ketones 15a–i Using Alkoxy Esters of Type 13 and Grignard Reagents



[a] Substrates **14a-f** were generated by mixing *i*PrMgCl·LiCl (1.05 equiv) and the corresponding glycol monoesters **13a-f** at 0 °C in THF for 5 min in batch.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04254.

Full experimental details and ^{1}H, ^{19}F, and ^{13}C spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.knochel@cup.uni-muenchen.de.

ORCID

Benjamin Martin: 0000-0001-6272-1653
Paul Knochel: 0000-0001-7913-4332

Present Address

†Novartis Pharma AG, Postfach, 4002 Basel, Switzerland.

Author Contributions

‡B.H. and D.D. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Albermarle (Hoechst, Germany) and BASF for the gift of chemicals. B.H. thanks Novartis Pharma AG for the fellowship.

REFERENCES

(1) (a) Nahm, S.; Weinreb, M. S. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Bergbreiter, D. E.; Killough, J. M. *J. Org. Chem.* **1976**, *41*, 2750−2753. (c) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777−1780. (d) Wattanasin, S.; Kathawala, F. G. *Tetrahedron Lett.* **1984**, *25*, 811−814. (e) Fujisawa, T.; Iida, S.; Uehara, H.; Sato, T. *Chem. Lett.* **1983**, *12*, 1267−1270. (f) Fujisawa, T.; Mori, T.; Sato, T. *Tetrahedron Lett.* **1982**, *23*, 5059−5062. (g) Anderson, M. W.; Jones, R. C. F.; Saunders, J. *J. Chem. Soc., Chem. Commun.* **1982**, *5*, 282−283. (h) Mattson, M. N.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6071−6074. (i) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188−3191. (j) Park, J. K.; Shin, W. K.; An, D. K. *Tetrahedron Lett.* **2013**, *54*, 3199−3203. (k) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.***1983**, *48*, 2260−2266.

(2) For transition-metal catalysis on selective preparation of ketones see: (a) Lutter, F. H.; Grokenberger, L.; Hofmayer, M. S.; Knochel, P. *Chem. Sci.* **2019**, *10*, 8241−8245. (b) Li, H.; Xu, Y.; Shi, E.; Wei, W.; Suo, X.; Wan, X. *Chem. Commun.* **2011**, *47*, 7880−7882. (c) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613−1618. (d) Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. *Org. Lett.* **2019**, *21*, 1253−1257. (e) Meng, G.; Szostak, M. *Org. Lett.* **2018**, *20*, 6789−6793. (f) Li, G.; Shi, S.; Lei, P.; Szostak, M. *Adv. Synth. Catal.* **2018**, *360*, 1538−1543. (g) Wu, X.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986−5009. (h) Schranck, J.; Wu, X.; Neumann, H.; Beller, M. *Chem. - Eur. J.* **2012**, *18*, 4827−4831.

(3) Whitmore, F. C.; Forster, W. S. *J. Am. Chem. Soc.* **1942**, *64*, 2966−2968.

(4) (a) Odille, F. G. J.; Stenemyr, A.; Pontén, F. *Org. Process Res. Dev.* **2014**, *18*, 1545−1549. (b) Webb, D.; Jamison, T. F. *Org. Lett.* **2012**, *14*, 568−571. (c) Fukuyama, T.; Chiba, H.; Kuroda, H.; Takigawa, T.; Kayano, A.; Tagami, K. *Org. Process Res. Dev.* **2016**, *20*, 503−509. (d) Hafner, A.; Mancino, V.; Meisenbach, M.; Schenkel, B.; Sedelmeier, J. *Org. Lett.* **2017**, *19*, 786−789. (e) Stueckler, C.; Hermsen, P.; Ritzen, B.; Vasiloiu, M.; Poechlauer, P.; Steinhofer, S.; Pelz, A.; Zinganell, C.; Felfer, U.; Boyer, S.; Goldbach, M.; De Vries, A.; Pabst, T.; Winkler, G.; LaVopa, V.; Hecker, S.; Schuster, C. *Org. Process Res. Dev.* **2019**, *23*, 1069−1077. (f) Ganiek, M. A.; Becker, M. R.; Berionni, G.; Zipse, H.; Knochel, P. *Chem. - Eur. J.* **2017**, *23*, 10280. (g) Weidmann, N.; Ketels, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 10748−10751. (h) McQuade, D. T.; Seeberger, H. *J. Org. Chem.* **2013**, *78*, 6384−6389. (i) Chen, Y.; Hone, C. A.; Gutmann, B.; Kappe, C. O. *Org. Process Res. Dev.* **2017**, *21*, 1080−1087. (j) Price, G. A.; Hassan, A.; Chandrasoma, N.; Bogdan, A. R.; Djuric, S. W.; Organ, M. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 13347−13350. (k) Teci, M.; Tilley, M.; McGuire, M. A.; Organ, M. G. *Org. Process Res. Dev.* **2016**, *20*, 1967−1973. (l) Newby, J. A.; Blaylock, D. W.; Witt, P. M.; Turner, R. M.; Heider, P. L.; Harji, B. H.; Browne, D. L.; Ley, S. V. *Org. Process Res. Dev.* **2014**, *18*, 1221−1228.

(5) (a) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026−5030. (b) Yamazaki, T.; Terajima, T.; Kawasaki-Taskasuka, T. *Tetrahedron* **2008**, *64*, 2419−2424. (c) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, *7*, 564−566.

(6) (a) Nagaki, A.; Sasatsuki, K.; Ishiuchi, S.; Miuchi, N.; Takumi, M.; Yoshida, J. *Chem. - Eur. J.* **2019**, *25*, 4946−4950. (b) Moon, S.; Jung, S.; Bin Kim, U.; Kim, W. *RSC Adv.* **2015**, *5*, 79385.

(7) Nagaki, A.; Ichinari, D.; Yoshida, J. *Chem. Commun.* **2013**, *49*, 3242−3244.

(8) For further information see Supporting Information.

(9) For batch procedures for trifluoromethyl ketone formation see: (a) Funabiki, K.; Hayakawa, A.; Inuzuka, T. *Org. Biomol. Chem.* **2018**, *16*, 913−918. (b) Wiedemann, J.; Heiner, T.; Mloston, G.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 820−821.

(10) Eftekhari-Sis, B.; Zirak, M. *Chem. Rev.* **2015**, *115*, 151−264.

(11) (a) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288−2289. (b) Ziegler, D. S.; Karaghiosofff, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 6701−6704.