OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

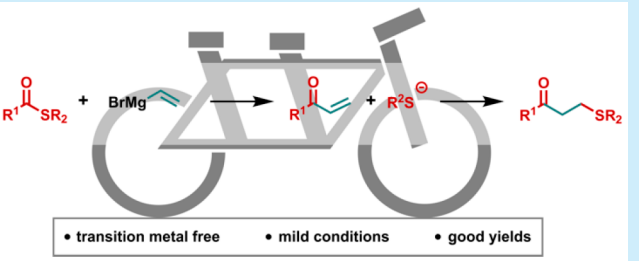
Tandem Acyl Substitution/Michael Addition of Thioesters with Vinylmagnesium Bromide

Vera Hirschbeck,[†] Marlene Böldl,[†] Paul H. Gehrtz,[‡] and Ivana Fleischer*

Institute of Organic Chemistry, University of Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

Supporting Information

ABSTRACT: A tandem reaction of thioesters with vinylmagnesium bromide is reported. The initial acyl substitution provides an α,β-unsaturated ketone which further reacts with the liberated thiolate. This transition-metal-free synthesis of β-sulfanyl ketones takes place under mild reaction conditions, whereas the addition of a second Grignard molecule is almost completely suppressed. The carefully chosen parameters enabled the transformation of different substrates in moderate to good yields.



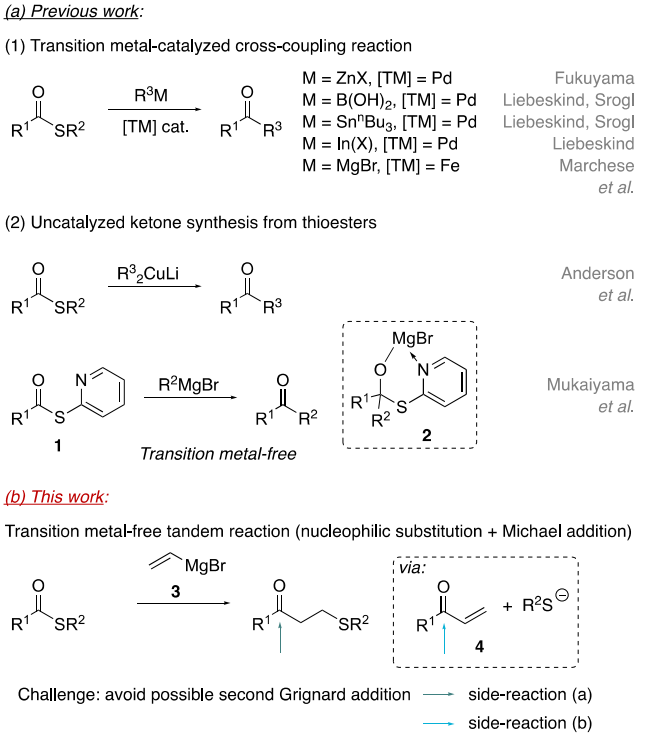
Org. Lett.

Thioesters are more reactive than alcohol-derived esters due to the poorer orbital overlap between the sulfur atom and the carbonyl group. They can be synthesized by various methods based on acylation chemistry[1] or metal-catalyzed transformations.[2] Therefore, they are of great importance in numerous synthetic applications,[3] for example, in the synthesis of ketones by a nucleophilic substitution with organometallic reagents. In general, this transformation was intensively investigated using various carboxylic acid derivatives.[4] The main issue is the control of chemoselectivity because a second attack of the C-nucleophile to the desired ketone generates a tertiary alcohol, which has to be avoided (overaddition). Thioesters are less affected by this problem than oxoesters, since they are more reactive than the resulting ketones, but the overaddition can only be prevented by an inconvenient controlled slow addition of the nucleophile.

Fortunately, transition-metal (TM) catalyzed cross-coupling reactions can be used as an alternative. The oxidative addition of the TM into the C(O)−S bond, followed by transmetalation with an organometallic compound and reductive elimination, enables the chemoselective formation of ketones (Scheme 1a). In their pioneering works, Fukuyama, Liebeskind, and Strogl reported a number of couplings employing different organometallic compounds (based on Zn, B, Sn, and In) in combination with a palladium catalyst.[5] Nickel-catalyzed versions were reported, as well.[6] Moreover, the reaction of thioester and Grignard reagent was shown by Marchese et al.[7] The transformation was catalyzed by 4 mol % $Fe(acac)_3$ and conducted under mild reaction conditions (0 °C, 5−10 min) in THF using aromatic and aliphatic Grignard reagents.

Since the employment of some transition metals is expensive, uncatalyzed versions are always of considerable interest (Scheme 1a). Anderson et al. reported the generation of ketones from *S*-alkyl and *S*-aryl thioesters with organocopper(I) complexes (e.g., $(^nBu)_2CuLi$) in good yields.[8] By the application of 1.0 equiv of ^{n}BuMgBr, the tertiary alcohol and the starting material were obtained in equal amounts,

Scheme 1. Transition-Metal-Catalyzed and -Free Synthesis of Ketones from Thioesters



whereas use of 1.5 equiv of ^{n}BuMgBr·CuI led to the desired ketone in >80% yield. A successful TM-free conversion of *S*-(2-pyridyl)thioates (**1**) with Grignard reagent without the formation of a tertiary alcohol was shown by Mukaiyama et al.[9] They argued that these substrates are able to form a six-

Received: February 12, 2019

DOI: 10.1021/acs.orglett.9b00538
Org. Lett. XXXX, XXX, XXX−XXX

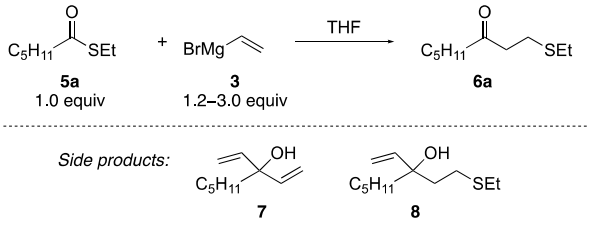
membered complex **2**, with nitrogen being coordinated to the magnesium ion. This complex reacts very slowly with a second Grignard molecule in comparison to the starting material and therefore enables a complete suppression of the side-product formation. Thus, 2-pyridyl thioesters can be considered as alternatives to Weinreb amides.[4b]

Herein, we report a transition metal free tandem reaction of thioesters with vinylmagnesium bromide (**3**) under mild reaction conditions (0 °C, 1 h) (Scheme 1b). An initial nucleophilic substitution of the thioester with **3** generates the Michael acceptor **4**, followed by a nucleophilic addition of the free thiolate to furnish β-sulfanyl ketones, which show unique synthetic[10] and also potential medicinal[11] applications. We also proposed the formation of a six-membered complex, which enables a chemoselective formation of ketones, whereas overaddition is almost completely suppressed. This reactivity was also inadvertently observed by Chen et al. in the synthesis of (+)-biotin.[12] In the application of other Grignard reagents, such as 1-propenyl- and isopropenylmagnesium bromide, no selective ketone formation was observed, which emphasizes the unique reactivity of **3** (see the Supporting Information for details).[13]

The first experiments were performed using thioester **5a** and vinylmagnesium bromide (**3**) in THF. At the beginning of this project, we struggled with reproducibility problems. We came to the conclusion that crystallization of **3** from the reaction mixture, which can already take place below 25 °C, might be the source of the problem. Since crystallization is strongly influenced by purity and temperature, it is extremely important to ensure the same conditions for each reaction. Therefore, the batch of purchased vinylmagnesium bromide (different purities), cooling system (different cooling capacity of Dewar and crystallizing dish), and reaction flask (different wall thickness and volume of the flask) might influence crystallization and cannot be varied during the comparison of different reaction parameters. Thus, every new batch of **3** was applied in a test reaction in order to see if the yield has changed. If crystallization is taking place, the problem can be overcome by increasing the amount of solvent.

In the initial optimization using **5a** as a test substrate, different temperatures, reaction times, and equivalents of Grignard reagents and additives were tested (Table 1). As expected, no reaction was observed at −78 °C because vinylmagnesium bromide crystallized instantly. On the other hand, side reactions became more likely at room temperature, resulting in a yield of only 51% (Table 1, entry 4). The best result was observed at 0 °C (Table 1, entry 3), providing **6a** in 75% yield with almost full conversion of thioester. Since a lower amount of Grignard reagent might prevent a second attack of vinylmagnesium bromide either to product **6a** yielding alcohol **8** or to the intermediate **4** (to give **7**), 1.2 and 2.0 equiv of **3** were applied. However, the yields dropped significantly (Table 1, entries 5 and 6). The combination of a low concentration of the substrate (0.12 mol/L) and a large excess of the Grignard reagent could facilitate the side reaction (b) (Scheme 1), which might be avoided by the addition of external EtSH (Table 1, entry 7). Interestingly, lower amounts of the product were formed. Despite the small concentration of free thiolate, the high selectivity for the nucleophilic addition of EtSH instead of **3** to the Michael acceptor **4** is remarkable. Therefore, we suggest the formation of chelate **10** via 1,4-addition of intermediate **9**, in which the thiol is not leaving the coordination sphere and is able to attack the Michael acceptor rapidly (Figure 1).

Table 1. Initial Optimizations[a]



entry	temp (°C)	time (h)	3 (equiv)	additive	conv (%)	yield (%)
1	−78	1	3		0	0
2	−10	1	3		89	73
3	0	1	3		97	75
4	rt	1	3		100	51
5	0	1	1.2		70	48
6	0	1	2		88	64
7	0	1	3	EtSH[b]	92	66
8[c]	0	1	3		99	65
9	0	1	3	LiCl[d]	96	74
10	0	2	3		100	64
11	0	4	3		99	65

[a]Reaction conditions: **5a** (163 mg, 1.02 mmol, 1.0 equiv), **3** (0.89 M in THF), THF (5 mL); yields and conversions were determined by quant GC−FID using *n*-pentadecane as an internal standard. [b]EtSH (1.0 equiv). [c]THF (1 mL). [d]LiCl (0.2 equiv).

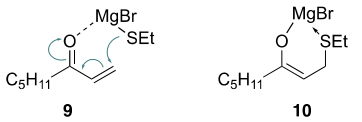


Figure 1. 1,4-Addition and proposed intermediates.

Lowering the amount of solvent and thereby increasing the substrate concentration leads to lower yield due to the partial crystallization of **3**, which was observed during the reaction (Table 1, entry 8). LiCl might accelerate the nucleophilic attack to **5a** or **4** (Table 1, entry 9) or modulate the reactivity of **3**,[14] but no effect was observed. Longer reaction time led to decomposition (mainly overaddition) of the product under the reaction conditions. The general difference between conversion and yield can be explained by the formation of small amounts of several different side products, which were observed by GC−MS of the crude mixture but could not be assigned.

Since the reaction time plays an important role, the reaction progress was evaluated in order to find the optimum balance between product formation and degradation (Figure 2). Indeed, highest yield and full conversion were observed after 1 h. In the further course of the reaction, the side reactions became prevalent. Interestingly, upon treatment of isolated **6a** with vinylmagnesium bromide (3.0 equiv) in THF at 0 °C for 1 h, **8** was generated in 83% yield (100% conversion). In the reaction progress study, only 11% of the product reacted with the remaining Grignard reagent. Therefore, it can be assumed that chelate **10** is formed in the reaction mixture, which impedes the attack of the second vinylmagnesium bromide molecule. In conclusion, the best result was observed using 3.0 equiv of **3** at 0 °C for 1 h. Compound **6a** was generated in a

DOI: 10.1021/acs.orglett.9b00538
Org. Lett. XXXX, XXX, XXX−XXX

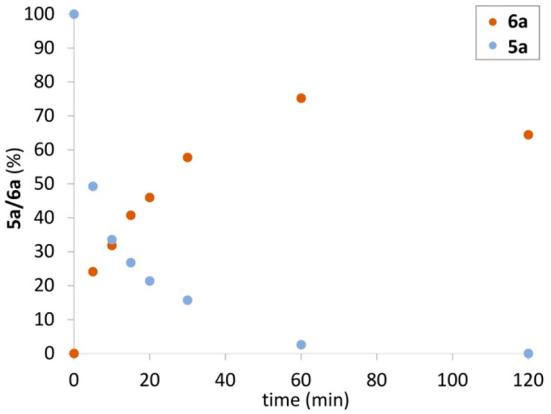


Figure 2. Reaction profile for the conversion of **5a** with vinylmagnesium bromide (**3**). Reaction conditions: **5a** (160 mg, 998 μmol, 1.0 equiv), **3** (0.52−0.89 M in THF, 3.0 equiv), THF (5 mL), 0 °C, 2 h. Yields were determined by quant GC−FID using *n*-pentadecane as an internal standard.

yield of 75%, which is satisfactory for a two-step tandem reaction.

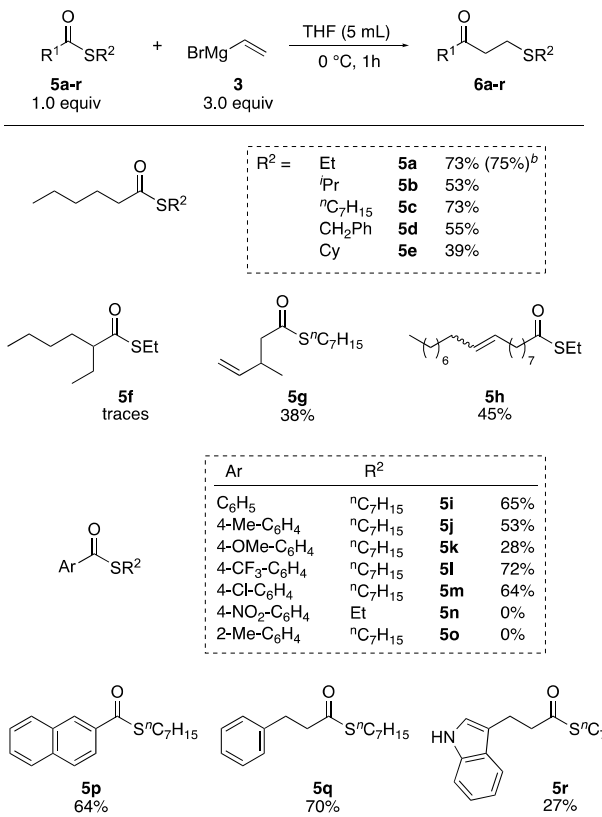
With the optimized conditions in hand, the substrate screening was performed beginning with the investigation of the influence of the S-substituent (Scheme 2). The same yield was observed by using **5c** instead of the ethyl thioester **5a**. The transformation of **5a** was also conducted on a 10 mmol scale with the same result (75% yield). The sterically more demanding thioesters **5b**, **5d**, and **5e** were less reactive, generating a significantly lower yield. S-Phenyl-substituted analogue led to a sluggish reaction and NMR yield of 14%. Then the carbonyl substituent was varied. Disappointingly, only traces of the product were observed for the *α*-substituted **5f**, whereas *β*-substituted **5g** provided **6g** in 38% yield. The long chain thioester **5h** was also less reactive, furnishing **6h** in 45% yield.

Furthermore, different aryl-substituted benzothioates (**5i**−**o**) were tested. The unsubstituted **5i** showed a yield of 65%, whereas the electron-donating substituents present in **5j** and **5k** led to lower reactivity. Increasing the electron density at the carbonyl center reduces the electrophilicity of thioester, and therefore, the nucleophilic attack of **3** is slower. As expected, the electron-deficient CF_3 group in the *para*-position increased the yield to 72% (**6l**). Chlorinated substrate **5m** showed the same reactivity as the unsubstituted one, which can be explained by "chameleon-like" inductively electron-withdrawing (−I) and electron-donating mesomeric (+M) effects. The nitro group was not tolerated, which is not surprising since reactions of nitroarenes with Grignard reagents are known in the literature.[15] In addition, substitution at the *ortho*-position seems to be a limitation of the catalytic system, since no yield was observed by using **5o**. Moreover, **5p** showed a similar reactivity as **5i**, with a yield of 64%, whereas **5q** is more compatible with **5a**. Indole-substituted thioester **5r** was transformed in a yield of 27%, showing that a protection step is not needed. The yield could not be increased by using 4 equivalents of **3**. In most lower yielding reactions, the main component of the crude reaction mixture was the unreacted starting material and not one of the side products.

The synthesized *β*-sulfanyl ketones can be used to generate *β*-sulfonyl ketones in one oxidation step with mCPBA, which was shown in an exemplary way by using **6a** as a substrate (Scheme 3). *β*-Sulfonyl ketones are important structural motives in biologically active molecules[16] and are also common in organic synthesis.[17] Their treatment with DBU led to the elimination of the sulfonyl moiety and formation of valuable vinyl ketone **13**. Moreover, **6a** was reduced to the corresponding 3-thio-substituted alcohol **12**.

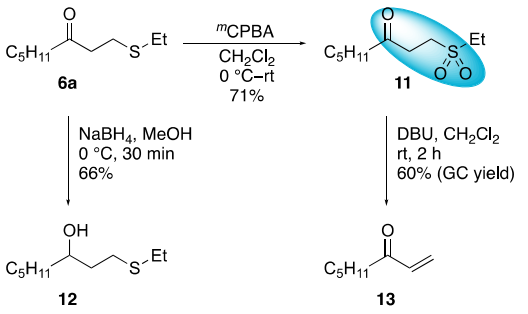
In conclusion, a transition-metal-free two-step tandem reaction of thioesters with vinylmagnesium bromide was investigated. The likely formation of a chelate complex hinders the attack of a second Grignard molecule and, hence, the formation of a tertiary alcohol. Low temperature (0 °C) and short reaction times (1 h) enabled the transformation of various substrates in moderate to good yields. The obtained

Scheme 2. Substrate Screening[a]



[a]Reaction conditions: **5a**−**r** (1.0 mmol, 1.0 equiv), **3** (0.52−0.89 M in THF, 3.0 equiv), THF (5 mL), 0 °C, 1 h. Isolated yields. [b]Reaction at 10 mmol scale.

Scheme 3. Synthesis of *β*-Sulfonyl Ketones 11 from *β*-Sulfanyl Ketones 6a



DOI: 10.1021/acs.orglett.9b00538
Org. Lett. XXXX, XXX, XXX−XXX

products can be used as building blocks for other synthetic transformations, e.g., the generation of β-sulfonyl ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00538.

Experimental procedures, analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ivana.fleischer@uni-tuebingen.de.

ORCID

Ivana Fleischer: 0000-0002-2609-6536

Present Address

‡(P.H.G.) Department of Organic Chemistry, Weizmann Institute of Science, 234 Herzl St, Rehovot, Israel.

Author Contributions

†V.H. and M.B. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Fonds der Chemischen Industrie (Liebig Fellowship, I.F.; PhD fellowship, V.H., the University of Tübingen (Institutional Strategy of the University of Tübingen; Deutsche Forschungsgemeinschaft, ZUK63), and the University of Regensburg for financial support.

■ REFERENCES

(1) Kazemi, M.; Shiri, L. Thioesters synthesis: recent adventures in the esterification of thiols. *J. Sulfur Chem.* **2015**, *36*, 613−623.

(2) For selected examples, see: (a) Lüssem, B. J.; Gais, H.-J. Palladium-Catalyzed Enantioselective Allylic Alkylation of Thiocarboxylate Ions: Asymmetric Synthesis of Allylic Thioesters and Memory Effect/Dynamic Kinetic Resolution of Allylic Esters. *J. Org. Chem.* **2004**, *69*, 4041−4052. (b) Sawada, N.; Itoh, T.; Yasuda, N. Efficient copper-catalyzed coupling of aryl iodides and thiobenzoic acid. *Tetrahedron Lett.* **2006**, *47*, 6595−6597. (c) Cao, H.; McNamee, L.; Alper, H. Palladium-Catalyzed Thiocarbonylation of Iodoarenes with Thiols in Phosphonium Salt Ionic Liquids. *J. Org. Chem.* **2008**, *73*, 3530−3534. (d) Huang, Y.-T.; Lu, S.-Y.; Yi, C.-L.; Lee, C.-F. Iron-Catalyzed Synthesis of Thioesters from Thiols and Aldehydes in Water. *J. Org. Chem.* **2014**, *79*, 4561−4568. (e) Hirschbeck, V.; Gehrtz, P. H.; Fleischer, I. Regioselective Thiocarbonylation of Vinyl Arenes. *J. Am. Chem. Soc.* **2016**, *138*, 16794−16799.

(3) For reviews, see: (a) Hirschbeck, V.; Gehrtz, P. H.; Fleischer, I. Metal-Catalyzed Synthesis and Use of Thioesters: Recent Developments. *Chem. - Eur. J.* **2018**, *24*, 7092−7107. (b) Pan, F.; Shi, Z.-J. Recent Advances in Transition-Metal-Catalyzed C−S Activation: From Thioester to (Hetero)aryl Thioether. *ACS Catal.* **2014**, *4*, 280−288. (c) Wang, L.; He, W.; Yu, Z. Transition-metal mediated carbon−sulfur bond activation and transformations. *Chem. Soc. Rev.* **2013**, *42*, 599−621.

(4) For selected examples, see: (a) Posner, G. H.; Whitten, C. E.; McFarland, P. E. Organocopper chemistry. Halo-, cyano-, and carbonyl-substituted ketones from the corresponding acyl chlorides and organocopper reagents. *J. Am. Chem. Soc.* **1972**, *94*, 5106−5108. (b) Nahm, S.; Weinreb, S. M. N-methoxy-N-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (c) Enda, J.; Kuwajima, I. General method for generation of 3-siloxyallylmetallic species and their synthetic application. *J. Am. Chem. Soc.* **1985**, *107*, 5495−5501. (d) Ryu, I.; Ikebe, M.; Sonoda, N.; Yamato, S.-Y.; Yamamura, G.-H.; Komatsu, M. Chemistry of ketone α,β-dianions. Acylation reactions of dianion cuprates by acid chlorides. *Tetrahedron Lett.* **2002**, *43*, 1257−1259. (e) Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. Direct Conversion of N-Methoxy-N-methylamides (Weinreb Amides) to Ketones via a Nonclassical Wittig Reaction. *Org. Lett.* **2005**, *7*, 1427−1429. (f) 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. (g) Tsubouchi, A.; Onishi, K.; Takeda, T. Stereoselective Preparation of 1-Siloxy-1-alkenylcopper Species by 1,2-Csp^2-to-O Silyl Migration of Acylsilanes. *J. Am. Chem. Soc.* **2006**, *128*, 14268−14269. (h) Maloney, K. M.; Chung, J. Y. L. A General Procedure for the Preparation of β-Ketophosphonates. *J. Org. Chem.* **2009**, *74*, 7574−7576. (i) Štefane, B. Selective Addition of Organolithium Reagents to BF_2-Chelates of β-Ketoesters. *Org. Lett.* **2010**, *12*, 2900−2903. (j) Genna, D. T.; Posner, G. H. Cyanocuprates Convert Carboxylic Acids Directly into Ketones. *Org. Lett.* **2011**, *13*, 5358−5361. (k) Liu, C.; Achtenhagen, M.; Szostak, M. Chemoselective Ketone Synthesis by the Addition of Organometallics to N-Acylazetidines. *Org. Lett.* **2016**, *18*, 2375−2378. (l) Meng, G.; Szostak, M. N-Acyl-Glutarimides: Privileged Scaffolds in Amide N−C Bond Cross-Coupling. *Eur. J. Org. Chem.* **2018**, *2018*, 2352−2365. (m) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)−NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N−C/O−C Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589−2599.

(5) (a) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. A novel ketone synthesis by a palladium-catalyzed reaction of thiol esters and organozinc reagents. *Tetrahedron Lett.* **1998**, *39*, 3189−3192. (b) Liebeskind, L. S.; Srogl, J. Thiol Ester−Boronic Acid Coupling. A Mechanistically Unprecedented and General Ketone Synthesis. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261. (c) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. Ketone Synthesis under Neutral Conditions. Cu(I) Diphenylphosphinate-Mediated, Palladium-Catalyzed Coupling of Thiol Esters and Organostannanes. *Org. Lett.* **2003**, *5*, 3033−3035. (d) Fausett, B. W.; Liebeskind, L. S. Palladium-Catalyzed Coupling of Thiol Esters with Aryl and Primary and Secondary Alkyl Organoindium Reagents. *J. Org. Chem.* **2005**, *70*, 4851−4853.

(6) (a) Gehrtz, P. H.; Kathe, P.; Fleischer, I. Nickel-Catalyzed Coupling of Arylzinc Halides with Thioesters. *Chem. - Eur. J.* **2018**, *24*, 8774−8778. (b) Shimizu, T.; Seki, M. A novel synthesis of functionalized ketones via a nickel-catalyzed coupling reaction of zinc reagents with thiolesters. *Tetrahedron Lett.* **2002**, *43*, 1039−1042. (c) Wotal, A. C.; Weix, D. J. Synthesis of Functionalized Dialkyl Ketones from Carboxylic Acid Derivatives and Alkyl Halides. *Org. Lett.* **2012**, *14*, 1476−1479.

(7) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. A highly efficient synthetic route to ketones through sequential coupling reactions of Grignard reagents with S-phenyl carbonochloridothioate in the presence of nickel or iron catalysts. *Tetrahedron Lett.* **1985**, *26*, 3595−3598.

(8) Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. General ketone synthesis. Reaction of organocopper reagents with S-alkyl and S-aryl thioesters. *J. Am. Chem. Soc.* **1974**, *96*, 3654−3655.

(9) Mukaiyama, T.; Araki, M.; Takei, H. Reaction of S-(2-pyridyl) thioates with Grignard reagents. Convenient method for the preparation of ketones. *J. Am. Chem. Soc.* **1973**, *95*, 4763−4765.

(10) For selected examples, see: (a) Lauder, K.; Toscani, A.; Qi, Y.; Lim, J.; Charnock, S. J.; Korah, K.; Castagnolo, D. Photo-biocatalytic One-Pot Cascades for the Enantioselective Synthesis of 1,3-Mercaptoalkanol Volatile Sulfur Compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 5803−5807. (b) Trost, B. M.; Keeley, D. E. New synthetic methods. Secoalkylative approach to grandisol. *J. Org. Chem.* **1975**, *40*, 2013. (c) Cohen, T.; Mura, A. J.; Shull, D. W.; Fogel, E. R.; Ruffner,

DOI: 10.1021/acs.orglett.9b00538
Org. Lett. XXXX, XXX, XXX−XXX

R. J.; Falck, J. R. Removal of sulfur groups from molecules by copper(I). Preparation of sulfur-substituted 1,3-dienes for the Diels-Alder reaction. *J. Org. Chem.* **1976**, *41*, 3218−3219. (d) Cherkauskas, J. P.; Cohen, T. Carbonyl-protected β-lithio aldehydes and ketones via reductive lithiation. A general preparative method for remarkably versatile homoenolate equivalents. *J. Org. Chem.* **1992**, *57*, 6−8.

(11) Kumar, A.; Tripathi, V. D.; Kumar, P.; Gupta, L. P.; Akanksha; Trivedi, R.; Bid, H.; Nayak, V. L.; Siddiqui, J. A.; Chakravarti, B.; Saxena, R.; Dwivedi, A.; Siddiquee, M. I.; Siddiqui, U.; Konwar, R.; Chattopadhyay, N. Design and synthesis of 1,3-biarylsulfanyl derivatives as new anti-breast cancer agents. *Bioorg. Med. Chem.* **2011**, *19*, 5409−5419.

(12) Huang, J.; Xiong, F.; Wang, Z.-H.; Chen, F.-E. Unexpected Ring Expansion of the (3aS,6aR)-γ-Thiolactone Moiety during the Introduction of the (+)-Biotin Side Chain. *Helv. Chim. Acta* **2009**, *92*, 1445−1449.

(13) Zhu, M.; Liu, L.; Yu, H.-T.; Zhang, W.-X.; Xi, Z. Alkenyl Magnesium Compounds: Generation and Synthetic Application. *Chem. - Eur. J.* **2018**, *24*, 19122−19135.

(14) (a) Krasovskiy, A.; Knochel, P. A LiCl-Mediated Br/Mg Exchange Reaction for the Preparation of Functionalized Aryl- and Heteroarylmagnesium Compounds from Organic Bromides. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333−3336. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. Highly Efficient Reagents for Br/Mg Exchange. *Angew. Chem., Int. Ed.* **2006**, *45*, 159−162.

(15) (a) Bartoli, G.; Leardini, R.; Medici, A.; Rosini, G. Reactions of nitroarenes with Grignard reagents. General method of synthesis of alkyl-nitroso-substituted bicyclic aromatic systems. *J. Chem. Soc., Perkin Trans. 1* **1978**, *1*, 692−696. (b) Bartoli, G. Conjugate addition of alkyl Grignard reagents to mononitroarenes. *Acc. Chem. Res.* **1984**, *17*, 109−115. (c) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. The reaction of vinyl grignard reagents with 2-substituted nitroarenes: A new approach to the synthesis of 7-substituted indoles. *Tetrahedron Lett.* **1989**, *30*, 2129−2132. (d) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. Mechanistic studies on the reaction of nitro- and nitrosoarenes with vinyl Grignard reagents. *J. Chem. Soc., Perkin Trans. 2* **1991**, *2*, 657−663.

(16) Messinger, P.; Borchert-Bremer, R. γ-Oxosulfone als Aldehyd-Dehydrogenase-Hemmer. *Arch. Pharm.* **1983**, *316*, 663−667.

(17) (a) Wan, X.; Meng, Q.; Zhang, H.; Sun, Y.; Fan, W.; Zhang, Z. An Efficient Synthesis of Chiral β-Hydroxy Sulfones via Ru-Catalyzed Enantioselective Hydrogenation in the Presence of Iodine. *Org. Lett.* **2007**, *9*, 5613−5616. (b) Liu, Y.; Qin, W.; Yan, H. Efficient Enrichment of Chiral β-Sulfonyl Ketones through Asymmetric β-Elimination. *Synlett* **2016**, *27*, 2756−2760. (c) Li, L.; Liu, Y.; Peng, Y.; Yu, L.; Wu, X.; Yan, H. Kinetic Resolution of β-Sulfonyl Ketones through Enantioselective β-Elimination using a Cation-Binding Polyether Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 331−335. (d) Hays, D.; Danielson, M.; Gerster, J.; Niwas, S.; Prince, R.; Kshirsagar, T.; Heppne, P.; Moser, W.; Moseman, J.; Radmer, M.; Kavanagh, M.; Strong, S.; Bonk, J. US Patent 20060100229, 2006.

DOI: 10.1021/acs.orglett.9b00538
Org. Lett. XXXX, XXX, XXX−XXX