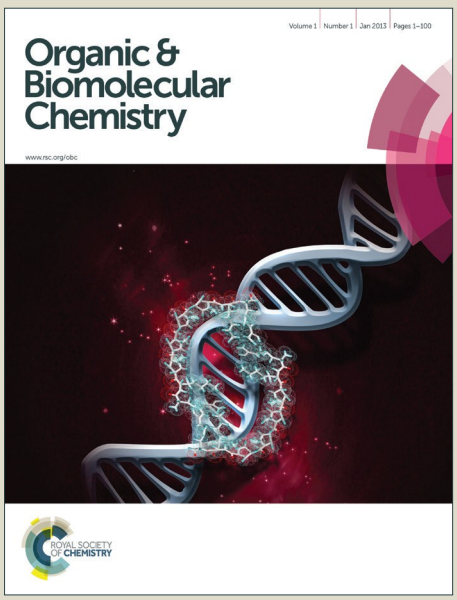
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Yuan, D. Zhao, L. Zhang, X. Pan, Y. Yang, P. Wang, H. Li and C. Da, *Org. Biomol. Chem.*, 2015, DOI: 10.1039/C5OB02072G.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C5OB02072G

Journal Name

ARTICLE

Isopropylmagnesium Chloride-promoted Unilateral Addition of Grignard reagents to β-Diketones: One-pot Syntheses of β-Tertiary Hydroxyl Ketones or 3-Substituted Cyclic-2-Enones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

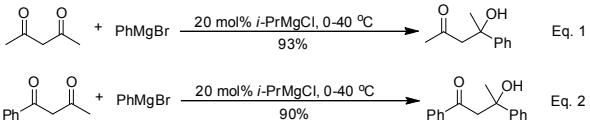
Rui Yuan,[a,b*] Dan Zhao,[a] Li-Yuan Zhang,[a] Xiang Pan,[a] Yan Yang,[a] Pei Wang,[a] Hong-Feng Li,[a] Chao-Shan Da[a,b,c*]

The regioselective unilateral additions of Grignard reagents to acyclic or cyclic β-diketones were effectively promoted by sub-stoichiometric amount of *i*-PrMgCl to afford β-tertiary hydroxyl ketones or 3-substituted cyclic-2-enones respectively. Also addition of Grignard reagents to acyclic β-diketones followed by reaction with cyclic β-diketones in one-pot was put forward. The reaction mechanism was discussed in detail to explain the high regioselectivity by chemistry experiment, hydrogen-deuterium exchange and mass spectrometry.

Introduction

β-Tertiary hydroxyl ketones or cyclic-2-enones are important intermediates in organic chemistry[1] and key motifs of many bioactive molecules.[2] Regioselective unilateral Grignard addition of 1,3-diones should have been expected to readily achieve these compounds. Addition of Grignard reagents to ketones is the known one, but the use of diketones usually gave mixtures of bilateral[3] and dehydration products[4] and resulted in low to moderate yield because that β-diketones transformed to enolate anions very quickly under the strong basicity of Grignard reagents.[5] By far, only two groups obtained unilateral addition product from Grignard addition of 1,3-diones.[6] One was a three-step procedure, in which the carbonyl protection and deprotection were necessary.[6a] The other method used the stoichiometric anhydrous cerium trichloride as catalyst.[6b] The substrates scope of these two methods was relatively narrow. Therefore, this transformation still remains some challenge.

We herein reported the efficient isopropylmagnesium chloride-promoted regioselective unilateral addition of Grignard reagents to β-diketones to synthesize β-tertiary hydroxyl ketones or 3-substituted cyclic-2-enones (Scheme **1**, Eq.**1** and **2**). The reaction mechanism was investigated in detail *via* chemistry experiments, hydrogen-deuterium exchange and mass spectrometry.



Scheme 1 The Protocol to Gain β-Tertiary Hydroxyl Ketones in This Work.

Results and discussion

The optimum of the reaction was tested firstly based on the reaction of acetylacetone and PhMgBr (Table **1**). The direct reaction of these two reactants only afforded 58% yield (Entry **1**) and the increasing PhMgBr loading only raised the yield to 78% (Entries **2**-**3**). When 20 mol% of *i*-PrMgCl was added in advance (Entries **4**-**9**), not only the yield (Entry **1** *vs* **4**) but also the efficiency (Entry **3** *vs* **4**) was raised. Lowering the reaction temperature introduced a little decrease in the yield (Entries **6**, **10**, **11**). Other chloride Grignard reagents could also raise the yield (Entries **1**, **15**-**18**) but didn't more efficient than *i*-PrMgCl. Bromide Grignard reagents such as *i*-PrMgBr and *t*-BuMgBr led to a big fall in the yield (Entries **19**-**20**) which may be attribute to the lower electronegativity of bromine than that of chlorine (Scheme **6**, reaction mechanism). When PhMgCl was used as substrate, the yield decreased from 93% to 57% (Entries **6** *vs* **21**). These results verified the reasonability of the mechanism supposed in Scheme **6**.

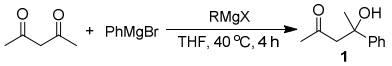
Under the optimized reaction conditions, the scope of substrates was explored (Table **2**). In the previous reported work,[5] only the electron-deficient *p*-CF_3-C_6H_4-MgBr got a 30% yield. This method was well tolerable to aryl Grignard reagents with both electron-donating and electron-withdrawing substituents. Even alkyl, alkenyl or alkynyl Grignard reagents afforded high yields (Entries **9**-**12**). Second, a series of other

[a] Institute of Biochemistry and Molecular Biology, School of Life Sciences, Lanzhou University, Lanzhou 730000, China.
[b] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China.
[c] Key Lab of Preclinical Study for New Drugs of Gansu Province, Lanzhou University, Lanzhou 730000, China.
†*Corresponding Author: E-mail: 18293133274@163.com Tel/Fax: +86-516-83500331.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5OB02072G

symmetrical 1,3-diones with two terminal alkyl, medicine-interesting trifluoromethyl[8] and aryl groups, benzoylacetone investigated. All of them gave high yields (Entries **13**-**18**). Asymmetric 1,3-diones were also checked with PhMgBr (Entries **19**-**30**) to give high yields from 87-91%. Even the 1,3-dione with the heteroaryl and trifluoromethyl group similarly afforded 77% yield (Entry **30**). It also shown in Table **2** that the steric hindrance of both Grignard reagents and 1,3-diones had no influence on the yields (Entries **8**, **10**, **13**-**18**).

Table 1 Optimization of the Reaction Conditions.[a]



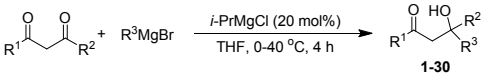
1

entry	RMgX (eq.)	PhMgBr (eq.)	yield (%)[b]
1	none	2.5	58
2	none	4.0	77
3	none	5.0	78
4	*i*-PrMgCl (0.1)	2.5	80
5	*i*-PrMgCl (0.15)	2.5	84
6	*i*-PrMgCl (0.2)	2.5	93
7	*i*-PrMgCl (0.25)	2.5	89
8	*i*-PrMgCl (0.3)	2.5	91
9	*i*-PrMgCl (0.5)	2.5	92
10	*i*-PrMgCl (0.2)	2.5	87[c]
11	*i*-PrMgCl (0.2)	2.5	89[d]
12	*i*-PrMgCl (0.2)	1.2	50
13	*i*-PrMgCl (0.2)	2.0	59
14	*i*-PrMgCl (0.2)	3.0	93
15	*n*-BuMgCl (0.2)	2.5	87
16	PhMgCl (0.2)	2.5	82
17	*i*-BuMgCl (0.2)	2.5	90
18	*c*-HexMgCl (0.2)	2.5	90
19	*i*-PrMgBr (0.2)	2.5	27
20	*t*-BuMgBr (0.2)	2.5	30
21	*i*-PrMgCl (0.2)	2.5	57[e]

[a]The acetylacetone loading was 0.5 mmol. [b]Isolated yield. [c]At 0°C. [d]At room temperature. [e]PhMgCl was used to replace PhMgBr.

When cyclic 1,3-diones were used, only 3-substituted enones, another important synthons with its varied 1,2- and 1,4-reactivity in organic synthesis,[9-10] were achieved due to the intramolecular dehydration (Table **3**). To our knowledge, the one-step procedure from cyclic 1,3-diones to 3-substituted enones has not been reported so far.[10] It was glad to see that β-cyclohexanedione afforded good to high yield to all the investigated Grignard reagents (Entries **1**-**7**). The yield became dropped without addition of *i*-PrMgCl (Entry **2**). For β-cyclopentanedione, the yield was generally lower than that of β-cyclohexanedione and the amount of promotor *i*-PrMgCl should be 30 mol% (Entries **8**-**13**) due to its lower reactivity than that of β-cyclohexanedione.

Table 2 The Grignard Reaction of 1,3-Diones.

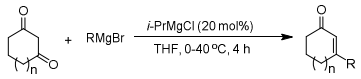


1-30

entry	R_1	R_2	R_3	Yield (%)[a]
1	Me	Me	Ph	93
2	Me	Me	2-naphthyl	91
3	Me	Me	4-$MeOC_6H_4$	87
4	Me	Me	3,5-$(CF_3)_2$-C_6H_3	93
5	Me	Me	4-CF_3-C_6H_4	86
6	Me	Me	4-MeC_6H_4	88
7	Me	Me	3-MeC_6H_4	88
8	Me	Me	2-MeC_6H_4	83
9	Me	Me	*n*-heptyl	84
10	Me	Me	*i*-Pr	80
11	Me	Me	*i*-butenyl	60
12	Me	Me	Ph-C≡C	81
13	CF_3	CF_3	Ph-C≡C	79
14	Et	Et	Ph	96
15	Ph	Ph	Ph	92
16	4-MeC_6H_4	4-MeC_6H_4	Ph	89
17	3-ClC_6H_4	3-ClC_6H_4	Ph	93
18	3-$MeOC_6H_4$	3-$MeOC_6H_4$	Ph	92
19	Ph	Me	Ph	90[b]
20	Ph	Me	2-naphthyl	91
21	Ph	Me	4-$MeOC_6H_4$	90
22	Ph	Me	Ph-C≡C	80
23	Ph	Me	n-heptyl	85
24	Ph	Me	2-thienyl	87
25	Ph	Me	*i*-Pr	80
26	Ph	Me	*i*-butenyl	86
27	4-MeC_6H_4	Me	Ph	87
28	3-ClC_6H_4	Me	Ph	91
29	2-naphthyl	Me	Ph	90
30	2-thienyl	CF_3	Ph	77

[a]Isolated yield. [c]40 mol% *i*-PrMgCl and 4.0 eq. PhMgBr were used.

Table 3 The Direct Addition of Grignard Reagents to Cyclic 1,3-Diones.



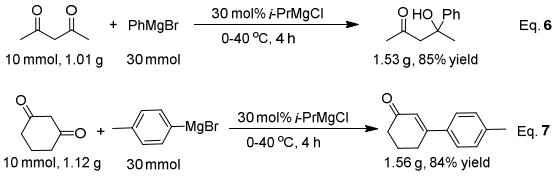
31-43

entry	compound	n	R	yield (%)[a]
1	31	1	Ph	82
2	32	1	4-MeC_6H_4	90 (56[b])
3	33	1	2-naphthyl	88
4	34	1	3,5-$Me_2C_6H_3$	70
5	35	1	3-$MeOC_6H_4$	79
6	36	1	4-$MeOC_6H_4$	84
7	37	1	*n*-Bu	70
8	38	0	Ph	81[c]
9	39	0	4-MeC_6H_4	78[c]
10	40	0	3,5-$Me_2C_6H_3$	76[c]
11	41	0	3-$MeOC_6H_4$	73[c]
12	42	0	4-$MeOC_6H_4$	78[c]
13	43	0	2-naphthyl	74[c]

[a]Isolated yield. [b]Without *i*-PrMgCl. [c]Promoted by 30 mol% of *i*-PrMgCl.

View Article Online
DOI: 10.1039/C5OB02072G

Then we successfully enlarged the reaction to gram scale (Scheme **2**, Eq. **6-7**). The high-yield results clearly indicated the practicality of this protocol.



Scheme 2 The Gram-Scale Direct Reaction of 1,3-Diones and the Grignard Reagents.

To figure out the reaction mechanism, the hydrogen-deuterium exchange was firstly carried out. 20 mol% *i*-PrMgCl and *i*-PrMgBr were added to acetylacetone in THF, respectively (Fig. **1**). After 30 min, the reaction was directly condensed to dryness in vacuum and the residue was directly characterized with ^{1}H NMR in $CDCl_3$, with a drop of D_2O added. The ratio of H_b to H_a: (1) 3.03:1; (2) 2.81:1; (3) 2.94:1 which indicated that *i*-PrMgCl can make the enolate be predominant to result in higher yield than *i*-PrMgBr (**(1)** *vs* **(2)**). It also suggested that the enolate was the key intermediate in the process.

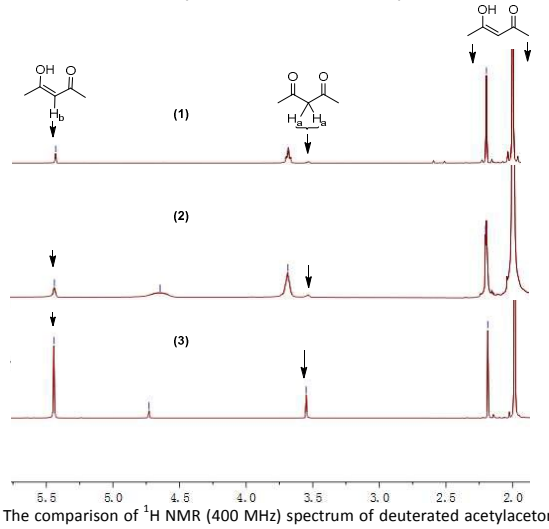
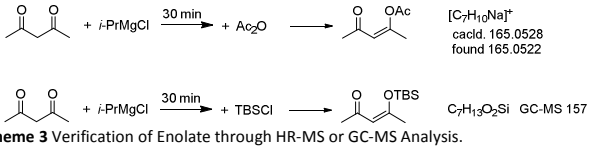


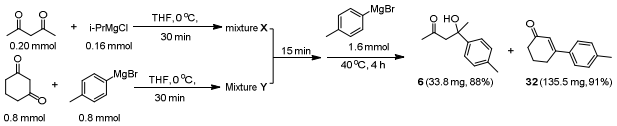
Fig. 1 The comparison of ^{1}H NMR (400 MHz) spectrum of deuterated acetylacetone in $CDCl_3$. **(1)** the deuterated acetylacetone after reacted with 20 mol% *i*-PrMgCl. **(2)** the deuterated acetylacetone after reacted with 20 mol% *i*-PrMgBr. **(3)** the deuterated acetylacetone without any Grignard reagents.

The presence of enolate was also comfirmed by the chemical experiments. 20 mol% of *i*-PrMgCl was added to acetylacetone in THF, after 30 min, acetic anhydride and TBSCl (*t*-butyldimethylsilyl chloride) was added respectively. The reactions were directly characterized with HR-MS or GC-MS. (Scheme **3**) The formation of two esters indicated the existance of enolate in the present of *i*-PrMgCl.



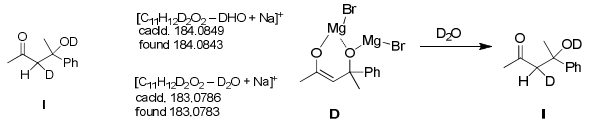
Scheme 3 Verification of Enolate through HR-MS or GC-MS Analysis.

Secondly, the mixture **X** (Scheme **4**) from the pre-mixed acetylacetone and *i*-PrMgCl, both in catalytic amounts, was added to the mixture **Y** (Scheme **4**) similarly from the pre-mixed β-cyclohexanedione and 4-MeC_6H_4MgBr. The excessive 4-MeC_6H_4MgBr was further added after 15 min. The yield of β-substituted cyclic enone **32** was realized in 91% and the result was as good as that in Table **3** (Entry **2**). It indicated that the Br^-/Cl^- exchange did exist in the Grignard addition. If the chloride ion on enolate intermediate **C** (Scheme **6**) didn't exchange with the bromide ion on the intermediate **A'** that formed by 4-MeC_6H_4MgBr and β-cyclohexanedione, the yield of 4-hydroxy-4-(p-tolyl)pentan-2-one would be as good as that shown in Table **2** (Entry **6**) while the yield of **32** would drop to 56% (Table **3**, Entry **2**).



Scheme 4 The Experiment to Confirm the Br^-/Cl^- Exchange in the Process.

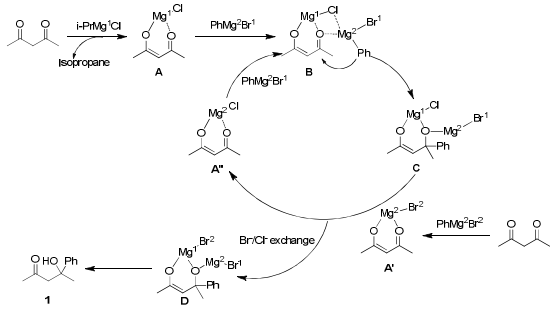
Finally, D_2O was used to quench the *i*-PrMgCl-promoted reaction of acetylacetone and PhMgBr instead of aqueous acetic acid. The purified product was analyzed with HR-MS. Two fragment peaks were determined at 183.0783 and 184.0843 which came from the dehydration of **I** showed in Scheme **6**. We supposed **I** came from **D** and D_2O as shown in Scheme **5**. Therefore, **D** was also a key intermediate in the process.



Scheme 5 The Deuterated Product Analyzed with HR-MS

Based on the results mentioned above, we supposed the reaction mechanism in Scheme **6**. Firstly, acetylacetone reacted with *i*-PrMgCl to constitute the chloromagnesium enolate intermediate **A**.[11] And then, PhMgBr coordinated **A** to form the intermediate **B**. The oxygen atom of the carbonyl group was coordinated by two magnesium atoms and the carbonyl group was thus activated.[12] PhMgBr subsequently attacked the carbonyl group of intermediate **B** to produce the adduct **C**. Similarly, PhMgBr deprotonates acetylacetone and generates the bromomagnesium enolate **A'**, which should enter the processes in Scheme **6** without *i*-PrMgCl. Herein, the enolates **A'** and **C** undergo a rarely discovered Br^-/Cl^- exchange (which can explain the result shown in Table **1**, Entries **6** *vs* **21**) with each other to produce the regenerated catalytic intermediate **A''** and the pre-product **D**, respectively. The intermediate **A''** accepted another PhMgBr and started the reactive cycle again. Therefore, *i*-PrMgCl was not really a catalyst but played the catalyst-like role in the Grignard reaction of acetylacetone.[13] The catalytic factor "MgCl" cannot exist independently but has to attach to the enol of acetylacetone to form the catalytic intermediate **A**. Therefore, the chloromagnesium enolate **A** significantly catalyzes the subsequent Grignard reaction of the intermediate **A** itself.

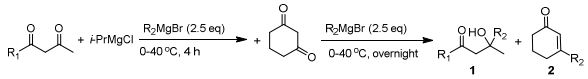
View Article Online
DOI: 10.1039/C5OB02072G



Scheme 6 The Proposed Reaction Mechanism.

Based on the reaction mechanism and the results shown in Scheme **6**, we supposed that *i*-PrMgCl may promote the one-pot successive Grignard reactions of the acyclic 1,3-dione and cyclic 1,3-dione[14]. Relative experimental results reached the target as expected (Table **4**). The results in Table **4** showed that the sub-stoichiometric amount of *i*-PrMgCl can successfully promoted the one-pot successive Grignard reactions to obtain two different adducts compared to the one-substrate-one-product method[14]. The two products β-tertiary hydroxyl ketone and β-substituted enone can be readily separated and purified by one column. The *i*-PrMgCl loading in the successive two Grignard reactions was actually decreased by 50% in comparison with the one-substrate-one-product method and thus its catalytic efficiency was greatly increased. Such a one-pot successive two-substrate-for-two-product Grignard reaction has not yet been reported.

Table 4 The Successive Grignard Reactions.[a]



entry	R_1	R_2	yield of **1** (%)[b]	yield of **2** (%)[b]
1[c]	Me	Ph	56	47
2	Me	Ph	90	82
3	Me	2-naphthyl	89	85
4	Me	4-$MeOC_6H_4$	85	79
5	Ph	Ph	88	81
6	Ph	2-naphthyl	88	86
7	Ph	*n*-heptyl	76	68

[a]In THF. The amounts of the two 1,3-diones were both 0.5 mmol, and the total 20 mol% *i*-PrMgCl was used. [b]Isolated yield based on the respective theoretical yield. [c]Without *i*-PrMgCl.

Conclusions

This work developed a first effective unilateral one-step additions of Grignard reagents to acyclic or cyclic β-diketones promoted by sub-stoichiometric amount of *i*-PrMgCl to afford β-tertiary hydroxyl ketones or 3-substituted cyclic-2-enones respectively. A new method to gain β-tertiary hydroxyl ketones and 3-substituted cyclic enones from β-diketones in one-pot was also put forward. The reaction mechanism was discussed in detail to explain the high regioselectivity by chemistry experiments, hydrogen-deuterium exchange and mass spectrometry. An interesting Br^-/Cl^- exchange was discovered firstly in the process.

Acknowledgements

We are grateful to the financial support of NSFC (No. 21072087).

Notes and references

1 (a) N. Halland, P. S. Aburel and K. A.Jøgensen, *Angew. Chem.*, 2004, **116**, 1292; *Angew. Chem. Int. Ed.*, 2004, **43**, 1272; (b) K. Yoshida, T Toyoshima and T. Imamoto, *Chem. Commun.*, 2007, 3774; (c) M. Raj, N. Veerasamy and V. K. Singh, *Tetrahedron Lett.*, 2010, **51**, 2157; (d) P. Zhang and C. Wolf, *J. Org. Chem.*, 2012, **77**, 8840; (e) S. Takizawa, F. A. Arteaga, K. Kishi, S. Hirata and H. Sasai, *Org. Lett.*, 2014, **16**, 4162.
2 (a) J. Piel, K. Hoang and B. S. Moore, *J. Am. Chem. Soc.*, 2000, **122**, 5415; (b) C. Seo, Y. H. Choi, J. H. Sohn, J. S. Ahn, J. H. Yim, H. K. Lee and H. Oh, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 772; (c) X. Chen, Q. Shi, G. Lin, S. Guo and J. Yang, *J. Nat. Prod.*, 2009, **72**, 1712; (d) H. E. Byeon, S. H. Um, J. H. Yim, H. K. Lee and S. Pyo, *Life Sci.*, 2012, **90**, 396.
3 P. Canonne and H. Bilodeau, *Can. J. Chem.*, 1966, **44**, 2849.
4 N. J. A. Martin and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13368.
5 P. Canonne and L. C. Leitch, *J. Can. Chem.*, 1967, **45**, 1761.
6 (a) I. Stahl and J. Gosselck, *synthesis*, 1980, 561; (b) C. Bartoli, E. Marcantoni and M. Petrini, *Angew. Chem.*, 1993,**105**, 1115; *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1061.
7 W. Schlenk and W. Jr. Schlenk, *Chem. Ber.*, 1929, **62**, 920.
8 W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Acen, K. Izawa, H. Liu and V. A. Soloshonok, *J. Fluor. Chem.*, 2014, **167**, 37.
9 (a) M. M. Hussain and P. J. Walsh, *Acc. Chem. Res.*, 2008, **41**, 883; (b) I. H. Chen, L. Yin, W. Itano, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 11664; (c) W. P. Hong, A. V. Iosub and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 13664; (d) X. Chen, H. Zhou, K. Zhang, J. Li and H. Huang, *Org. Lett.*, 2014, **16**, 3912; (e) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi and F. Zanardi, *J. Am. Chem. Soc.*, 2014, **136**, 11107.
10 (a) Y. Moritani, D. H. Appella, V. Jurkauskas and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 6797; (b) S. Kehrli, D. Martin, D. Rix, M. Mauduit and A. Alexakis, *Chem. Eur. J.*, 2010, **16**, 9890; (c) M. Zhou, T. L. Liu, M. Cao, Z. Xue, H. Lv and X. Zhang, *Org. Lett.*, 2014, **16**, 3484; (d) O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Farès, I. Polyak, G. Gopakumar, W. Thiel and B. List, *J. Am. Chem. Soc.*, 2013, **135**, 6677.
11 C. Grison, Preparation and reactivity of magnesium enolates. In *The Chemistry of Organomagnesium Compounds*; Z. Rapporport, and I. Marek, Eds.; John Wiley & Sons, Chichester, 2008, chapter 11, pp 437.
12 S. Yamabe and S. Yamazaki, Theoretical studies of the addition of RMgX to carbonyl compounds. In *The Chemistry of Organomagnesium Compounds*; Z. Rapporport, and I. Marek, Eds.; John Wiley & Sons, Chichester, 2008; chapter 9, pp 369.
13 (a) E. A. Standley and T. F. Jamison, *J. Am. Chem. Soc.*, 2013, **135**, 1585; (b) F. Proutiere, M. Aufiero and F. Schoenebeck, *J. Am. Chem. Soc.*, 2012, **134**, 606; (c) T. Kinzel, Y. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 14073; (d) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *J. Am. Chem. Soc.*,

View Article Online
DOI: 10.1039/C5OB02072G

2014, **136**, 254; (e) J. A. Bexrud, J. D. Beard, D. C. Leitch and L. L. Schafer, *Org. Lett.*, 2005, **7**, 1959; (f) B. Schmidt and S. Krehl, *Chem. Commun.*, 2011, **47**, 5879; (g) S. R. Lee, Z. J. Bryan, A. M. Wagner and A. J. McNeil, *Chem. Sci.*, 2012, **3**, 1562.

14 For examples: (a) A. Izumiseki and H. Yamamoto, *J. Am. Chem. Soc.*, 2014, **136**, 1308; (b) H. Wang, G. Li, K. M. Engle, J. Q. Yu and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6774; (c) B. M. Trost, B. R. Taft, J. T. Masters and J. P. Lumb, *J. Am. Chem. Soc.*, 2011, **133**, 8502; (d) W. J. Yoo, H. Miyamura and S. Kobayashi, *J. Am. Chem. Soc.*, 2011, **133**, 3095; (e) H. Y. Kim, L. Salvi, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2010, **132**, 402; (f) S. Shekhar, B. Trantow, A. Leitner and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 11770.