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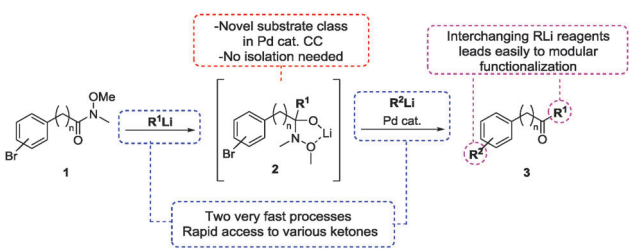
One-pot sequential 1,2-addition, Pd-catalysed cross-coupling of organolithium reagents with Weinreb amides†

M. Giannerini, C. Vila, V. Hornillos and B. L. Feringa*

An efficient sequential 1,2-addition/cross-coupling of Weinreb amides with two organolithium reagents is reported. This synthetic approach allows access to a wide variety of functionalized ketones in a modular way. The one-pot procedure presented here takes advantage of a kinetically stable tetrahedral Weinreb intermediate during subsequent Pd-catalyzed cross-coupling with the second organolithium reagent leading, within short reaction times and under mild conditions, to the formation of ketones in excellent overall yields.

Organolithium compounds are highly versatile reagents in organic synthesis[1] finding widespread application also in the preparation of ketones,[2] a common structural motif present in a variety of natural products, drugs[3] and fragrancies.[4] For instance the use of organolithium reagents in combination with carboxylic acids,[5a] nitriles,[5a,b] dialkylamides[5a,c] and acyl chlorides[6] to afford the corresponding ketones has been explored for a long time.[5,6] Hatton, Jamison and co-workers provided an elegant solution in their continuous flow synthesis of ketones from carbon dioxide and organolithium and Grignard reagents.[7] Other advances to unsymmetrical ketones include the use of dithianes as dianion equivalents by the groups of Tietze[8] and Smith[9] and, more recently, a pyrrole bearing formyl carbonyl dication linchpin reagent introduced by Sarpong and co-workers.[10] While all these methodologies deal with the preparation of ketones, still the use of organolithium compounds in the modification of molecules containing unprotected ketones has major constraints. 1,2-Addition to the carbonyl rapidly takes place with organolithium reagents and prior protection of the ketone seems often inevitable. Yoshida and co-workers reported the formation in flow of aryllithium reagents containing unprotected ketones that, due to the short residence time, immediately react preventing self-condensation to take place.[11] Notably, while this flow protocol affords valuable transformations of substrates bearing ketone moieties, it does not account for the synthesis of the ketone itself which has to be planned in an earlier separate synthetic step. Recently our group developed a protocol for the direct Pd-catalysed cross-coupling of organolithium reagents at room temperature.[12–16] We were attracted by the possibility to explore this cross-coupling methodology toward a novel one-pot procedure that, for the first time, would combine the synthesis and further modification of unprotected ketones with organolithium compounds. We envisioned that this could be achieved by performing a 1,2-addition of an organolithium reagent to a Weinreb amide[17] followed by a direct Pd-catalysed cross-coupling[18] with a second organolithium compound. The well-established stable tetrahedral intermediate **2**, arising from the 1,2-addition of R^1Li to a Weinreb amide, would act as a masked ketone moiety allowing a safe addition of a second equivalent of an organolithium for the cross-coupling step (R^2Li, Scheme 1).

Despite the fact that cross-coupling of softer organometallic reagents[19] with ketone-containing molecules has been established, the combination of the processes involving direct cross-coupling of organometallic reagents with the synthesis of the ketone moiety is unprecedented. Consequently, the ketone is generally synthesized separately requiring an extra synthetic step and an eventual purification. The process we present here affords, in a one-pot operation, various unsymmetric ketones using organolithium reagents without the necessity to separately prepare, purify and protect/deprotect the ketone.



Scheme 1 One-pot 1,2-addition/Pd-catalyzed cross-coupling with Weinreb amides.

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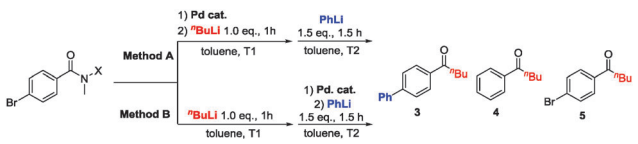
To the best of our knowledge, combined 1,2-addition to a Weinreb amide and Pd-catalysed cross-coupling in the presence of the tetrahedral intermediate in a one-pot procedure is unprecedented.[20,21] The modular combination of two different RLi reagents in the two sequential steps allows easy access to a range of structurally diverse ketones from simple starting materials. Despite the clear potential for the anticipated approach (Scheme 1), we realized that the nature of the intermediate **2** might also provide an unsurmountable obstacle due to the presence of a metal coordinating site (*i.e.* the charged adduct of the amide) that could potentially interfere with the Pd-catalyst in the cross-coupling step.

Initially we compared the performance of a dimethyl amide derivative against the Weinreb amide to use sequential C–C bond formation combining two different lithium reagents (1 eq. of ^{n}BuLi followed by 1.5 eq. of PhLi) using 5 mol% of Pd-PEPPSI-IPent catalyst[22] at room temperature (Table 1, Method A).

Under these conditions, using the dimethylamide, the expected 1,2-addition takes place but the subsequent cross-coupling of the bromo-ketone **5** to the final product **3** did not proceed (Table 1, entry 1). It is also evident from this experiment that the 1,2-addition proceeds prior to any cross-coupling or dehalogenation process. Reversing the order by first adding the ^{n}BuLi (Table 1, Method B) followed by the Pd catalyst and finally phenyllithium, up to 50% of cross-coupling is observed although dehalogenation is a major competing reaction (entry 2). Similar experiments with the corresponding Weinreb amide **1a** looked more promising (see also ESI,† Table S1). Cross-coupling was observed when the Pd-catalyst was introduced prior to (entry 3) or after addition of ^{n}BuLi (entry 4), while the selectivity was significantly improved when the temperature was raised to 40 °C (entry 5). A brief ligand screening allowed us to optimize the conversion (81% isolated yield of **3**) and selectivity (>99% cross-coupled product; dehalogenation completely suppressed), identifying 2.5 mol% $Pd_2(dba)_3$/10 mol% XPhos[18i] as the most efficient catalyst (entry 6).

Table 1 Optimization for the one-pot 1,2-addition, cross-coupling of Weinreb amides



Entry[a]	X	Method	Pd cat. mol%	T1/T2	3/4/5[b] (%)
1	Me	**A**	PEPPSI-IPent 5	r.t/r.t.	—/—/99
2	Me	**B**	PEPPSI-IPent 5	r.t/r.t.	50/24/14[c]
3	OMe	**A**	PEPPSI-IPent 5	r.t/r.t.	41/4/56
4	OMe	**B**	PEPPSI-IPent 5	r.t/r.t.	48/6/46
5	OMe	**B**	PEPPSI-IPent 5	r.t/40 °C	84/5/11
6	OMe	**B**	$Pd_2(dba)_3$ 2.5 XPhos 10	r.t/40 °C	99/—/— 81% yield[d]

[a] Reaction conditions method A: ^{n}BuLi (1 eq. over 1 h) added to a mixture of Pd_2dba_3 2.5 mol%, XPhos 10 mol% and 0.3 mmol of substrate in toluene, followed by the addition of PhLi (1.5 eq. over 1.5 h). Method B: ^{n}BuLi (1 eq. over 1 h) added to a solution of 0.3 mmol of substrate in toluene followed by addition of Pd complex and by PhLi (1.5 eq. over 1.5 h). [b] Determined by GC and ^{1}H NMR. [c] 12% of 1,1-diphenyl-1-pentene was observed. [d] Isolated yield.

With the optimized catalytic system in hand we set out to explore the scope, synthetic utility and efficiency of the new procedure for unsymmetric ketone formation. In particular with the modular choice of different lithium reagents, structurally diverse ketones can be obtained rapidly from simple starting materials. Using aryl- and alkyllithium in the first step and aryl- and heteroaryllithium reagents (commercially available or prepared either *via* halogen/lithium exchange or direct lithiation[23]) in combination with Weinreb amide **1a** provided alkyl biaryl ketones (Table 2, entries 1–3) and aryl biaryl ketones (Table 2, entries 4, 5) in excellent yields in less than 3 h. To further demonstrate the versatility of the procedure the use of alkylLi/alkylLi (including the cyclopropyl moiety[24]) and heteroaryl/heteroaryllithium reagents in both steps proved to be successful in the one-pot transformation as well (entries 6–9). As a variety of ketones was obtained successfully from the aromatic amide **1a**, we continued to explore the use of alkyl Weinreb amide **1b** to enable the preparation of alkyl–alkyl ketones. To our delight the one-pot reaction readily took place also in this case giving rise to a series of alkyl–alkyl ketones featured with heteroaryl (entry 10), aryl (entries 11–13), funtionalized alkyl (entry 14) and hindered di-*ortho*-substituted 1,3-dimethoxyphenyl moieties (entry 15). A limitation is seen when using a homobenzylic Weinreb amide as the acidity of the benzylic protons prevent effective use or RLi reagents (see ESI,† Table S1). It was, however, possible to successfully access (hetero)aryl–alkyl ketones from amide **1b** with the same efficiency noted for the benzamide **1a** (entries 16–19). Highlighting the short reaction times featuring this procedure, the coupling of furyllithium in the second step was performed successfully in 5 min affording, in an overall reaction time slightly above 1 h, the propiophenone **3p** in 80% yield (entry 16). Furthermore, the protocol was found efficient also with *ortho*- and importantly *meta*-substituted aryl bromides (entries 20–23).[25] Notably the latter gives access to *meta*-acylated aromatic compounds difficult to obtain *via e.g.* Friedel–Crafts acylation while various *meta*-substituted benzophenones are important building blocks like in the case of a BACE inhibitor.

Finally, we implemented the one-pot 1,2-addition, cross-coupling procedure to prepare cyclopropyl aryl ketones. These ketones are versatile intermediates for a range of pharmaceuticals, allowing transformation both at the ketone and the cyclopropyl moiety (Scheme 2, eqn (1)). Starting with Weinreb amide **1d** the sequential addition of cyclopropyllithium and phenyllithium provided **3x** (85% yield), a known precursor for the HIV protease binding agent.

In conclusion we developed a modular and highly efficient one-pot sequential 1,2-addition, cross-coupling from Weinreb amides using two distinct organolithium reagents. Avoiding the work-up/purification of the intermediate bromo-ketone and taking advantage of the extremely fast cross-coupling with organolithium compounds under mild conditions, the overall process requires only 1 to 2.5 h reaction time. Structure diversity in the products is readily achieved starting with a range of easily accessible organolithium reagents. Advantage is taken here of the *in situ* protection of the ketone (after the first

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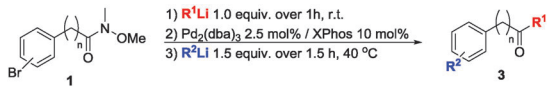
Table 2 Scope of the reaction



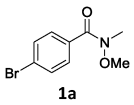
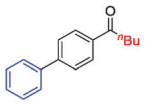
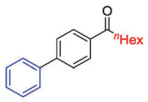
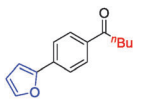
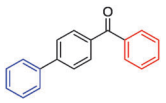
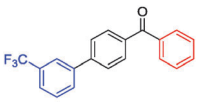
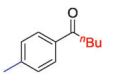
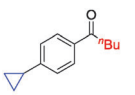
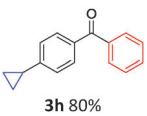
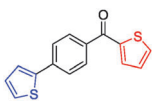
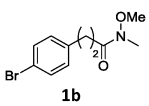
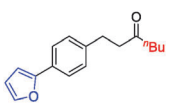
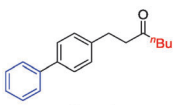
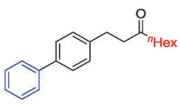
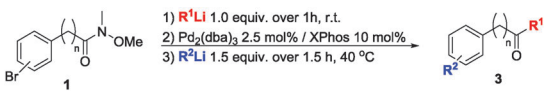
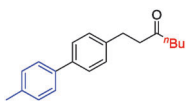
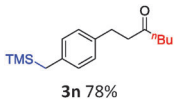
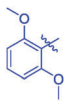
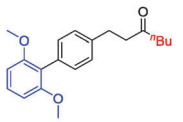
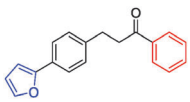
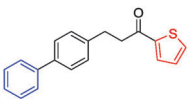
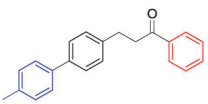
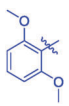
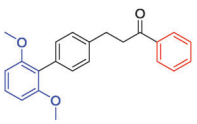
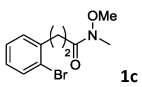
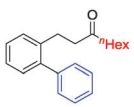
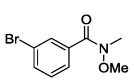
Entry[a]	Substrate	R^1	R^2	Product[b]
1	 **1a**	^{n}Bu	Ph	 **3a** 81%
2	**1a**	^{n}Hex	Ph	 **3b** 76%
3	**1a**	^{n}Bu		 **3c** 84%
4	**1a**	Ph	Ph	 **3d** 85%
5	**1a**	Ph		 **3e** 84%
6	**1a**	^{n}Bu	Me	 **3f** 87%
7	**1a**	^{n}Bu		 **3g** 80%
8	**1a**	Ph		 **3h** 80%
9[c]	**1a**			 **3i** 86%
10	 **1b**	^{n}Bu		 **3j** 81%
11	**1b**	^{n}Bu	Ph	 **3k** 77%
12	**1b**	^{n}Hex	Ph	 **3l** 74%

Table 2 (*continued*)



Entry[a]	Substrate	R^1	R^2	Product[b]
13	**1b**	^{n}Bu		 **3m** 83%
14	**1b**	^{n}Bu		 **3n** 78%
15	**1b**	^{n}Bu		 **3o** 71%
16[d]	**1b**	Ph		 **3p** 80%
17	**1b**		Ph	 **3q** 71%
18	**1b**	Ph		 **3r** 89%
19	**1b**	Ph		 **3s** 84%
20	 **1c**	^{n}Hex	Ph	 **3t** 67%
21	 **1d**	Me	Ph	**3u** 72%
22	**1d**	^{n}Bu	Ph	**3v** 71%
23	**1d**	Ph		**3w** 72%

[a] Reaction performed on 0.3 mmol of substrate dissolved in toluene. R^1Li was diluted to 0.8 ml with toluene and added over 1 h. Then the Pd complex, formed in 0.5 ml of toluene, was added, followed by slow addition of a diluted solution of R^2Li 1.5 eq. over 1.5 h. [b] Isolated yields. [c] 1.5 eq. of TMEDA were added when performing the addition of R^2Li. [d] R^2Li was added over 5 min.

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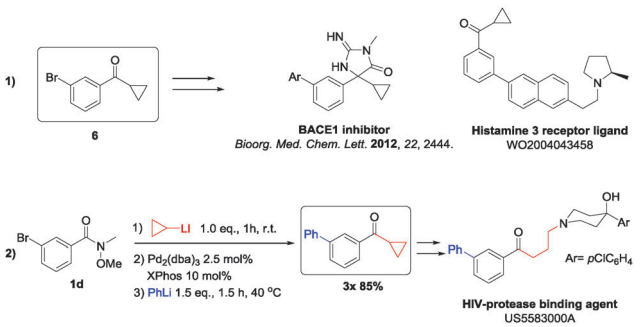

Scheme 2 Synthetic applicability of the one-pot 1,2 addition, cross-coupling with Weinreb amides.

1,2-addition of the organolithium to the Weinreb amide) allowing uncompromised addition and cross-coupling of a second organolithium reagent. This methodology significantly broadens the functional group tolerance of palladium catalysed cross-couplings with highly reactive organolithium reagents making it amenable to the synthesis of molecules bearing sensitive carbonyl moieties.

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Notes and references

1 R. Luisi and V. Capriati, *Lithium Compounds in Organic Synthesis: From Fundamentals to Applications*, Wiley-VCH, Weinheim, 2014.
2 (*a*) N. J. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1739; (*b*) J. Otera, *Modern Carbonyl Chemistry*, Wiley-VCH, Weinheim, 2000.
3 F. Z. Dörwald, in *Lead Optimization for Medicinal Chemists: Pharmacokinetic Properties of Functional Groups and Organic Compounds*, ed. F. Z. Dörwald, Wiley-VCH, Weinheim, 2012, ch. 30.
4 H. Surburg and J. Panten, *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*, Wiley-VCH, Weinheim, 5 edn, 2006.
5 (*a*) M. J. Jorgenson, *Org. React.*, 1970, **18**, 1; (*b*) P. Izzo and S. J. Safir, *J. Org. Chem.*, 1959, **24**, 701; (*c*) G. J Sumrell, *J. Org. Chem.*, 1954, **19**, 817.
6 K. R. Dieter, *Tetrahedron*, 1999, **55**, 4177.
7 J. Wu, X. Yang, Z. He, X. Mao, A. T. Hatton and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2014, **53**, 8416.
8 L. F. Tietze, H. Geissler, J. A. Gewert and U. Jakobi, *Synlett*, 1994, 511.
9 (*a*) A. B. Smith III and A. M. Boldi, *J. Am. Chem. Soc.*, 1997, **119**, 6925; (*b*) A. B. Smith III, S. M. Condon and J. A. McCauley, *Acc. Chem. Res.*, 1998, **31**, 35; (*c*) A. B. Smith III, S. M. Pitram, A. M. Boldi, M. J. Gaunt, C. Sfouggatakis and W. H. Moser, *J. Am. Chem. Soc.*, 2003, **125**, 14435.
10 S. T. Heller, J. N. Newton, T. Fu and R. Sarpong, *Angew. Chem., Int. Ed.*, 2015, **54**, 9839.
11 (*a*) H. Kim, A. Nagaki and J. Yoshida, *Nat. Commun.*, 2011, **2**, 264; (*b*) for a comprehensive review on the use of organolithium reagents in flow see; J. Yoshida, Y. Takahashi and A. Nagaki, *Chem. Commun.*, 2013, **49**, 9896.
12 (*a*) M. Giannerini, M. Fañanás-Mastral and B. L. Feringa, *Nat. Chem.*, 2013, **5**, 667; (*b*) V. Hornillos, M. Giannerini, C. Vila, M. Fañanás-Mastral and B. L. Feringa, *Org. Lett.*, 2013, **15**, 5114; (*c*) M. Giannerini, V. Hornillos, C. Vila, M. Fañanás-Mastral and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2013, **52**, 13329; (*d*) C. Vila, M. Giannerini, V. Hornillos, M. Fañanás-Mastral and B. L. Feringa, *Chem. Sci.*, 2014, **5**, 1361; (*e*) V. Hornillos, M. Giannerini, C. Vila, M. Fañanás-Mastral and B. L. Feringa, *Chem. Sci.*, 2015, **6**, 1394; (*f*) C. Vila, V. Hornillos, M. Giannerini, M. Fañanás-Mastral and B. L. Feringa, *Chem. – Eur. J.*, 2014, **20**, 13078; (*g*) L. M. Castelló, V. Hornillos, C. Vila, M. Giannerini, M. Fañanás-Mastral and B. L. Feringa, *Org. Lett.*, 2015, **17**, 62; (*h*) D. Heijnen, V. Hornillos, B. P. Corbet, M. Giannerini and B. L. Feringa, *Org. Lett.*, 2015, **17**, 2262.
13 J. D. Firth and P. O'Brien, *ChemCatChem*, 2015, **7**, 395.
14 (*a*) For the indirect cross-coupling of organolithium reagents see: A. B. Smith III, A. T. Hoye, D. Martinez-Solorio, W. Kim and R. Tong, *J. Am. Chem. Soc.*, 2012, **51**, 4533; (*b*) D. Martinez-Solorio, A. T. Hoye, M. H. Nguyen and A. B. Smith III, *Org. Lett.*, 2013, **15**, 2454; (*c*) M. H. Nguyen and A. B. Smith III, *Org. Lett.*, 2014, **16**, 2070.
15 (*a*) For a seminal work in Pd-catalyzed cross-coupling with lithium reagents see: S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita and K. Kondo, *J. Org. Chem.*, 1979, **44**, 2408; (*b*) S. Murahashi, *J. Organomet. Chem.*, 2002, **653**, 27.
16 For the use of flow-chemistry technology for the Pd-catalyzed cross-coupling with lithium reagents see: A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J. Yoshida, *Angew. Chem., Int. Ed.*, 2010, **49**, 7543.
17 (*a*) S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815; (*b*) S. Balasubramaniam and I. S. Aidhen, *Synthesis*, 2008, 3707.
18 (*a*) E. Negishi, *Angew. Chem., Int. Ed.*, 2011, **50**, 6738; (*b*) A Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 6723; (*c*) A. de Meijere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2004, vol. 1; (*d*) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062; (*e*) G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555; (*f*) N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440; (*g*) A. Zapf, A. Ehrentraut and M. Beller, *Angew. Chem., Int. Ed.*, 2000, **39**, 4153; (*h*) N. Kataoka, Q. Shelby, J. P. Stambuli and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553; (*i*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.
19 (*a*) For selected examples see: K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442; (*b*) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177.
20 (*a*) For discussion on the benefits of one-pot procedures see: R. A. Sheldon, *Chem. Commun.*, 2008, 3352; (*b*) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (*c*) R. Dach, J. J. Song, F. Roschangar, W. Samstag and C. H. Senanayake, *Org. Process Res. Dev.*, 2012, **16**, 1697.
21 (*a*) I. S. Young and P. S. Baran, *Nat. Chem.*, 2009, **1**, 193; (*b*) R. W. Hoffmann, *Synthesis*, 2006, 3531.
22 (*a*) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson and M. G. Organ, *Chem. – Eur. J.*, 2006, **12**, 4743; (*b*) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah and M. G. Organ, *Angew. Chem., Int. Ed.*, 2012, **51**, 3314.
23 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
24 For a review on the relevance of arylcyclopropanes and their synthesis *via* cross-coupling see: A. Gagnon, M. Duplessis and L. Fader, *Org. Prep. Proced. Int.*, 2010, **42**, 1.
25 The corresponding *p*-chloro-substituted benzamide is not reactive toward the cross-coupling under the optimized conditions.