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A Telescoped Knochel-Hauser / Kumada-Corriu Coupling Strategy to Functionalized Aromatic Heterocycles

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ABSTRACT

The direct application of Knochel-Hauser derivative arylmagnesium halides in Kumada-Corriu couplings is described. By utilizing the in situ-generated Grignard reagents, the transmetalation with stoichiometric zinc salts to known Negishi coupling conditions is avoided, thereby streamlining the transformation. Several aromatic hetereocycles participate in the deprotonation and couple with a variety of phenyl iodides and bromides in isolated yields up to 81%. The parent system is demonstrated on 6 g scale with 79% yield, and monitored via ReactIR to show the stability of the Grignard and progression of the deprotonation / C-C coupling reaction.

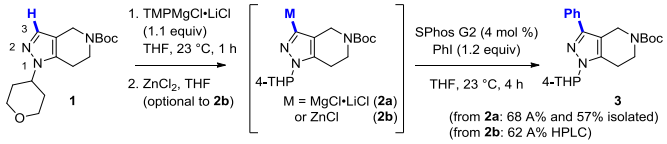
1. Introduction

Selective substitution of heterocycles is of great importance for the construction of increasingly complex molecular targets, particularly in the pharmaceutical industry. Recent years have seen a bounty of work exploring methods of C-H bond functionalization to replace the need for pre-functionalized substrates. These C-H transformations have been guided by two modes: innate reactivity or under guided conditions.[1] In cases where innate reactivity does not permit the desired transformation, other chemistry can allow for a different path to achieve the functionalization objective. To this end, directed ortho metalation approaches have enabled the selective deprotonation of arene substrates to facilitate subsequent substitution. More recently, pioneering reagents have provided access to reactive intermediates containing sensitive functionality under mild conditions via kinetic deprotonations.

Over the years, Knochel and others have introduced lithium chloride-attenuated reagents that facilitate selective metalation, deprotonation or nucleophilic additions.[2] The magnesium base derivatives have been harnessed for selective deprotonations and functionalization via ensuing treatment with electrophilic species. In some cases, the reactive intermediates were steered into more sophisticated C-C bond formation reactions via a palladium-catalyzed Negishi protocol following transmetalation of the organomagnesium halides with zinc salts.[3] However, only select reports with thiophene substrates have described a C-C coupling sequence with the heteroarylmagnesium species[4] in a direct coupling, with the work focused not on discrete molecular products but rather polymerization of these heterocycles.[5] Herein we describe the direct application of Knochel-Hauser base to generate a RMgX species for a telescoped Kumada-Corriu C-C coupling methodology with a series of diverse heterocycles. We include a detailed study of the parent reaction by ReactIR to evaluate the key attributes of the stepwise transformation.

2. Results / Discussion

Scheme 1. C-C sp^2-sp^2 coupling of interest

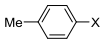
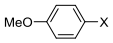
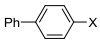
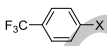
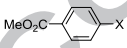


While investigating a pipeline project, we came across the need to functionalize fused pyrazolopiperidine intermediate **1** in the 3-position. During the course of our research, we found that TMPMgCl·LiCl was uniquely suited for selective deprotonation and later derivatization with an electrophile quench under ambient temperature.[6] Curious about the further reactivity of **1**,[7] we subsequently reproduced literature Negishi conditions with a Pd catalyst and iodobenzene, following transmetalation with $ZnCl_2$ (Scheme 1, 62 A% **3** by HPLC via intermediate **2b**). When we probed whether the original organomagnesium chloride (**2a**) would also react with PhI in the presence of a catalyst, we were surprised that this coupling worked equally well (68 A% **3**). After appropriate work-up conditions were identified (see Supporting Information) to deal with the suspended Mg salts, we isolated the phenyl-substituted derivative in good yield (57% isolated yield from **2a**).

When screening other variables of the reaction, we learned that PhBr and PhOTf also successfully participated in the original

telescoped reaction conditions at ambient temperature. Other strong bases could not facilitate the reaction and stoichiometry of TMPMgCl·LiCl base was important. Varying deprotonation times indicated that Grignard formation was achieved quickly and that intermediate reagent stability was on the order of hours. A preliminary screen of other catalysts demonstrated that only Pd complexes appeared to work and SPhos[8] G2 was most adept at facilitating the C-C coupling segment of the reaction.[9] Solvent screening uncovered anisole as a more advantageous co-medium for the PhI coupling.[10] Further studies with **1** were conducted with this anisole protocol.

Table 1. Coupling of pyrazole **1** with diverse ArX[a]

entry	coupling partner	X =	Time (h)	%isol. yield[b, c]
1		I[d]	2	--- (81)
		Br	2	68 (83)
2		I	1	36
		Br	2	68
3		I	1	74
		Br	2	64
4		I	1	81
		Br	2	72
5		I	1	60
		Br	2	35
6		I	1	71
		Br	2	72
7		I	3	53
		Br	2	55
8		I	1	40
		Br	2	66
9		I	3	55
		Br	2	36
10		I	1	59
		Br	2	40
11		I	1	56
		Br	2	41

[a] Metalated species **2a** in anisole/THF/toluene treated with 1.2 equiv ArX and catalyst precursor in anisole at 23 °C. Unless otherwise noted, all experiments were conducted with 0.651 mmol **1**.

[b] Isolated following work-up and column chromatography.

[c] Parenthetical values are % HPLC assay yields for 2 h reaction time points against a standard solution of product of known purity.

[d] Experiment run at 0.325 mmol scale of **1**.

When applied to a variety of ArI and ArBr partners, moderate to good yields of C-C coupling products were observed in most cases (Table 1).[11] For the parent system, in situ assay yields were > 80% for both iodo- and bromobenzene with the isolated yield of the latter at 68% (entry 1). Electron-rich substrates generally gave higher yields, though variability was noted between the iodides and bromides in certain cases.

Process Analytical Technology (PAT) is a powerful approach to monitor pharmaceutical manufacturing processes but can also be applied in reaction development. ReactIR has proven to be a very useful tool to provide greater insight into reaction rate and mechanism. To this end, we utilized a scale-up of our telescoped reaction with PhBr to evaluate reaction attributes. In-situ FTIR was first used to evaluate the hydrogen-metal exchange (deprotonation) to intermediate **2** and its stability, which was durable over 14 h. In a second experiment, FTIR was utilized to understand the C-C coupling en route to product **3**. The combined ReactIR data demonstrated that deprotonation is very fast (< 15 min) and the coupling is similarly rapid on addition of a catalyst / PhBr solution (< 20 min, see Fig 1).[12] The 20 mmol (6.2 g) reaction performed as expected, with the quick deprotonation / coupling delivering product **3** in 79% isolated yield and >95 A% HPLC purity following silica chromatography.

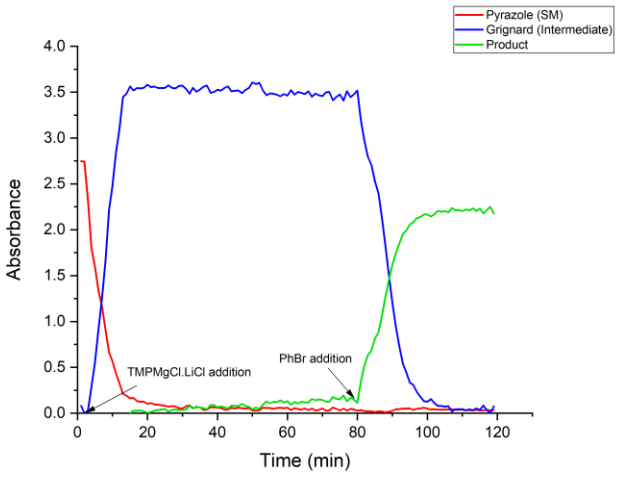


Figure 1. ReactIR evaluation of coupling of **1** with PhBr

Curious to see if the identified ambient temperature conditions provided a general method for heterocycle functionalization, we screened several other substrates that had previously been reported in Knochel-Hauser deprotonation / electrophilic quench transformations (Table 2).[13] 1-Methylindazole **4** reacted with PhI to provide the 3-substituted product in 67% yield (entry 1).[14] Isoquinoline **5** returned the desired product in a 53% yield with the aryl iodide but only a 32% yield with the equivalent bromide (entries 2 and 3). Meanwhile, 2,6-dichloropyridine **6** generated the 4-substituted product with PhI but only in 22% yield (entry 4). A further experiment with 30% assay yield proved that degradation during isolation was not the cause for the low output (entry 5).

Table 2. Coupling of diverse heterocycles with ArX[a]

entry	coupling partner	ArX	%isol. yield[b]
1[c]	**4** 		67
2	**5** 		53
3[d]			32
4[e]			22
5[c, d]	**6** 		--- (30)
6[f]			58

7[f]		62

[a] Unless otherwise noted, all experiments were conducted with 0.651 mmol of coupling partner in anisole/THF/toluene, 1.1 equiv TMPMgCl•LiCl, 1.2 equiv ArX, and catalyst precursor in anisole at 23 °C for 1 h, followed by work-up and isolation after column chromatography.

[b] Parenthetical values are % HPLC assay yields for 3 h reaction time points against a standard solution of product of known purity.

[c] Experiment run at 0.325 mmol scale of C-H coupling partner.

[d] Experiment conducted for 3 h.

[e] Experiment run at 6.62 mmol scale in THF/toluene (no anisole) for 1 h.

[f] 1.1 equiv TMP_2Mg•2LiCl used as base.

The failure of the disubstituted pyridine substrate (**6**) was perplexing so we investigated this particular reaction in more detail. We reexamined solvent composition, other catalysts and other conditions for this substrate but to no avail. Only when we looked at a variant of the base, TMP_2Mg•2LiCl, did we again see the desired, higher output of the coupling product with 58% isolated yield (Table 2, entry 6). Though TMPMgCl•LiCl is a powerful kinetic base, Knochel et al. reported that TMP_2Mg•2LiCl is a stronger and more selective variant, with best results from freshly prepared solutions.[3] In addition, after deprotonation ArMgTMP•2LiCl may be stabilized due to decreased nucleophilicity and greater steric bulk, as reported by Eaton and coworkers based on their work with the uncomplexed (no lithium chloride) TMP_2Mg base,[15] thus allowing for greater success in transmetalation and C-C bond formation. These revised conditions with **6** were applied to 2-iodotoluene to give the desired product in 62% yield (entry 7). While TMP_2Mg•2LiCl is not commercially-available, this base can easily be prepared from the monomeric TMP magnesium chloride-lithium chloride complex and offers another option with challenging substrates in this telescoped transformation.[16]

3. Conclusion

This report describes the direct application of two Knochel-Hauser bases – TMPMgCl•LiCl and TMP_2Mg•2LiCl – to generate RMgX species for a two-step, telescoped Kumada-Corriu C-C coupling method with a series of heterocycles and iodo- or bromobenzene derivatives. The ambient temperature procedure allows for a mild C-C cross-coupling to a diverse array of heterocyclic derivatives. The direct application of the initial RMgX species enables omission of stoichiometric zinc salt. Further details about the stepwise progression of the TMPMgCl•2LiCl reaction were monitored with ReactIR to show that both the deprotonation and C-C coupling are rapid processes.

Supplementary Material

Supporting Information associated with this article has been provided as a separate PDF file.

References and notes

K. C. and S. H. contributed equally to this work. The authors would like to acknowledge Colin Masui for contributions to high-throughput experimentation, Harshada Natekar for conducting high-resolution mass spectrometric analysis, and Mengling Wong for purification of select compounds.

[1] Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826-839.

[2] Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958-2961.

[3] Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. Knochel also reported a direct zincation with TMP_2Zn or TMPZnCl•LiCl to skip the transmetalation prior to the Negishi coupling step. See: (a) Unsinn, A.; Knochel, P. *Chem. Commun.* **2012**, *48*, 2680-2682; (b) Balkenhohl, M.; Salgues, B.; Hirai, T.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2018**, *20*, 3114-3118.

[4] In a resource-constrained world where certain elements – including zinc – are recognized as "endangered" it is sensible to explore chemistries that can eliminate stoichiometric applications thereof. See: Sackett, P. Endangered Elements: Conserving the Building Blocks of Life. *Solutions*, **2012**, *3*, 56-62.

[5] (a) Tamba, S.; Shono, K.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 9700-9703; (b) Tanaka, S.; Tamba, S.; Tanaka, D.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 16734-16737; (c) Mori, A. J. *Synth. Chem. Jpn.* **2011**, *69*, 1202-1211; (d) Tanaka, S.; Tamba,S.; Sugie, A.; Mori, A. *Heterocycles*, **2012**, *86*, 255-266; (e) Tamba, S.; Mitsuda, S.; Tanaka, F.; Sugie, A.; Mori, A. *Organometallics* **2012**, *31*, 2263-2267. Additional Zn-free examples make use of BF_3·OEt_2 to mask an atom while a Knochel-Hauser deprotonation / C-C coupling is achieved utilizing cryogenic temperatures. See: Klatt, T.; Roman, D. S.; Leon, T.; Knochel, P. *Org. Lett.* **2014**, *16*, 1232-1235.

[6] We also looked at $Zn(TMP)_2$, LDA, $Mg(DA)_2$, and *i*-PrMgCl•LiCl. These other bases all failed to give metalation that could productively be carried forward into a C-C coupling. TMP_2MgCl•2LiCl also failed for **1** but was later shown to work with dichloropyridine **6**.

[7] (a) G. Dahmann, H. Dollinger, C. Gnamm, D. Fiegen, M. Hoffmann, D. J. Lamb, J. Klicic, A. Schnapp, *Preparation of aminoindolyl-substituted imidazolylpyrimidines as Syk kinase inhibitors for treatment of disease, WO Patent Application No. 2013/156608*; published 24 October, 2013; (b) H. Chobanian, B. Pio, Y. Guo, F.-X. Ding, S. Dong, S. P. Walsh, J. Jiang, D. Kim, *Preparation of heterocyclic inhibitors of the renal outer medullary potassium channel for therapy, WO Patent Application No. 2015/095097*; published 25 June, 2015; (c) H.-P. Buchstaller, *Preparation of bicyclic heterocyclic derivatives as pyruvate dehydrogenase kinase (PDHK) inhibitors, WO Patent Application No. 2017/020981*; published 9 February, 2017.

[8] (a) Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844-3845; (b) Hua, X.; Masson-Makdissi, J.; Sullivan, R. J.; Newman, S. G. *Org. Lett.* **2016**, *18*, 5312-5315.

[9] A subsequent HTE screen of palladium catalysts confirmed SPhos G2 to be preferred mediator, though RuPhos G2 was also shown to accomplish the transformation.

[10] Anisole is present as approx. 66% of the total solvent since TMPMgCl•LiCl is commercially-available as a solution in 1:1 THF/toluene. This aromatic ether solvent has been shown to benefit arylmagnesium halide basicity, presumably through stability and solubility factors. See: Westera, G.; Blomberg, C.; Bickelhaupt, F. *J. Organomet. Chem.* **1978**, *155*, C55-C57. Interestingly, other aryl ethers (EtOPh, CyOPh, *t*-BuOPh, *i*-PrOPh, *p*-TolOMe) did not facilitate the reaction in the same manner but also showed poorer overall solubility, indicating that steric accessibility of the ether could be a critical aspect to anisole's benefit.

[11] The electrophiles that did not perform well contained pendant functional groups (CHO, NO_2, Ac) which were presumably attacked by the Grignard intermediate directly without action of the catalyst in the productive C-C coupling cycle.

[12] See SI for more detail.

[13] Compounds that failed to participate successfully in our telescoped reaction included several C-H heterocycles (benzothiazole, benzothiophene, 3-bromopyridine, 3-bromoquinoline, 3-chloropyridine, ethyl-1-naphthoate, furan, 1-methylpyrazole, 4-phenylpyridine, thiazole, and thiophene) and X-Ar derivatives (chlorobenzene, 4-iodoacetophenone, 4-iodobenzaldehyde, and 1-iodo-4-nitrobenzene). The reasons for these failed reactions could include one of several steps necessary for the full sequence: (1) inability to achieve deprotonation, (2) poor transmetalation, or (3) unsuccessful reductive elimination. These compounds were not investigated further.

[14] Substrate **4** reacted cleanly with our reaction conditions. This result stands in contrast to a recent report indicating that N-substituted indazoles quickly give the *o*-aminobenzonitrile via a Kemp-type ring opening elimination. See: Ganley, J. M.; Yeung, C. S. *J. Org. Chem.* **2017**, *82*, 13557−13562.

[15] Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016-8018.

[16] For preparation of TMP_2Mg•2LiCl from TMPMgCl•LiCl, see reference 3.

Highlights for *A Telescoped Knochel-Hauser / Kumada-Corriu Coupling Strategy to Functionalized Aromatic Heterocycles*:

- C-H functionalization via Knochel-Hauser deprotonation under mild conditions
- Telescoped Kumada-Corriu cross-coupling to variety of heterocycles
- Exclusion of stoichiometric zinc salts (and transmetalation for Negishi coupling)
- Benign conditions: room temperature, common solvents, short reaction timeframe
- Monitoring reaction progress by ReactIR to demonstrate straightforward methodology

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