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Modified Shapiro Reactions with Bismesitylmagnesium As an Efficient Base Reagent

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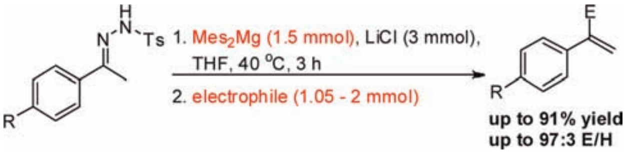
ABSTRACT



Bismesitylmagnesium has been shown to successfully mediate the Shapiro reaction. A range of tosylhydrazones has been subjected to the developed system, which furnishes exceptionally high incorporation of the introduced electrophiles and good yields of the functionalized styrenes. At conveniently accessible temperatures and with a comparably small excess of base reagent, this protocol offers an efficient alternative to the lithium-mediated process. Importantly, 1.05 equiv of Weinreb amides are sufficient to obtain aryl enones in good yields.

Main-group organometallics have played a major role in modern organic chemistry from the 1960s and have gained appreciably in significance over the intervening years.[1] As the understanding of their fundamental properties, behavior in reactions, and the associated mechanistic insight has steadily grown through advances in analytical technologies, the application of such species in organic synthesis has continued to escalate. In this regard, organolithium reagents, such as lithium amides and alkyllithiums, are among the most widely employed compounds of this general class, especially within deprotonation and C−C bond forming reactions.[1] Having stated this, certain practical issues are associated with these classes of compounds,[2] as they can exhibit limited thermal stability as well as a complex and capricious solution behavior, which dictate that careful addition of solution additives is required. Organomagnesium compounds, on the other hand, are most widely used as nucleophilic Grignard reagents and only over recent years have further preparative endeavors sparked expanding interest in the development of a series of new hetero- and homoleptic magnesium based reagents.[3] In this regard and in work from our own laboratory, chiral magnesium bisamides and alkylmagnesium amides have been successfully employed in the enantioselective deprotonation of a range of prochiral ketones.[4] As part of further investigations, a novel class of non-nucleophilic carbon-centered magnesium bases has also emerged, providing highly efficient reagents for use in the preparation of silyl enol ethers outside of the

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(1) (a) March, J.; Smith, M. B. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley-Interscience: Hoboken, NJ, 2007. (b) *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Pergamon Press: New York, 2007; Vol. 9.

(2) (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (b) Gessner, V. H.; Däschlein, C.; Strohmann, C. *Chem.—Eur. J.* **2009**, *15*, 3320.

(3) Henderson, K. W.; Kerr, W. J. *Chem.—Eur. J.* **2001**, *7*, 3430.

(4) (a) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Chem. Commun.* **2000**, 479. (b) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Synlett* **2001**, 1253. (c) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Chem. Commun.* **2001**, 1722. (d) Anderson, J. D.; García García, P.; Hayes, D.; Henderson, K. W.; Kerr, W. J.; Moir, J. H.; Fondekar, K. P. *Tetrahedron Lett.* **2001**, *42*, 7111. (e) Carswell, E. L.; Hayes, D.; Henderson, K. W.; Kerr, W. J.; Russell, C. J. *Synlett* **2003**, 1017. (f) Henderson, K. W.; Kerr, W. J.; Moir, J. H. *Tetrahedron* **2002**, *58*, 4573. (g) Bassindale, M. J.; Crawford, J. J.; Henderson, K. W.; Kerr, W. J. *Tetrahedron Lett.* **2004**, *45*, 4175. (h) Bennie, L. S.; Kerr, W. J.; Middleditch, M.; Watson, A. J. B. *Chem. Commun.* **2011**, *47*, 2264. (i) Kerr, W. J.; Middleditch, M.; Watson, A. J. B. *Synlett* **2011**, 177.

(5) (a) Kerr, W. J.; Watson, A. J. B.; Hayes, D. *Chem. Commun.* **2007**, 5049. (b) Kerr, W. J.; Watson, A. J. B.; Hayes, D. *Org. Biomol. Chem.* **2008**, *6*, 1238. (c) Kerr, W. J.; Watson, A. J. B.; Hayes, D. *Synlett* **2008**, 1386.

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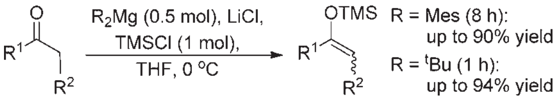
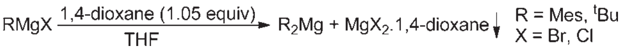
asymmetric domain (Scheme 1; Mes = 2,4,6-trimethylphenyl; mesityl).[5]

Scheme 1. Selective Deprotonation of Enolizable Ketones



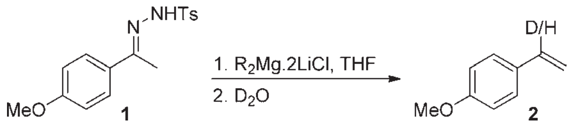
At conveniently accessible temperatures of 0 °C and above, no side reactions from nucleophilic addition of the carbon-centered base reagent or reduction of the ketone substrate could be detected. Moreover, the magnesium system operates effectively with comparatively lowered amounts of electrophile and, perhaps more importantly, without any amine reagent being required. The requisite diaryl/dialkylmagnesium species can be readily preformed from the parent Grignard reagent or, for a more practicable one-pot protocol, is generated *in situ* (Scheme 2).[5,6] In both cases excellent reaction efficiencies for the desired transformation were observed.[5]

Scheme 2. Preparation of Dialkyl/Diarylmagnesium



Based on these discoveries, we were encouraged to probe further effective and more focused applications of our carbon-centered magnesium bases. In relation to this, a magnesium-mediated alternative of the Shapiro reaction[7,8] was considered. The corresponding lithium-based processes generally require either a large excess of base, and consequently an electrophile, TMEDA as an additive, or the employment of the more expensive reagent, trisylhydrazine.[7] Additionally, an elaborate varying (low) temperature protocol is required to induce the fragmentation of the hydrazone substrate and the subsequent quench with an electrophile.[7] In relation to this, we herein report our progress in developing a preparatively effective magnesium base-mediated Shapiro reaction and its application with a range of electrophilic quench reagents and tosylhydrazone substrates.

Table 1. Optimization of Reaction Conditions[a]



entry	Mg reagent	conditions	yield (%)[c]	D:H[d]
1	$(TMP)_2Mg$	0 °C, 3 h	97	50:50
2	Mes_2Mg	0 °C, 3 h	11	98:2
3	Mes_2Mg	40 °C, 3 h	69	92:8
4[b]	Mes_2Mg	40 °C, 3 h	90	94:6
5[b]	$^tBu_2Mg$	40 °C, 3 h	58	91:9

[a] Reaction conditions: *p*-methoxyacetophenone tosylhydrazone **1** (1 mmol), magnesium base reagent (1.25 mmol), LiCl (2.5 mmol), THF (5 mL). [b] 1.5 mmol of Mg-base reagent and 3 mmol of LiCl were used. [c] Isolated yield after column chromatography. [d] Ratio was determined by ^{1}H NMR of the crude reaction mixture.

In initial experiments and optimization studies, tosylhydrazone **1** (1 mol)[9] was exposed to magnesium bisamide $Mg(TMP)_2$ (1.25 mol) and LiCl (2.5 mol) for 3 h at 0 °C in THF, followed by the addition of D_2O as an electrophilic quench (Table 1, entry 1). The styrene product H/D-**2** was isolated in an excellent 97% yield. However, only a 50% selectivity toward the introduced electrophilic quench reagent was observed, presumably due to the *in situ* formation of TMP-H which can act as a proton source for the generated vinyl anion. In contrast, the carbon-centered magnesium base, Mes_2Mg, furnished an excellent H/D-styrene ratio of 98:2 (D:H) under the same reaction conditions, albeit in only 11% yield. The low conversion was compensated for by moderately elevating the reaction temperature to 40 °C, coupled with an increase in quantity of base reagent to 1.5 mol, giving rise to a 90% yield of the desired styrene (Table 1, entry 4). The dialkylmagnesium base, $^tBu_2Mg$, which has also been shown to act efficiently as a non-nucleophilic base reagent,[5c] returned starting material quantitatively at 0 °C and displayed a distinctly lower reactivity than Mes_2Mg at more elevated temperatures (Table 1, entry 5). It is worth noting here that LiCl is key for the desired reactivity of these magnesium base systems, as the reactivity drops significantly if less than 2 equiv of LiCl, with respect to Mes_2Mg, are used. This has previously been observed in various magnesium base systems.[4] With regard to Mes_2Mg, the formation of an 'ate-type complex is presumed, thus accounting for the enhanced reactivity observed.[5b]

This brief optimization had delivered a magnesium base-mediated Shapiro process at the conveniently accessed temperature of 40 °C and with relatively low levels of required base (1.5 mol). With the developed conditions in hand, our investigations continued by exploring the scope of the introduced electrophiles. In general, 2 mol of the respective electrophile were necessary to furnish good yields of the functionalized styrene products **3a**–**d** (Table 2); this was believed to be largely due to the competitive nucleophilic addition of excess Mes reagent into the added electrophile (to give **4**). Nonetheless, the

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(6) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995.

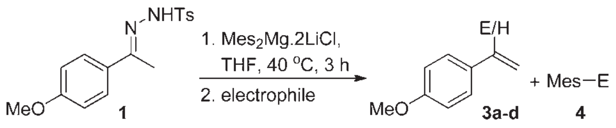
(7) (a) Shapiro, R. H.; Hornaman, E. C. *J. Org. Chem.* **1974**, *39*, 2302. (b) Chamberlin, A. R.; Stempke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147 and references therein. (c) For a review, see: Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

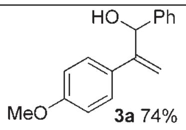
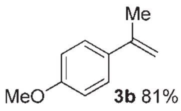
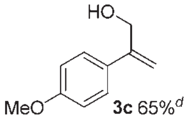
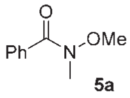
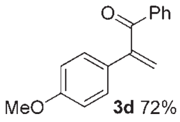
(8) For recent applications of lithium-mediated Shapiro reactions in total synthesis, see: (a) Tamiya, J.; Sorensen, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9556. (b) Reiter, M.; Torell, S.; Lee, S.; MacMillan, D. W. C. *Chem. Sci.* **2010**, *1*, 37. (c) Lau, S. Y. W. *Org. Lett.* **2011**, *13*, 347.

(9) Tosylhydrazones were prepared from the corresponding ketones and *p*-toluenesulfonylhydrazine in EtOH with catalytic amounts of HCl.

developed conditions compare favorably with the analogous lithium systems (which generally require 3.5−4 equiv of the base reagent and 3 equiv of electrophile).[7b,c] In relation to this, the application of benzoyl chloride to form the corresponding enone product was unsuccessful. In contrast, on moving to the Weinreb amide **4a** a good 72% yield of the desired enone **3d** was obtained, coupled with a pleasing 97:3 E:H ratio (Table 2, entry 4). Interestingly and at least as importantly, none of the undesired mesitylene addition byproduct was observed with this Weinreb amide electrophile. Consequently, the quantity of amide **4a** could be, in turn, lowered to 1.05 mol (Table 3, entry 1), for even more efficient delivery of the desired enone.

Table 2. Electrophile Scope[a]

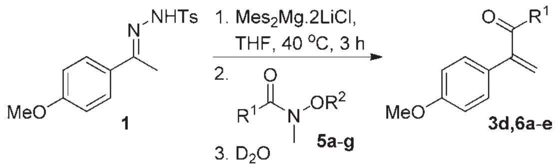


entry	electrophile	quench conditions	yield (%)[b]	E:H[c]
1	PhCHO	-10 °C, 0.5 h	 **3a** 74%	90:10
2	MeI	0 °C, 1 h	 **3b** 81%	93:7
3	DMF	0 °C, 1 h	 **3c** 65%[d]	90:10
4	 **5a**	40 °C, 0.5 h	 **3d** 72%	97:3

[a] Reaction conditions: *p*-methoxyacetophenone tosylhydrazone **1** (1 mmol), Mes$_2$Mg (1.5 mmol), LiCl (3 mmol), THF (5 mL), 40 °C, 3 h, then addition of electrophile (2 mmol). [b] Isolated yield after column chromatography. [c] Ratio was determined by ^{1}H NMR of the crude reaction mixture. [d] Yield over two steps; due to difficulties in enal isolation,[10] the crude reaction mixture was subjected to Luche reduction to give alcohol **3c**.

To demonstrate the potential of this magnesium *C*-centered base-mediated transformation for efficient enone synthesis, a range of alkyl-substituted Weinreb amides was synthesized and applied within the developed protocol. As shown in Table 3, the standard (methoxy) Weinreb amides delivered generally good yields of the desired products (entries 1−5). In order to establish that all of the formed vinyl anion intermediate from **1** had reacted within the reaction manifold (with **5a**−**f**), D$_2$O was added to the reaction mixture prior to workup. In this way, any unreacted vinyl anion species would yield the deuterated styrene **D-2**. Moreover, any observed protonated styrene **H-2** would thus have been formed by a competitive protonation reaction during the Shapiro reaction process, rather than on workup. Monitoring the reactions in this way proved to be very valuable, as Weinreb amide **5b** returned lowered yields but no **D-2** under the quench conditions employed. Considering the steric bulk of the ^{t}Bu-group, addition to **5b** may be expected to be slower and competing demethoxylation can occur.[11] Accordingly, Weinreb amide **5f**, with an *N*-O^{t}Bu substituent in place, was employed in attempts to circumvent this side reaction (entry 6). Surprisingly, the reaction with the Weinreb amide **5f** proceeded much more rapidly, delivering an 85:0:15 (E:D:H) ratio after only 1 h, albeit with a slightly lower 53% yield.

Table 3. Application of Weinreb Amides As Electrophiles[a]



entry		R^1, R^2	quench conditions	yield (%)[b]	E:D:H[c]
1	**5a**	Ph, Me	40 °C, 1 h	**3d** 75	93:0:7
2	**5b**	^{t}Bu, Me	40 °C, on	**6a** 64	83:0:17
3	**5c**	^{i}Pr, Me	40 °C, 0.5 h	**6b** 72	93:0:7
4	**5d**	Et, Me	40 °C, 1 h	**6c** 77	92:0:8
5[d]	**5e**	Me, Me	0 °C, 2 h	**6d** 45	65:0:35
6	**5f**	^{t}Bu, ^{t}Bu	40 °C, 1 h	**6a** 53	85:0:15
7[e]	**5g**	CD$_3$, Me	0 °C, 2 h	**6e** 72	84:0:16

[a] Reaction conditions: *p*-methoxyacetophenone tosylhydrazone (1 mmol), Mes$_2$Mg (1.5 mmol), LiCl (3 mmol), THF (5 mL), 40 °C, 3 h, then addition of electrophile (1.05 mmol). [b] Isolated yield after column chromatography. [c] Ratio was determined by ^{1}H NMR of the crude reaction mixture. [d] 2 mmol of electrophile were used. [e] H$_2$O used as the reaction quench.

Unexpectedly, the least hindered Weinreb amide **5e** gave a disappointingly low yield, as well as increased levels of H pickup. It was envisaged that the increased amount of protonated styrene **H-2** arises from the deprotonation of the methyl group α to the carbonyl. In attempts to verify this, the corresponding deuterated Weinreb amide **5g** was employed, with the reaction ultimately being quenched with H$_2$O. Surprisingly, only trace amounts of the deuterated styrene **D-2** were observed and the desired enone **6e**

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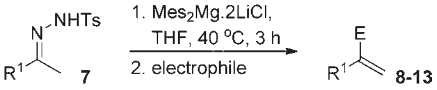
(10) Davies, H. M. L.; Dai, X. *J. Org. Chem.* **2005**, *70*, 6680.

(11) (a) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269. (b) Labeeuw, O.; Phansavath, P.; Genet, J.-P. *Tetrahedron Lett.* **2004**, *45*, 7107.

was isolated in 72% yield (entry 8). This implies a subtle but pivotal kinetic isotope effect, where D in **5g** is abstracted less readily than the equivalent H in Weinreb amide **5e**.[12]

Overall, this set of results clearly highlights the advantages of the developed Mes_2Mg-system for the Shapiro reaction with respect to the low base and electrophile quantities used, as well as the preparatively simple temperature protocol. As a direct comparison and as part of this study, using equivalent reaction conditions and employing 3 equiv of ^{n}BuLi as base, in combination with 1.05 equiv of **5a** as the electrophile, led to the isolation of none of the enone **3d**.

Table 4. Substrate Scope[a]



entry	R^1	electrophile	yield (%)	(E:D):H[d]
1	**7a** Ph	D_2O	**8a** 57[b]	92:8
		5a	**8b** 79[c]	(95:0):5
2	**7b** p-Cl-C_6H_4	D_2O	**9a** 94[b]	97:3
		5a	**9b** 70[c]	(97:0):3
3	**7c** p-^{t}Bu-C_6H_4	D_2O	**10a** 91[b]	91:9
		5a	**10b** 75[c]	(94:0):6
4	**7d** p-Ph-C_6H_4	D_2O	**11a** 85[c]	96:4
		5a	**11b** 91[c]	(93:0):7
5	**7e** p-$(CH_2)_4N$-C_6H_4	D_2O	**12a** 63[c]	90:10
		5a	**12b** 52[c]	(95:0):5
6[e]	**7f** ^{t}Bu	PhCHO	**13a** 46[c]	–
		5a	–	–

[a] Reaction conditions: tosylhydrazone (1 mmol), Mes_2Mg (1.5 mmol), LiCl (3 mmol), THF (5 mL), 40 °C, 3 h, then addition of D_2O (0.2 mL) or **5a** (1.05 mmol, 40 °C, 1 h) followed by D_2O. [b] NMR yield after column chromatography. [c] Isolated yield after column chromatography. [d] Ratio was determined by ^1H NMR of the crude reaction mixture. [e] Reaction mixture was heated to reflux over 3 h prior to addition of PhCHO (2 mmol, −10 °C, 1 h) or **5a** (1.05 equiv, 40 °C, 1 h).

Having probed the electrophile scope thus far, we moved to investigate a variety of hydrazone substrates (Table 4). Alkyl-, aryl-, and halide-substituted aryl tosylhydrazones gave consistently high selectivities toward the introduced electrophiles and good yields of the desired functionalized styrene products (entries 1−5). Unfortunately, substrates with more electron-withdrawing nitrile and nitro groups led to decomposition of the starting material, even when the reaction temperature and time were decreased.

To this point, exclusively tosylhydrazones bearing aromatic groups had been subjected to the developed system. Consequently, *tert*-butylmethylketone tosylhydrazone was selected as a suitable alkyl-substituted substrate and treated under the optimized conditions. However, only when heated to reflux, followed by quenching with benzaldehyde, could the functionalized alkene product be isolated (entry 6). Somewhat disappointingly, the yield of the functionalized alkene did not exceed 46%, even when the reaction time was prolonged to 16 h. None of the deuterated or protonated alkene products were detected, as a result of their low boiling point. Additionally, attempts to quench the Shapiro reaction of **7f** with Weinreb amide **5a** were unsuccessful.

In summary, an efficient new system employing the carbon-centered magnesium base, Mes_2Mg, has been developed to mediate the Shapiro reaction of simple tosylhydrazones and deliver functionalized styrene products. Exceptionally high selectivity toward the introduced electrophiles (over *in situ* proton pickup) and good yields are achieved under practically convenient temperature protocols (at 40 °C). Moreover, Weinreb amides have been found to be unreactive toward nucleophilic attack by the parent base reagent and thus merely 1.05 equiv of this class of electrophile are required to furnish consistently good yields of the corresponding aryl enones. The developed system offers a preparatively effective alternative to the traditional lithium-mediated Shapiro process, as the less expensive tosylhydrazones (*cf.* trisylhydrazones) can be used in conjunction with a comparably small excess of the magnesium base and, at least as importantly, electrophile.

Acknowledgment. We would like to thank MSD for financial support and the EPSRC Mass Spectrometry Service, University of Wales, Swansea for analyses.

Supporting Information Available. Experimental procedures, spectroscopic analysis of products and Weinreb amides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a monograph on isotope effects, see: Melander, L.; Saunders, W. H. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980.

The authors declare no competing financial interest.