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Controlled Anion Migrations with a Mixed Metal Li/K-TMP Amide: General Application to Benzylic Metalations

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S Supporting Information

ABSTRACT: A general method is described for benzylic metalation of *o*-, *m*-, and *p*-substituted toluenes using a mixed metal amide base generated from BuLi/KO*t*Bu/TMP at −78 °C in THF. The excellent selectivity achieved can be rationalized by the ability of the mixed metal amide base to facilitate an anion migration from the kinetic (*o*-aryl) to the benzylic metalation site. Remarkably, this controlled anion migration is achievable with catalytic amounts of TMP at −78 °C.

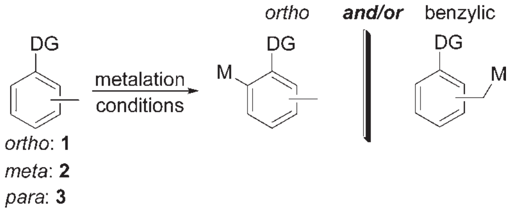
Direct aryl and alkyl metalation reactions are steeped in the historical traditions of Wittig and Gilman yet have stood the test of time and remain at the cutting edge of modern synthetic methods. The concept of directed *o*-aryl deprotonation using organolithium bases, first with the *o*-lithiation of anisole, ushered in a new era of selective metalation chemistry.[1] Since its inception, the synthetic utility of this transformation class has continually grown; in parallel, the mechanisms by which regioselectivity is obtained have been comprehensively studied.[2] The ongoing development of enhanced reactivity and selectivity profiles for direct aryl metalations using mixed Li/Zn- and Li/Mg-tetramethylpiperidide (TMP) amides illustrates the continued importance of this class of transformation.[3] Arguably of equal synthetic utility is the associated metalation of the benzylic position of substrates **1**, **2**, and **3** which is, by default, in competition with *o*-metalation and can be, depending upon the substrate, surprisingly challenging to achieve with good selectivity (Scheme 1).[4] As such, a general method for the benzylic metalation of substituted toluenes with high and predictable regiospecificity would be of particular interest due to the obvious synthetic potential of such organometallics (Scheme 1).

In contrast to the development of mixed metal amide systems for aryl metalations, their application to benzylic metalations remains unexplored. In what may appear at first glance a distantly related example, we have recently shown that, for *o*-OMOM-substituted *cis*-stilbene **4**, regioselective vinyl C−H metalation to produce **5** required the mixed metal amide system LiTMP/KO*t*Bu (Scheme 2).[5] In contrast, when alkyllithium base was utilized, predominately *o*-aryl metalation was obtained. As other reported uses of this Li/K-TMP amide are very rare, substantial scope for development of this reagent exists.[6]

Herein we illustrate the first general use of a mixed Li/K-TMP amide for benzylic metalations and an understanding of the metalation selectivity obtained. As a starting point, the OMOM substrates **1a**, **2a**, and **3a** were chosen as, to the best of our knowledge, the benzylic metalation of these substrates is unreported.[7] This can be attributed to the fact that the OMOM group is a strong *ortho*-directing substituent, therefore favoring kinetic-controlled *o*-aryl metalated products. In order to achieve benzylic metalation, reaction conditions that could overcome or bypass the competing *ortho*-directing influence of the OMOM group would be required. The three substrates were investigated under identical reaction conditions by sequential treatment with BuLi/KO*t*Bu/TMP in THF, −78 °C, followed by quenching of the reactions with CD_3OD after 15 min. In order to illustrate and gain an understanding of the influence of the mixed metal amide on metalation regioselectivity, reactions were also carried out with the mixed metal alkyl base BuLi/KO*t*Bu under otherwise identical conditions.[8] In addition to routine analysis, products were also analyzed by ^{2}H NMR to give a conclusive view of the site(s) of deuterium incorporation.

^{2}H NMR analysis of the products from the treatment of substrates **1a**, **2a**, and **3a** with BuLi/KO*t*Bu (conditions A) showed highly selective *o*-metalation with >93% incorporation of D (Table 1, entries 1−3; Figure 1, spectra i, iii, v). In contrast, reaction with BuLi/KO*t*Bu/TMP (conditions B) gave almost exclusively benzylic deuterated products with little or no detectable

Scheme 1. *Ortho* and Benzylic Metalation Sites of Substituted Toluenes (DG = directing group; M = metal)



Scheme 2. Selective Metalation of OMOM-Substituted *cis*-Stilbene (M = K/Li)

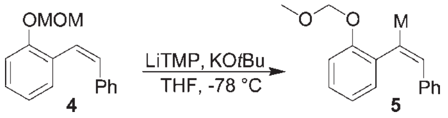


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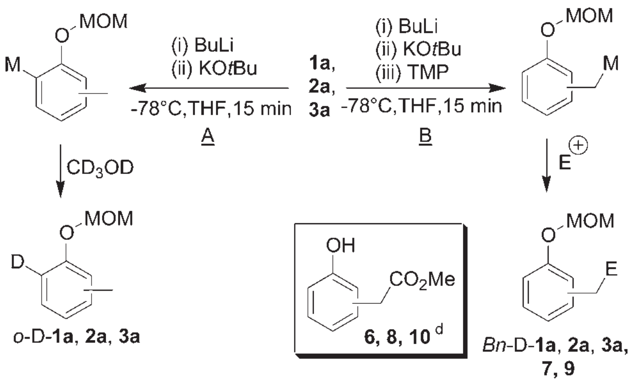
Table 1. Selective Benzylic Metalations of OMOM-Substituted Toluenes 1a, 2a, and 3a (M = K/Li)



entry	starting material	conditions	product	E	% D[a]	% yield
1	**1a**	A	*o*-D-**1a**	D	98[b]	92
2	**2a**	A	*o*-D-**2a**	D	93[b]	76
3	**3a**	A	*o*-D-**3a**	D	96	81
4	**1a**	B	*Bn*-D-**1a**	D	80[c]	75
5	**2a**	B	*Bn*-D-**2a**	D	88[c]	84
6	**3a**	B	*Bn* D-**3a**	D	20[c]	89
7	**1a**	B	**6**	CO_2Me	–	51[d]
8	**1a**	B	**7**	$Sn(Bu)_3$	–	69
9	**2a**	B	**8**	CO_2Me	–	59[d]
10	**2a**	B	**9**	$SnBu_3$	–	68
11	**3a**	B	**10**	CO_2Me	–	25[d]

[a] Based on ^{1}H NMR integration and confirmed with ^{2}H NMR. [b] Trace benzylic D observed in ^{2}H NMR. [c] Trace *o*-D observed in ^{2}H NMR. [d] OMOM deprotected and crude material converted to ester prior to purification (inset).

o-D (Table 1, entries 4–6; Figure 1, spectra ii, iv, vi). While selectivity of D incorporation into the benzylic positions was excellent, levels of D incorporation varied across the substrates **1a**, **2a**, and **3a** at 80, 88, and 20%, respectively (Table 1, entries 4–6). This reflects the relative acidities of the benzylic protons with, as would be expected, the 4-substituted derivative **3a** being the least acidic. Reaction of metalated **1a** and **2a** with other electrophiles such as CO_2 and Bu_3SnCl gave the expected benzylic substituted products **6**–**9** (Table 1, entries 7–10). The low product yield achieved from *para*-substituted **3a** limits the effective use of this substrate for general electrophile reactions (Table 1, entry 11).

Examination of the related anisole series **1b** and **2b** with conditions A gave mixtures of *ortho* and benzylic deuterium incorporation of 60:40 and 50:50, respectively (Table 2, entries 1, 2). The contrasting lack of *ortho* selectivity for **1b** and **2b** in comparison to the corresponding OMOM substrates **1a** and **2a** can be rationalized in terms of the superior *ortho*-directing power of the OMOM group. In contrast, when the mixed metal amide conditions B were utilized and metalated intermediates reacted with CD_3OD, the benzylic deuterated products were obtained with excellent selectivity, yield, and D incorporation (Table 2, entries 3, 4; SI for ^{2}H NMR spectra). Alternative electrophiles provided the methoxyphenylacetic acids **11** and **13** and methoxybenzylstannanes **12** and **14** in good yields (Table 2, entries 5–8).

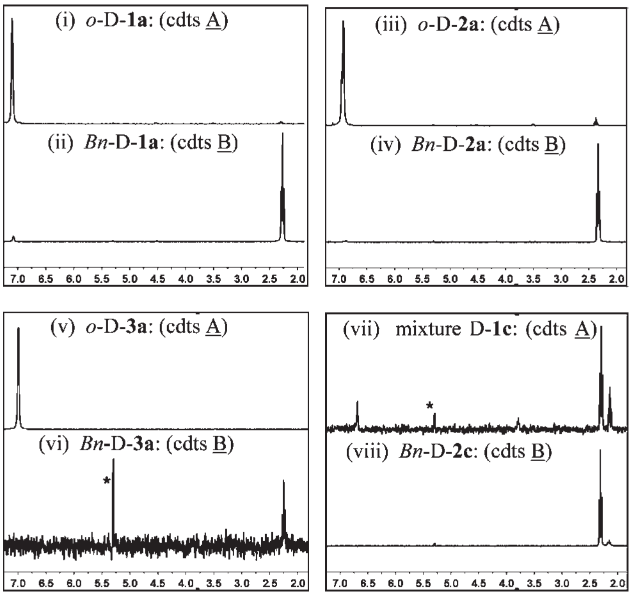
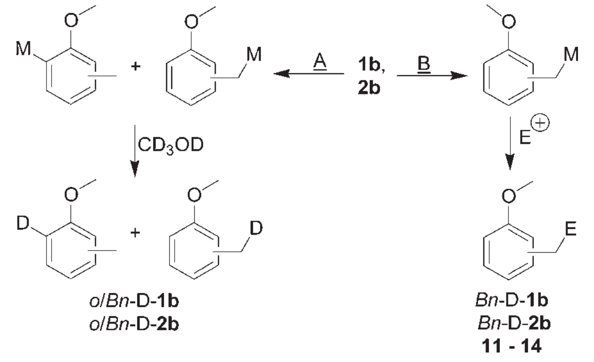


Figure 1. ^{2}H NMR spectra of deuterated products from metalation of **1a**, **2a**, **3a**, and **1c** with conditions A and B. *, CD_2Cl_2 peak.

We next examined the ability of the mixed metal amide conditions to differentiate between two benzylic positions on the same molecule. For example, 2,5-dimethylanisole **1c** offers three possible sites for metalation: *o*-aryl, *o*-benzylic, and *m*-benzylic. Reaction with BuLi/KO*t*Bu gave no selectivity, with a mixture of all possible deuterated isotopomers obtained following CD_3OD quench (Table 3, entry 1; Figure 1, spectrum vii).

Remarkably, metalation utilizing amide conditions B gave excellent selectivity for the *m*-benzylic position as based upon D incorporation (Table 3 entries 2, 3; Figure 1, spectrum viii). These results are significant, as it is apparent that heteroatom

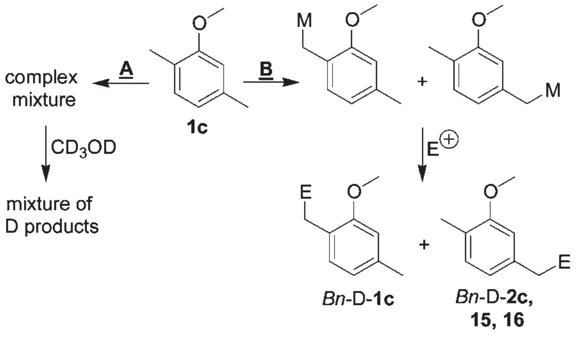
Table 2. Selective Benzylic Metalations of OMe-Substituted Toluenes 1b and 2b (M = K/Li)



entry	starting material	conditions	product(s)	E	*o*/Bn ratio[a]	% yield
1	**1b**	A	*o*/*Bn*-D-**1b**	D	60:40	71
2	**2b**	A	*o*/*Bn*-D-**2b**	D	50:50	83
3	**1b**	B	*Bn*-D-**1b**	D	1:99	80[b]
4	**2b**	B	*Bn*-D-**2b**	D	5:95	96[c]
5	**1b**	B	**11**	CO_2H	–	70
6	**1b**	B	**12**	$Sn(Bu)_3$	–	76
7	**2b**	B	**13**	CO_2H	–	72
8	**2b**	B	**14**	$Sn(Bu)_3$	–	72

[a] Based on ^{1}H NMR integration and confirmed with ^{2}H NMR. [b] 90% D incorporation. [c] 97% D incorporation.

Table 3. Selective Benzylic Metalation of 2,5-Dimethylanisole **1c** (M = K/Li)



entry	conditions	product	E	*Bn*-D **1c**:**2c**	% yield (D)
1	A	mixture	D	–	–
2	B	*Bn*-D-**2c**	D	5:95	88 (75)
3	B	*Bn*-D-**2c**	D	5:95	86 (98)[a]
4	B	**15**	CO_2H	–	60[a]
5	B	**16**	$SnBu_3$	–	60[a]

[a] Increased equivalents used: 2 equiv of BuLi, 2 equiv of KO*t*Bu, 1 equiv of TMP.

coordination is not a factor to be considered in the overall outcome under these metalation conditions and that the *m*-benzylic position, being the most acidic in this particular substrate, is the favored site of deprotonation. Again the use of alternative electrophiles confirmed the metalation selectivity (entries 4, 5).

As illustrated above, the amide portion of the mixed metal amide plays a key role in the selectivity obtained. The need for an amide rather than a coordinating amine was investigated by using *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine in the reaction instead of TMP with substrates **1a** and **2a**. In both cases, following CD_3OD quench, only *o*-D products were observed. To exemplify this role, the use of *catalytic* TMP with BuLi/KO*t*Bu was investigated with **1a** and **2a** as substrates. The experiments were designed to show the reaction progress over time with samples removed and deuterated at different time points following treatment of the substrates with BuLi/KO*t*Bu and 10% TMP. After 5 min, both reactions showed a mixture of *o*- and benzylic-D products. Yet analysis after 15 min for **1a** and 60 min for **2a** gave exclusively benzylic-D products (Scheme 3, ^{2}H NMR spectra). This remarkable process can be viewed as an *in situ* C_{aryl} to C_{benzyl} anion migration.[9] In effect, this triad of reagents can correct for any *o*-metalation that occurs under the reaction conditions, leading to highly regioselective benzylic metalated products. The migration process required the addition of TMP, as holding the reaction for prolonged periods without TMP did not facilitate the migration.

Scheme 3. C_{aryl} to C_{benzyl} Anion Migration with Catalytic TMP for **1a** and **2a**

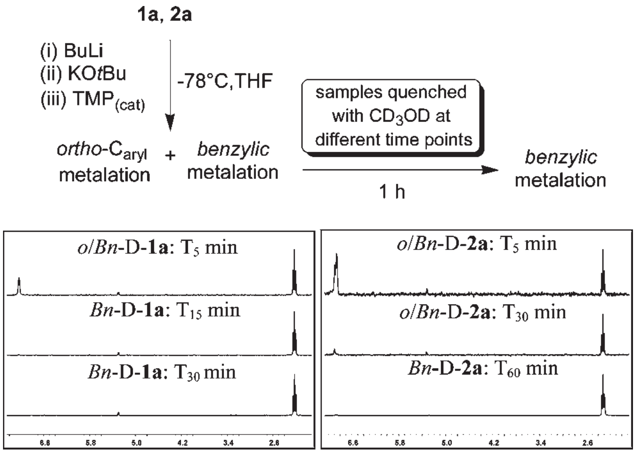
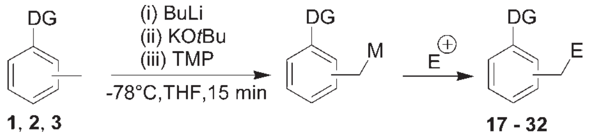
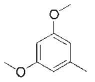
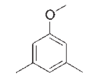


Table 4. Selective Benzylic Metalations (M = K/Li)



entry	sm	DG	*o*, *m*, *p*	prod	E	%yield
1	**1b**	OMe	*o*	**17**	TMS	60
2	**1d**	$N(Me)_2$	*o*	**18**	D (98%)	83
3	**1d**	$N(Me)_2$	*o*	**19**	$SnBu_3$	80
4	**1e**	F	*o*	**20**	CO_2H	69
5	**1e**	F	*o*	**21**	$Sn(Bu)_3$	65
6[a]	**2d**		*m*	**22**	D (90%)	91
7[a]	**2d**		*m*	**23**	CO_2H	67
8[a]	**2d**		*m*	**24**	$Sn(Bu)_3$	55
9	**2e**		*m*	**25**	D (90%)	87
10	**2e**		*m*	**26**	CO_2H	84
11	**2e**		*m*	**27**	$Sn(Bu)_3$	77
12	**3c**	CON*i*Pr_2	*p*	**28**	D (90%)	90
13	**3c**	CON*i*Pr_2	*p*	**29**	CO_2H	84
14	**3c**	CON*i*Pr_2	*p*	**30**	$SnBu_3$	67
15[a,b]	**3d**	SO_2NHEt	*p*	**31**	D (95%)	80
16[a,b]	**3d**	SO_2NHEt	*p*	**32**	CO_2H	66

[a] Substrate added to base mixture at −78 °C. [b] Increased equivalents of reagents used: 3.2 equiv of BuLi, 3.2 equiv of KO*t*Bu, 3 equiv of TMP.

Several other *ortho*-, *meta*-, and *para*-substituted toluenes, substituted with various groups including amino, fluoro, amido, and sulfonamido, have been metalated and reacted with electrophiles (Table 4). A consistent high degree of benzylic selectivity was maintained for all the different substituents when deutero products were analyzed (Table 4, entries 2, 6, 9, 12, 15; SI). The *p*-amide- and *p*-sulfonamide-substituted toluenes gave excellent results, as their electron-withdrawing nature promoted *p*-benzylic deprotonation, in contrast to the OMOM group (Table 4, entries 12−16). In addition, dimethoxy- and methoxy(dimethyl)-substituted toluenes **2d** and **2e** also gave good results under our reaction conditions (Table 4, entries 6−11).

In conclusion, the use of BuLi/KO*t*Bu/TMP to *in situ* generate a mixed Li/K metal amide has proven to be an efficient and general method to achieve hitherto difficult benzylic metalations with excellent selectivity. When added sequentially, the triad of reagents can link together to facilitate an anion migration from the *ortho* to the benzylic positions at −78 °C. Further investigations of the synthetic applications of this reagent mixture and its mechanistic basis are ongoing, the findings of which will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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