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Selective Vinyl C−H Lithiation of *cis*-Stilbenes

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Directed aryl deprotonation utilizing organolithium bases has its origins in the pioneering work of Wittig and Gilman.[1] Since that time the direct *ortho*-lithiation of aryl rings to provide **1** has become a fundamental transformation in organic chemistry with numerous different directing groups being employed (Figure 1).[2] Likewise the lateral lithiation of *ortho*-alkyl groups to generate **2** has also become readily achievable.[3] The extension of these directed lithiations to vinyl lithiation thereby generating **3** appears unlikely to be successful as it is known that unactivated alkenes, including ethene, β-methylstyrenes, and *trans*-stilbenes, undergo efficient carbolithiation chemistry (Figure 1).[4]

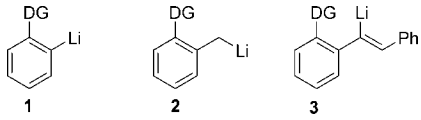


Figure 1. Ortho, lateral, and vinyl lithiation (DG = directing group).

Yet, it has been recognized that double bond stereochemistry, specifically in the case of *trans*- and *cis*-stilbene, has a significant influence upon the acidity of vinyl C−H protons.[5] We recently showed it is possible to synthetically exploit this C−H acidity difference by effectively deprotonating *cis*-stilbene with *s*BuLi in THF at −25 °C with no carbolithiation observed.[6] In addition, strongly coordinating solvents allowed the initially formed (*Z*)-1-lithio-1,2-diphenylethene to isomerize to (*E*)-1-lithio-1,2-diphenylethene **3a** (Figure 1, DG = H).[6,7] These results prompted us to investigate the basis for this stereocontrolled reactivity pattern and demonstrate its potential for synthetic chemistry.

First, comparative DFT studies at the B3LYP/6−31+G(d) level of the carbolithiation and vinyl C−H lithiation of *trans*- and *cis*-stilbene were undertaken. As expected, carbolithiation was strongly favored over vinyl deprotonation for *trans*-stilbene by 13 kJ/mol (Supporting Information, SI). In contrast, the opposite was observed for *cis*-stilbene with vinyl C−H lithiation favored by 6 kJ/mol, a difference of sufficient size to indicate potential general use for low temperature synthetic chemistry (Figure 2, SI). The significantly lower reactivity of *cis*-stilbene to carbolithiation can be attributed to the spatial shielding of the double bond by both phenyl rings requiring a reorientation to an almost orthogonal conformation of the phenyl rings in the transition state (Figure 2A). In contrast, the double bond of the planar *trans*-isomer can easily be approached by the alkyllithium for carbolithiation without conformational change (SI). In the case of vinyl C−H lithiation the torsion of the phenyl rings in the *cis* isomer makes proton abstraction more accessible in comparison to the *trans*-isomer (Figure 2B). An examination of conditions for the metalation of *cis*-stilbene identified 1 equiv of BuLi/*t*BuOK[8] at −78 °C for 1 h as sufficient to

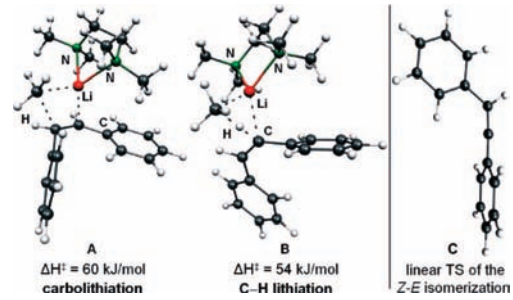
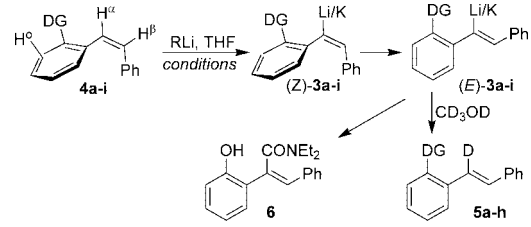


Figure 2. Transition states [B3LYP/6−31+G(d)] for (A) *cis*-stilbene C=C carbolithiation with MeLi/TMEDA; (B) *cis*-stilbene vinyl C−H lithiation with MeLi/TMEDA; (C) (*Z*) to (*E*) isomerization of deprotonated stilbene.

give an excellent yield of *trans*-deuterio-stilbene **5a** following CD_3OD quench (Table 1, entry 1). Motivated by the ease of this reaction a series of unsymmetrical *ortho*-substituted *cis*-stilbenes **4b**−**i** were examined for regioselective vinyl C−H$^{\alpha}$ metalation over the two alternative deprotonation sites at H^{o} and H$^{\beta}$ (Table 1). The *ortho*-substituents included known directing groups OMe, OMOM, CH_2NHBoc, NHBoc, oxazoline, SO_2NEt_2, and $O(C{=}O)NEt_2$ along with the atypical group $SiMe_3$.

Table 1. Vinyl Lithiation Conditions



entry	4	DG	RLi/additive	temp. (C°)	product	yield (%)
1	**a**	H	BuLi/*t*BuOK	-78	**5a**	80
2	**b**	$SiMe_3$	BuLi/*t*BuOK	-78	**5b**	80
3	**c**	OMe	BuLi	-25/-10	**5c**	71
4	**d**	OMOM	LiTMP/*t*BuOK	-78	**5d**	85
5	**e**	CH_2NHBoc	BuLi	-10	**5e**	61
6	**f**	NHBoc	*t*BuLi/PMDTA	-25	**5f**	62[6]
7	**g**		BuLi	-78	**5g**	85
8	**h**	SO_2NEt_2	BuLi	-30	**5h**	87
9	**i**	$O(C{=}O)NEt_2$	LiTMP/*t*BuOK	-78	**6**[a]	52

[a] Stereochemistry confirmed by X-ray crystallography (SI).

In each case it was possible to identify conditions that gave rise to highly regioselective α-vinyl deprotonation with only one

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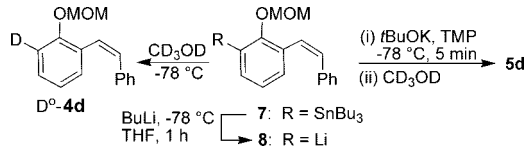
regioisomer (>95%) being observed as judged by NMR analysis (prior to purification) following treatment of the metallated compounds with CD_3OD (Table 1). Additionally, only one stereoisomer of each product was observed with this excellent stereochemical outcome attributable to complete lithiated-alkene isomerization. DFT studies of deprotonated *cis*- and *trans*-stilbene confirmed the energetical preference of the (*E*)-isomer by 18 kJ/mol (SI). Moreover, the (*Z*)−(*E*) isomerization showed a low barrier of 14 kJ/mol with a linear arrangement of the vinyl group in the transition state (Figure 2C).[9]

The selection of base, additive, and temperature as described in Table 1 was a result of yield and regioselectivity optimization. In the cases where *t*BuOK was employed as an additive with BuLi, identical regioselectivity was observed with BuLi alone except in a lower conversion (Table 1, entries 1, 2). For the methoxy, oxazoline, and sulfonamide substituents, good yields were obtained without any additive (entries 3, 7, 8). In the cases of the OMOM and *O*-carbamoyl directing groups, it was found essential to use a combination of lithium tetramethylpiperidide (LiTMP)/*t*BuOK to achieve the desired products **5d** and **6**, respectively (entries 4, 9).[10] The requirement of a mixed metal amide base can be rationalized in terms of facilitating reaction conditions that could permit a complex-induced proximity effect (CIPE) controlled kinetic deprotonation at H^o to undergo intermolecular anion migration from C_{aryl} to C_{vinyl} at −78 °C. Illustration of this for the OMOM directing group was achieved by generation of the anion **8**, by tin−lithium exchange of **7**, which when treated with CD_3OD provided the expected *o*-deuterated D^o-**4d** (Scheme 1). In contrast,

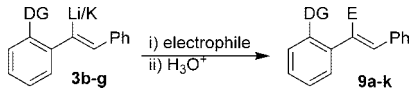
Scheme 1. Anion Migration from C_{aryl} to C_{vinyl}



treatment of **8** with *t*BuOK and tetramethylpiperidine (TMP) at −78 °C for 5 min facilitated a migration to the thermodynamic anion **3d** which upon addition of CD_3OD gave **5d** as the major product. For the *O*-carbamoyl derivative **4i**, subsequent rearrangement to **6** was achieved in a 52% yield, though a low 5% of competing Snieckus−Fries rearrangement to the *o*-aryl position was also observed (entry 9).[11]

Having defined the optimized conditions for α-vinylic lithiation, the reaction of **3b**−**g** with a representative selection of electrophiles allowed the stereoselective assembly of the trisubstituted alkenes **9a**−**k** (Table 2).[12] Additional synthetic value was achievable from subsequent intramolecular reaction of the *ortho*-substituents with the functional group introduced by the electrophile. Representative examples are the substituted benzofuran-2-one **10** obtained by treatment of **9f** with aqueous acid and the isocoumarin **11** which was accessible from **9k** in a one-pot operation by acid mediated ring closure and deprotection (Scheme 2). This vinyl-lithiation/electrophile trapping/ring closure reaction sequence was applied to the synthesis of the medicinally important natural product Coumestan **14** from bis-*ortho*-methoxy *cis*-stilbene **12**. Vinyl lithiation of **12** followed by CO_2 quench provided routine access to **13** upon which demethylation with BBr_3, treatment with base, and oxidative cyclization completed the synthesis of **14** (Scheme 2).

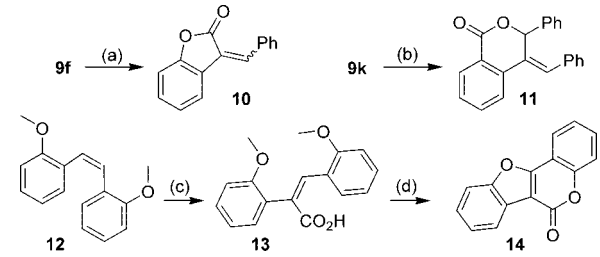
Table 2. Stereoselective Synthesis of Trisubstituted Alkenes[a]



entry	DG	electrophile	E	product	yield (%)
1	$Si(Me)_3$	CO_2	CO_2H	**9a**	61
2	$Si(Me)_3$	PhCHO	CHOHPh	**9b**	82
3	OMe	CO_2	CO_2H	**9c**	71
4	OMe	$B(OiPr)_3$	$B(OH)_2$	**9d**[b]	48
5	OMe	PhCHO	CHOHPh	**9e**	51
6	OMOM	CO_2	CO_2H	**9f**[c]	79
7	OMOM	$Br(CH_2)_2Br$	Br	**9g**	62
8	CH_2NBoc	CO_2	CO_2H	**9h**	60
9	NBoc	$B(OiPr)_3$	$B(OH)_2$	**9i**	59
10		Bu_3SnCl	$SnBu_3$	**9j**	71
11		PhCHO	PhCHOH	**9k**	c

[a] **3b**−**g** generated as in Table 1. [b] Stereochemistry confirmed by X-ray crystallography (SI). [c] Converted *in situ* to **11**, see Scheme 2.

Scheme 2. Benzofused Heterocycles and Coumestan Synthesis[a]



[a] Reagents and conditions: (a) HCl, MeOH, reflux, 4 h, (89%). (b) 2 M HCl, 3 h, rt, (63%), stereochemistry of **11** was confirmed by X-ray crystallography (SI). (c) (i) BuLi/*t*BuOK, −78 °C, 2 h; (ii) CO_2; (iii) H_3O^+ (83%). (d) (i) BBr_3, CH_2Cl_2, rt, 3.5 h; (ii) Et_3N, toluene, reflux, 1 h; (iii) DDQ, toluene, reflux, 24 h (38%).

In summary, a new stereoselective vinyl lithiation allows routine regio- and stereoselective access to polysubstituted alkenes and heterocycles. DFT studies explain the experimental observations with regard to chemo- and stereoselectivity, and a unique anion migration process offers insight into the regioselectivity of deprotonation. Further studies of related anion migrations are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures, NMR spectra, X-ray structures, and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) ^{1}H NMR study of the lithiation of *cis*-stilbene in THF-d_8 at −15 °C identified (*E*)-**3a** as the major component (SI).
(10) Lithiation of **4d** with BuLi alone gave the CIPE controlled *ortho*-lithiation.
(11) For a related reaction in which alkene lithiation was achieved with LDA, THF, −30 to 0 °C when the *ortho* position was blocked by TMS substitution, see: Reed, M. A.; Chang, M. T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297.
(12) The calculated HOMO of the energetically minimized deprotonated *trans*-stilbene revealed it to be more accessible from one side of the molecule, in agreement with the experimental results obtained (SI). Assumes an $S_E2$ret mechanism which may not be the case for all electrophiles.

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