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Development and Application of a Direct Vinyl Lithiation of *cis*-Stilbene and a Directed Vinyl Lithiation of an Unsymmetrical *cis*-Stilbene

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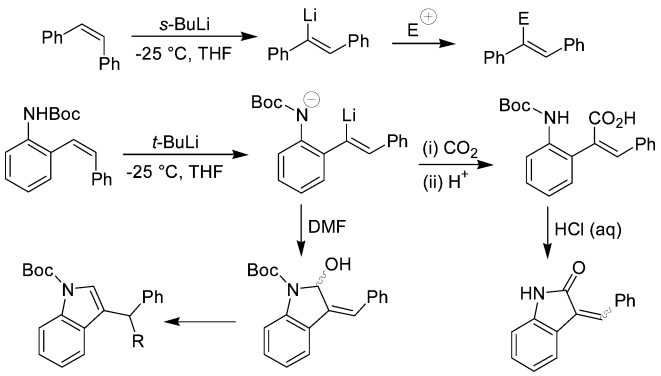
ABSTRACT



The vinyl deprotonation of *cis*-stilbene can be readily achieved using *s*-BuLi in THF at −25 °C. The generated 1-lithio-1,2-diphenylethene undergoes an in situ *Z*-to-*E* isomerization, and subsequent reaction with electrophiles results in an efficient stereoselective synthesis of trisubstituted alkenes. A directed vinyl lithiation of the unsymmetrical *cis*-stilbene 2-styryl-phenyl-carbamic acid *tert*-butyl ester can be achieved regioselectively, thereby expanding this methodology for further synthetic applications in indole chemistry.

The synthetic value of organolithium chemistry is indisputable as the number of transformations accessible from organolithium compounds is vast. While many strategies exist for the preparation of lithiated compounds, their generation by a direct C−H deprotonation using commercially available lithium bases (alkyllithiums or lithium amides) is highly efficient from a synthetic viewpoint. This avoids additional synthetic steps to functionalize a starting substrate with a halogen or metal to effect a lithium exchange procedure. The direct lithiation of aryl and heteroaryl rings followed by in situ electrophile reaction has found extensive synthetic application. For example, the deprotonation of benzene has been achieved[1] and the direct *ortho*-lithiation of substituted aryl rings has gained widespead acceptance as a successful synthetic transformation for the generation of aryllithiums (Scheme 1, eq 1).[2] Likewise, the generation of benzyllithium via methyl deprotonation of toluene is known (eq 2; DG = H), and the directed lateral lithiation of benzylic alkyl groups has become a powerful tool for target-directed synthesis (eq 2, DG = directing group).[3,4] In contrast, the direct alkene deprotonation of 1,2-diphen-

(1) Rausch, M. D.; Ciappenelli, D. J. *J. Organomet. Chem.* **1967**, *10*, 127.

(2) (a) Wittig, G.; Pockels, U.; Dröge, H. *Chem. Ber.* **1938**, *71*, 1903. (b) Gilman, H.; Jacoby, H. L. *J. Am. Chem. Soc.* **1939**, *61*, 106. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(3) (a) Chalk, A.; Hoogeboom, J. T. J. *J. Organomet. Chem.* **1968**, *11*, 615. (b) Hage, M.; Ogle, C. A.; Rathman, T. L.; Hubbard, J. L. *Main Group Met. Chem.* **1998**, *21*, 777.

(4) (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: Oxford, U.K., 2002; pp 73−85.

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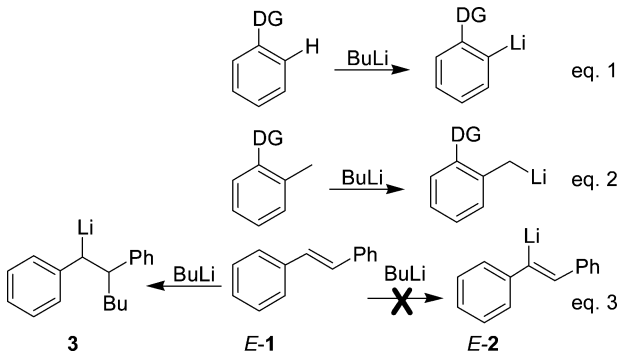
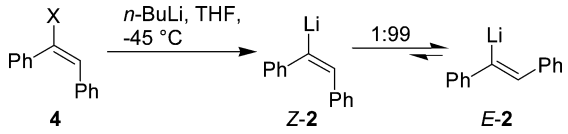
Scheme 1. Directed Lithiation Methods (DG = Directing Group)



ylethene (stilbene) *E*-**1** to produce a vinyl lithium *E*-**2** has not, to the best of our knowledge, been previously reported (eq 3). This can be attributed to the known propensity of alkenes, including *trans*-stilbene **1**, to readily undergo carbolithiation reactions to generate the benzylic lithiated species **3** (eq 3).[5] In fact, despite the obvious synthetic potential of this transformation, the direct vinyl deprotonation of substituted stilbenes is very rare, with one recent example of note being the deprotonation of an *ortho*-*O*-carbamoyl-substituted stilbene.[6]

Previously reported methods for the generation of 1-lithio-1,2-diphenylethene *E*-**2** have utilized the monoprotonation of 1,2-dilithio-1,2-diphenylethene (prepared by the reduction of diphenylacetylene with metallic lithium).[7] Alternatively, a lithium−mercury exchange of stilbene **4** at low temperature in THF has provided a route to *E*-**2** (Scheme 2).[8] It was

Scheme 2. Lithium−Mercury Exchange Route to *E*-**2**[a]



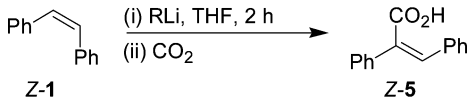
[a] X = Hg-stilbene.

shown that in these strongly coordinating solvent conditions the initially formed *Z*-**2** rapidly isomerized to generate, almost exclusively, the more thermodynamically stable *E*-**2**.

Despite the synthetic potential of *E*-**2** for further reaction with electrophiles, a principal drawback to the general utilization of this approach would be the requirement to synthesize the substituted stilbene from which the lithium−mercury exchange could be effected. Yet, if a direct lithiation method was available, this would open up the synthetic scope of *E*-**2** and other substituted analogues. To achieve this, a chemoselectivity shift for 1,2-diarylalkenes upon treatment with alkyllithiums from carbolithiation to deprotonation would be required.

As it is known that in general the carbolithiation of *cis*-1,2-disubstituted alkenes is less effective than the *trans* isomers, we speculated that conditions could be identified that would favor vinyl deprotonation over carbolithiation. Using *cis*-stilbene *Z*-**1** as a test substrate, we screened a series of organolithiums in conjunction with amine additives (Table 1). In each case the conversion, product yield, and stereo-

Table 1. Direct Lithiation of *Z*-Stilbene; Stereoselective Synthesis of α-Phenyl-*cis*-cinnamic Acid[a]



entry	RLi	equiv	temp (°C)	additive	yield (%)[b]
1	*s*-Bu	2	−25	PMDTA	76
2	*s*-Bu	1	−25	PMDTA	36
3	*s*-Bu	2	−25	none	66
4	*n*-Bu	2	−25	PMDTA	15
5	*t*-Bu	2	−25	PMDTA	55
6	LDA	2	−25	none	0
7	LTMP	2	−25	none	17
8	LTMP	1	0	none	30

[a] Only the *Z*-isomer was observed by ^{1}H NMR in each example. [b] Isolated purified yield (average of 2 runs).

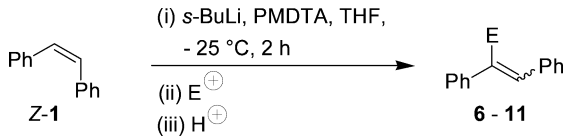
selectivity was determined by reacting the lithiated intermediate with CO_2, with the crude reaction products analyzed by NMR. Encouragingly, it was found that using 2 equiv of *s*-BuLi as base and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine[9] (PMDTA) as additive, in THF at −25 °C for 2 h, followed by addition of solid CO_2, a single stereoisomer of α-phenyl-*cis*-cinnamic acid Z-**5** was formed in an excellent 76% isolated yield (Table 1, entry 1). This route compares very favorably with the base-catalyzed Perkin condensation of phenylacetic anhydride and benzaldehyde or the transition-metal-catalyzed carboxylation of diphenylacetylene, which both predominately yield the opposite isomer α-phenyl-*trans*-cinnamic acid *E*-**5**.[10] It was found that the use of 1 equiv of *s*-BuLi with PMDTA or 2 equiv in the absence of the PMDTA additive both gave rise to a lowering of the isolated yield (entries 2 and 3). Both *n*-BuLi and *t*-BuLi also gave inferior yields when compared to *s*-BuLi as a result of inefficient deprotonation for *n*-BuLi and the generation of carbolithiation products for *t*-BuLi (entries 4 and 5). Examination of LDA as base revealed no product formation, but the stronger lithium tetramethyl piperidide (LTMP) gave an isolated yield of 17% (entries 6 and 7).

(5) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, *5*, 2055.
(6) Reed, M. A.; Chang, M. T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297.
(7) Maercker, A.; Kemmer, M.; Wang, H. C.; Dong, D.-H.; Szwarc, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2137 and references therein.
(8) Curtin, D. Y.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 1967.
(9) For the influence of PMDTA on organolithiums, see: Bauer, W.; Winchester, W. R.; von Ragué Schleyer, P. *Organometallics* **1987**, *6*, 2371.
(10) (a) Zimmerman, H. E.; Ahramjian, L. *J. Am. Chem. Soc.* **1959**, *81*, 2086. (b) Aoki, M.; Kaneko, M.; Izumi, S.; Ukai, K.; Iwasawa, N. *Chem. Commun.* **2004**, 2568 and references therein.

In an effort to provide a qualitative demonstration of the effect of the double bond stereochemistry on vinyl lithiation, both *cis*- and *trans*-stilbene were treated with the lithium amide LTMP (pK_a = 37.3) in THF at 0 °C, and the equilibrium mixture was treated with CO_2.[11] Under these reversible lithiation conditions a 30% isolated yield of *Z*-**5** was obtained from *cis*-stilbene (Table 1, entry 8). In contrast, when *trans*-stilbene *E*-**1** was used as a starting substrate, no product was isolated and only starting material was recovered.

Following the identification of the optimal lithiation conditions, a series of electrophiles was examined to stereoselectively generate the trisubstituted alkenes **6**−**11**. Reaction with formaldehyde gas or benzaldehyde provided a new route to the α,β-unsaturated alcohols **6** and **7** in reasonable yields and excellent stereoselectivity (Table 2, entries 1 and 2). Reaction of *E*-**2** with DMF generated the unsaturated aldehyde and alkylation was effectively achieved with methyl iodide (entries 3 and 4, respectively). The application of vinyl-silicon and boron reagents as convenient synthetic building blocks prompted us to test trimethylsilylchloride and triisopropylborate as electrophiles. Encouragingly, both reactions proceeded stereoselectively with the substituted vinyl silane **10** and vinyl boronic acid **11** isolated in high yields (entries 5 and 6).

Table 2. Stereoselective Synthesis of Substituted 1,2-Diphenyl Alkenes

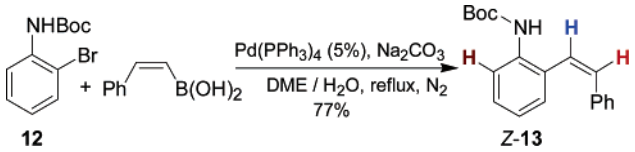


entry	product	E	*Z*:*E* ratio[a]	yield (%)[b]
1	**6**	CH_2OH	98:2	32[c]
2	**7**	CHPhOH	98:2	75
3	**8**	CHO	3:97	44[d]
4	**9**	Me	2:98	56
5	**10**	$Si(CH_3)_3$	98:2	68
6	**11**	$B(OH)_2$	2:98	60

[a] By ^1H NMR analysis. [b] Isolated purified yield. [c] 60% of *trans*-stilbene also isolated. [d] Isomerization during workup.

An additional synthetic scope of this methodology would exist if regioselective vinyl lithiation of unsymmetrical *cis*-stilbenes could be accomplished. Expanding upon the direct *ortho*-lithiation and the lateral lithiation methods, as shown in Scheme 1, it would be a formidable selectivity accomplishment if vinyl carbolithiation could be supressed (by the double bond stereochemistry) and a regioselective directed vinyl lithiation achieved. We chose the NHBoc group as a test directing group as it is a known direct *ortho*-lithiating group of moderate strength.[12] Compound **13** can be readily stereoselectively synthesized by the Suzuki−Miyaura cross coupling of *cis*-2-phenylvinylboronic acid with the Boc-protected 2-bromoaniline **12** (Scheme 3). The

Scheme 3. Synthesis of *cis*-2-Styryl-phenyl-carbamic Acid *tert*-Butyl Ester **13**[a]

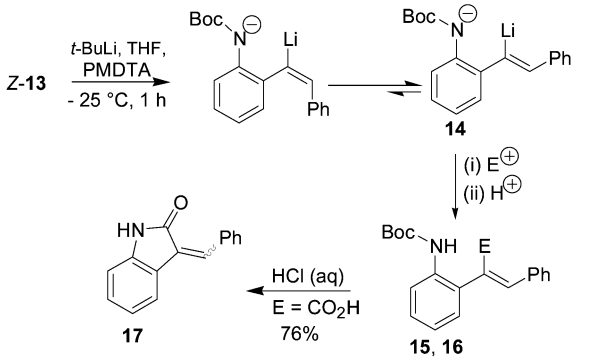


[a] Isolated purified yield.

selective deprotonation of an unsymmetrical stilbene such as **13** poses an interesting challenge as either vinylic protons (blue and red) or the *ortho*-proton to the Boc-protected aniline (brown) can be identified as plausable sites of lithiation.

The lithiation of *Z*-**13** with *t*-BuLi in THF in the presence of PMDTA additive generated the vinyl lithiated intermediate **14**, as judged by the product analysis following subsequent reaction with electrophiles. Deuteration with CD_3OD generated the vinyl-deuterated *trans*-stilbene **15** and reaction with solid CO_2 gave a 60% isolated yield of (*Z*)-2-(2-*tert*-butoxycarbonylamino-phenyl)-3-phenyl-acrylic acid **16**.[13] The double bond stereochemistry of **16** was confirmed by X-ray structural analysis (Supporting Information). As demonstration of the potential synthetic utility of this approach, **16** could be readily transformed into the 3-benzylidene-1,3-dihydro-indol-2-one **17** by treatment with aqueous acid.[14]

Scheme 4. Directed Vinyl Lithiation of *Z*-**13**[a]



entry	product	electrophile	E	*Z*:*E*	yield (%)
1	**15**	CD_3OD	D	2:98	60
2	**16**	CO_2	CO_2H	98:2	60

[a] Isolated purified yield.

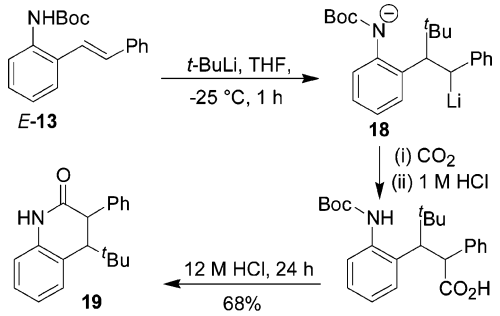
The chemoselectivity observed for *Z*-**13** is striking when compared to our recent report of the regioselective *carbo*-

(11) For a related study involving direct *ortho* lithiation, see: Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

(12) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

lithiation of *E*-**13** with *t*-BuLi under similar reaction conditions (Scheme 5). For this isomer, trapping of the benzylic lithiated intermediate **18** with CO_2 and subsequent cyclization provided an entry into the 3,4-dihydro-1*H*-quinolin-2-one ring system **19**.[15]

Scheme 5. Regioselective Carbolithiation of *E*-**13**[15]



Further insight to the synthetic potential of this novel lithiation approach was revealed by the conversion of *Z*-**13** in a 61% yield to 3-benzylidene-indole-2-ol **20** by directed vinyl lithiation followed by treatment with DMF and in situ cyclization. Compound **20** proved to be a versatile substrate for the synthesis of C-3 functionalized indoles.[16] Room-temperature reaction of **20** in CH_3CN with ethanol using 10% *p*-toluene sulfonic acid (tsa) generated the ethyl ether substituted indole **21** in excellent yield. This could be rationalized by the acid-catalyzed formation of an indolium cation, which would act as a reactive electrophile undergoing addition of the alcohol.[17] Treatment with thionyl chloride provided access to the chlorinated indole derivative **22** in 94% yield. Alternatively, $BF_3{\cdot}OEt_2$-mediated allyltrimethyl silane addition was efficiently achieved in CH_2Cl_2 at −78 °C to provide a route to the indole **23**.

(13) A carbolithiation by-product was isolated in 7% yield.

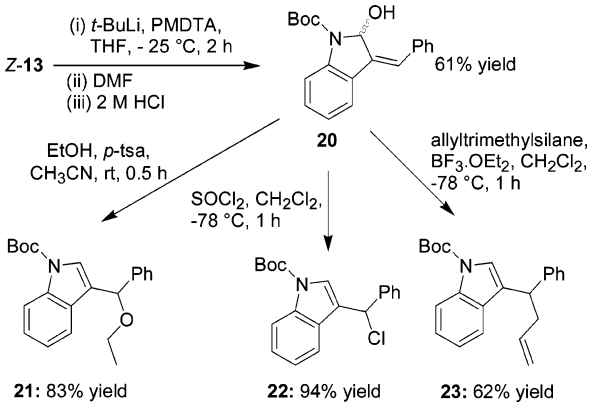
(14) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043. The double bond stereochemistry of **17** is acid-sensitive.

(15) Hogan, A.-M. L.; O'Shea, D. F. *Org. Lett.* **2006**, *8*, 3769.

(16) For carbolithiation approaches to indole synthesis, see: (a) Coleman, C. M.; O'Shea, D. F. *J. Am. Chem. Soc.* **2003**, *125*, 4054. (b) Kessler, A.; Coleman, C. M.; Charoenying, P.; O'Shea, D. F. *J. Org. Chem.* **2004**, *69*, 7836. (c) Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935. (d) Hogan, A-M. L.; O'Shea, D. F. *J. Am. Chem. Soc.* **2006**, *128*, 10360.

(17) For related reactions, see: (a) Howe, E. E.; Zambito, A. J.; Snyder, H. R.; Tishler, M. *J. Am. Chem. Soc.* **1945**, *67*, 38. (b) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869.

Scheme 6. C-3 Substituted Indole Synthesis[a]



[a] Isolated purified yield.

In summary, we have shown that stilbene stereochemistry can modulate its reactivity with butyllithium from vinyl carbolithiation for the *trans* isomer to vinyl deprotonation for the *cis* counterparts. 1-Lithio-1,2-diphenylethene generated by the direct lithiation of *cis*-stilbene is a versatile intermediate for the stereoselective synthesis of corresponding trisubstituted alkenes. Directed vinyl lithiation of the unsymmetrical *cis*-stilbene 2-styryl-phenyl-carbamic acid *tert*-butyl ester gives a new route into the indole ring system. The scope of this directed vinyl lithiation methodology for other directing groups is currently under investigation.

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Supporting Information Available: Procedures, analytical data, and NMR spectra for all new compounds and crystallographic data of **16** in CIF format. This material is free of charge via the Internet at http://pubs.acs.org

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