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Stereoselective Access to Substituted Enediyne Building Blocks

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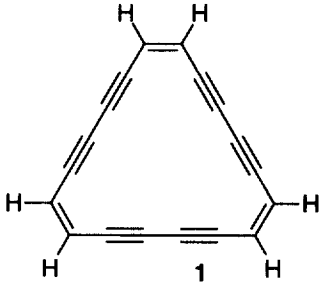
Abstract: Intermolecular coupling-elimination of disubstituted propargyl bromides gives rise to differentially substituted 3-hexen-1,5-diynes with E:Z selectivity as high as 100:1. Application of the methodology in the synthesis of key nanomaterial building blocks is demonstrated.

Conjugated 3-ene-1,5-diynes represent important chemical building blocks, the subunit found in systems as diverse as antitumor antibiotics, synthetic polymers and designed nanostructures. Representative examples of enediyne materials include the (explosive) dehydroannulenes **1**,[1] carbon-rod polydiacetylenes **2**,[2] and the molecular device **3** (R=dihydroazulene).[3] Though a number of methods are available for the construction of the *E* and *Z* enediynes needed for these materials they often present practical limitations and are specific to a narrow range of substrates.[4]



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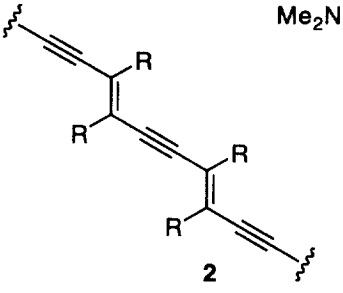

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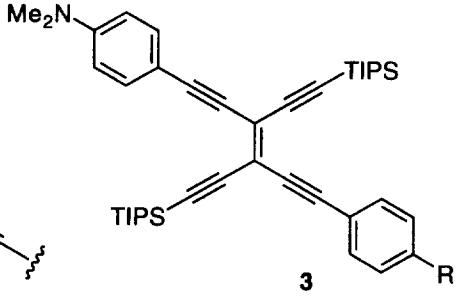

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Based on prior success in the the preparation of *Z* bis-trimethylsilyl-3-hexene-1,5-diyne using a carbenoid coupling-elimination reaction,[5] we became interested in modification of the process to provide a direct route to substituted core enediyne building blocks.[6] Specifically, we envisioned that conversion of substituted propargyl bromides **4** into the corresponding metallocarbenoids would allow intermolecular coupling to yield intermediate bromodiynes **5**, which, with appropriate choice of substituents (R_2) would eliminate via anti conformer **5b** to provide stereoselective access to *E* enediynes **6** (Scheme 1). Such a method would offer a clear advantage over the alternate Pd catalyzed approach to **6** wherein vinyl halides **7** are coupled with the desired alkyne. Such pathways, while effective in the case of *Z* enediynes are often problematic with *E* haloalkenes due to competing alkyne oligomerization reactions.

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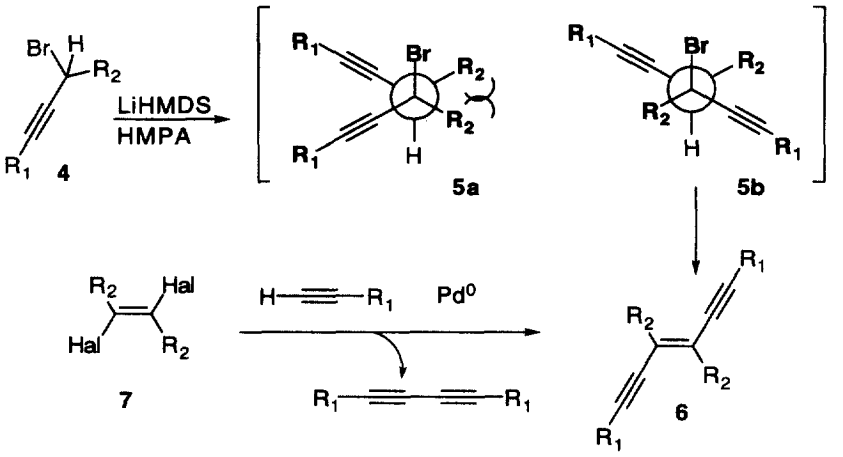
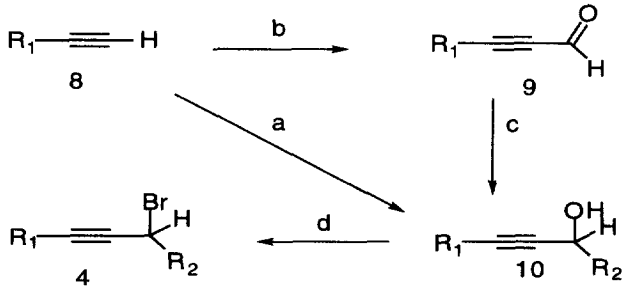


Scheme 1. *in situ* Coupling-Elimination Strategy for Synthesis of *E* Enediynes

A variety of disubstituted propargylic bromides were thus prepared (Scheme 2). The commercial availability of many common alkynes permitted the assembly of a diverse range of substrates using conventional methodology. Particularly noteworthy were the excellent yields of propargylic aldehydes **9** obtained by direct formylation of alkynes **8** using procedure developed by Cai and co-workers at Merck.[7] A modification of the procedure of Smith was adopted for bromination,[8] resulting in efficient conversion and circumventing ring opening (**10** R_2= cyclopropyl) encountered using alternate methods.

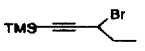
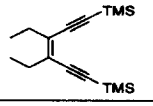
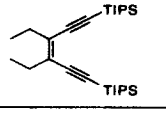
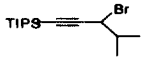
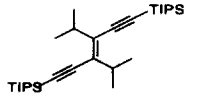
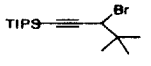
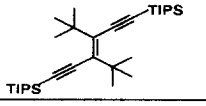
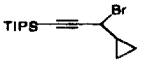
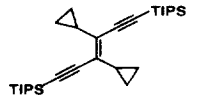
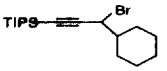
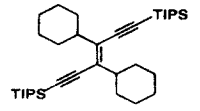
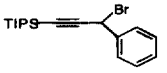
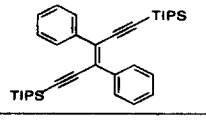
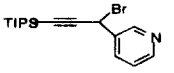
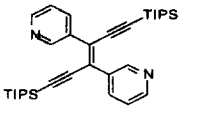
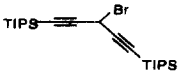
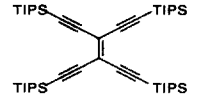
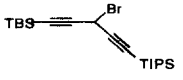
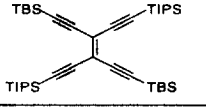


Scheme 2. Complimentary Routes to Propargylic Bromides

Legend: (a) BuLi,R_2CHO [90-99%]; (b)BuLi/DMF/KH_2PO_4 [93-98%];[7] (c) R_2Li [90-99%]; (d) $Br_2/PPh_3/CH_2Cl_2$, or Br_2 added to PPh_3/**10**/DMF/2,6-lutidine–15°C [80-95%].[8]

The coupling-elimination protocol was then investigated, involving slow addition of a mixture of LiHMDS (or LDA) and HMPA to a THF solution of bromide at –80°C. As predicted (Scheme 1) the subtle stereochemical bias that the vinyl substituents impart had a profound influence on product geometric isomer ratio (Table 1). Surprisingly, the ethyl substituent retained stereoselectivity in favor of the Z isomer (entries 1-2), suggesting the possibility of an additional syn elimination pathway which augments elimination via **5a**.[5] However, moving

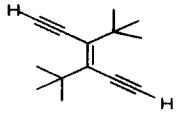
Table 1. Tetrasubstituted Enediynes via Coupling-Elimination[a]

Entry	Substrate	Product	%Yield[b]	E : Z[c]
1			75	1:2
2			85	1:3
3			87	>100:1
4[d]			70	>100:1
5			79	15:1
6			80	>100:1
7			95	11:1
8[e]			82	6:1
9			95	-
10			80	1:1

Legend: (a) LiHMDS/HMPA/THF –80°C/2h;(b) isolated yields following SGC; (c) determined via GPC of crude mixtures. Z:E isomers assigned using authentic samples; (d) LDA/HMPA/THF –80°C through RT/12h; (e) bromide decomposes rapidly.

to the isopropyl derivatives and beyond, selectivity was reversed and greatly enhanced in favor of the *E* isomer. In order to reduce product volatility and the potential for alkyne-allene isomerization, the triisopropylsilyl group was adopted for the entire series. The route provided ready access to disubstituted

primary, secondary, tertiary, cycloalkyl, aryl and heteroaryl enediynes (Table 1). In all cases examined, *in situ* elimination of the intermediate bromodiyne **5** resulted in direct formation of the enediynes **6**, in good to excellent yield. The stereoselectivity in the process correlates well with steric bulk of the vinyl substituent, consistent with antiperiplanar alignment for *in situ* E_2 elimination (**5b**). Exceptionally high levels of stereoselectivity are obtained in many cases (entries 3,4,6) and recovered yields are high even with sensitive substrates (entries 5, 8). To demonstrate the utility of the process, in the case of the diphenyl enediyne (entry 7) Pd catalyzed coupling of **8** [R=TIPS] with **7** [R_2=Ph, Hal=Cl] was attempted. *Even under a range of conditions, the maximum yield of E enediyne obtained was <1%, confirming the benefit of our method.* The synthesis of tetraalkynyl systems is also noteworthy [entries 9-10], complimenting existing stepwise methods.[4] Transformation of the products generated gives access to a number of useful synthons. Desilylation under standard conditions (TBAF, THF, -10°C / 0.5h) gave the corresponding terminal alkynes in every case examined. Substrates **11-14** and others (Table 1) can be expected to find application in metal catalyzed oligomerization sequences,[2] and possibly in the design of enediyne based molecular devices.[2-4]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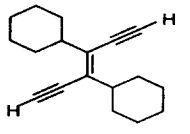
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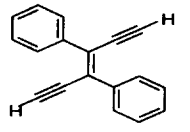
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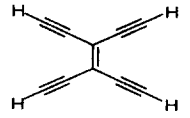
14

In summary, a carbenoid coupling-elimination route to substituted *E* enediynes has been demonstrated. The high levels of stereochemical control and chemical efficiency afforded by the process render it an effective alternative to existing methods for enediyne synthesis. Application of the process is the subject of ongoing investigation.[9]

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9. We wish to thank the NIH [1RO1GM57123] for generous financial support.