

Stereoselective synthesis of tetrasubstituted alkenes via a sequential carbocupration and a new sulfur–lithium exchange

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Letter

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Keywords:
alkenes; carbometalation; copper; regioselectivity; stereoselectivity

Beilstein J. Org. Chem. **2012**, *8*, 2202–2206.
doi:10.3762/bjoc.8.248

Received: 17 October 2012
Accepted: 05 December 2012
Published: 18 December 2012

This article is part of the Thematic Series "Carbometallation chemistry".

Guest Editor: I. Marek

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Abstract

We have designed a new sequential carbocupration and sulfur–lithium exchange that leads stereo- and regioselectively to trisubstituted alkenyllithiums. Subsequent trapping with various electrophiles yields tetrasubstituted olefins with good control of the double-bond geometry (*E/Z* ratio up to 99:1). The novel sulfur–lithium exchange could be extended to the stereoselective preparation of *Z*-styryl lithium derivatives with almost complete retention of the double-bond geometry.

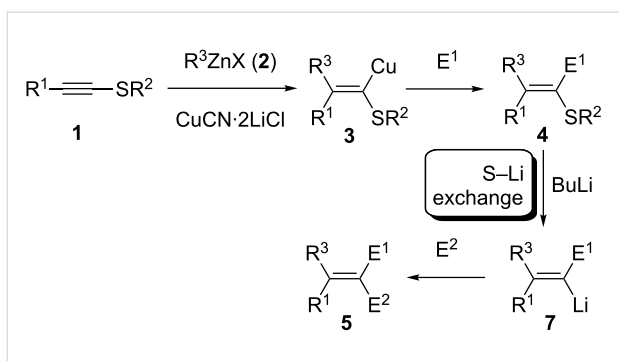
Introduction

The stereoselective synthesis of tetrasubstituted alkenes is an important synthetic goal, which may be achieved by carbometallation methods [1-9]. The Normant carbocupration of terminal acetylenes allows the stereoselective preparation of trisubstituted alkenes with excellent *E/Z* ratio [10-12]. However, in order to obtain tetrasubstituted alkenes, a carbometallation of an internal alkene is required. This reaction is usually difficult due to steric hindrance and proceeds only if electron-withdrawing groups are attached to the alkyne unit to facilitate the carbometallation step. Recently, we studied the chemistry of alkenyl sulfides and their use for carbometallation extensively [13].

Therefore, we envisioned using an alkynyl thioether such as **1** as an activated alkyne. After a carbocupration of the alkynyl

thioether **1** with the organozinc reagent **2** in the presence of CuCN·2LiCl [14], the alkenylcopper species **3** should be obtained. Stereoselective quenching with an electrophile (E^1) should afford the tetrasubstituted alkenyl thioether **4**. Extensive experimentation showed that thioethers **4** do not undergo Ni- or Pd-catalyzed cross couplings leading to products of type **5** ($R = Me, Ph$) [15,16]. Thus, we designed a new sulfur–lithium exchange (Scheme 1).

Sulfur–lithium exchanges proceed only readily with sulfoxides [17-19] and these reactions are often complicated by radical side reactions [20,21]. This new, direct sulfur–lithium exchange on an alkenyl thioether of type **4** involves the use of a bromobiphenyl R-group, which by treatment with BuLi at low



Scheme 1: Synthesis of tetrasubstituted olefins by a successive carbocupration and S-Li exchange.

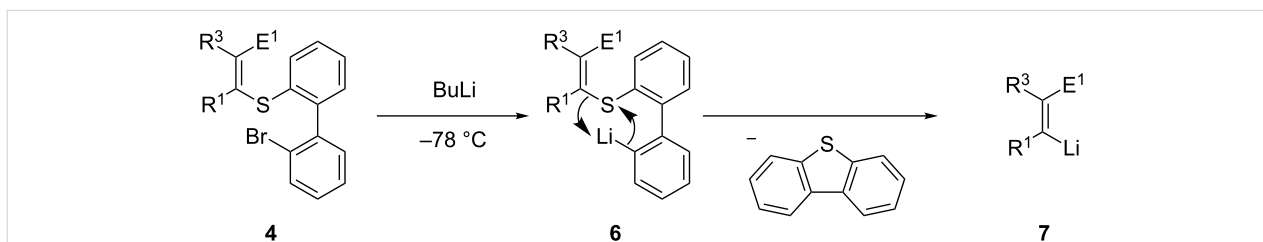
temperatures, undergoes first a fast bromine–lithium exchange leading to an intermediate biphenyllithium derivative of type 6, followed by an intramolecular ring-closing sulfur–lithium exchange [22] leading to the desired alkenyllithium 7 (Scheme 2).

Subsequent quenching with a different electrophile E^2 should afford the tetrasubstituted alkene of type 5; (Scheme 1). Herein,

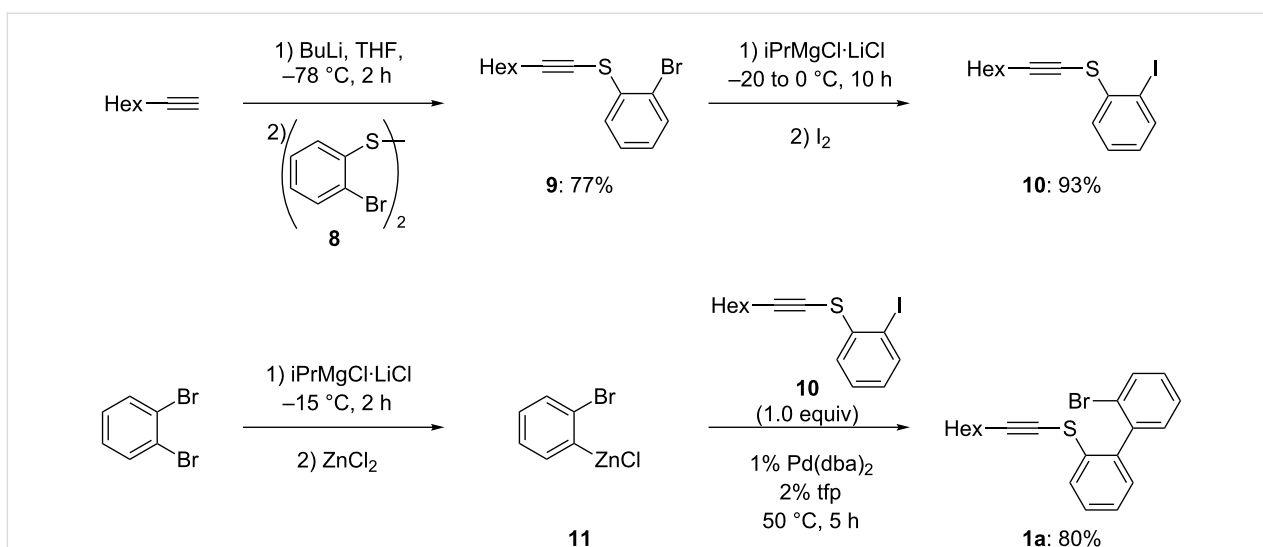
we demonstrate the feasibility of this methodology and thus prepare tetrasubstituted alkenes with *E/Z* stereoselectivities up to 99:1. Furthermore, we show that this sulfur–lithium exchange can be extended to the stereoselective preparation of *Z*-styryl derivatives.

Results and Discussion

First, we wish to report the synthesis of the alkynyl biphenyl thioether **1a** required for the carbometalation step. Thus, octyne was deprotonated with butyllithium (1.1 equiv, THF, -78°C , 2 h) followed by the addition of the diaryl disulfide [23] (**8**): 1.1 equiv, -78°C to 25°C , 3 h) providing the bromothioether **9** in 77% yield. Direct Pd-catalyzed Negishi cross-coupling [24–28] of **9** with an arylzinc derivative failed. However, the bromide **9** could be readily converted to the corresponding iodide **10** by a bromine–magnesium exchange using $iPrMgCl \cdot LiCl$ [29–35] followed by iodolysis leading to the iodide **10** in 93% yield. Treatment of 1,2-dibromobenzene with $iPrMgCl \cdot LiCl$ at -15°C for 2 h followed by a transmetalation with $ZnCl_2$ gives the required zinc reagent **11**, which undergoes a Negishi cross-coupling with the iodide **10** at 50°C (5 h) leading to the alkynyl thioether **1a** in 80% yield (Scheme 3).



Scheme 2: Proposed mechanism of the sulfur–lithium exchange starting with the alkenyl thioether **4**.



Scheme 3: Synthesis of the precursor **1a**.

The harsh cross-coupling conditions may be due both to the presence of the ortho-bromo substitution in the zinc reagent **11**, which considerably reduces the nucleophilicity of this arylzinc reagent by inductive effects, and also to the sulfur atom of the electrophile, which poisons the Pd catalyst. With the thioether **1a** in hand, we have performed the Normant carbocupration with di-*para*-anisylzinc (An_2Zn : **2a**) according to a procedure previously developed by us [36]. Thus, the reaction of **1a** (1.0 equiv) with An_2Zn (1.5 equiv, THF) in the presence of $CuCN \cdot 2LiCl$ (1.5 equiv) at 25 °C for 8 h produces the intermediate copper reagent **3a**, which, after allylation with allyl bromide, provides the thioether **4a** in 84% yield and an *E/Z* ratio of 99:1 (Scheme 4). The reaction of **3a** with other typical electrophiles is possible, but proceeds in moderate yields due to the low reactivity of copper reagent **3a**.

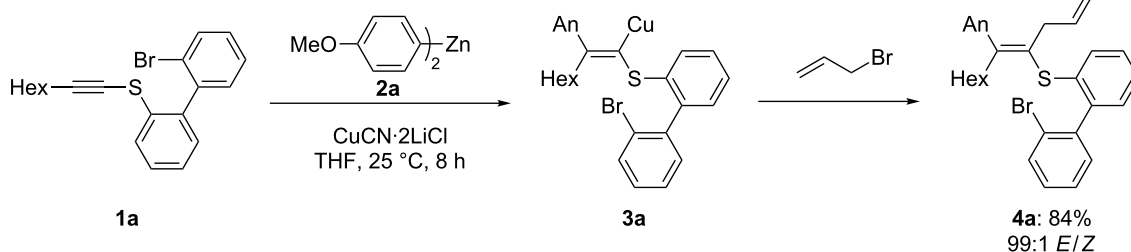
The bromothioether **4a** was then treated with *s*-BuLi (1.3 equiv, –78 °C, 10 min), leading to the formation of the intermediate aryllithium **6a**, which undergoes the desired intramolecular sulfur–lithium exchange affording the alkenyllithium reagent **7a** (Scheme 5).

This alkenyllithium was quenched with typical electrophiles with a high retention of the double-bond geometry. Thus, the treatment of **7a** with EtI (2 equiv, –78 °C, 15 min) provides the tetrasubstituted alkene **5a** in 75% yield and an *E/Z* ratio of 1:99. Direct carboxylation by the reaction with ethyl chloroformate

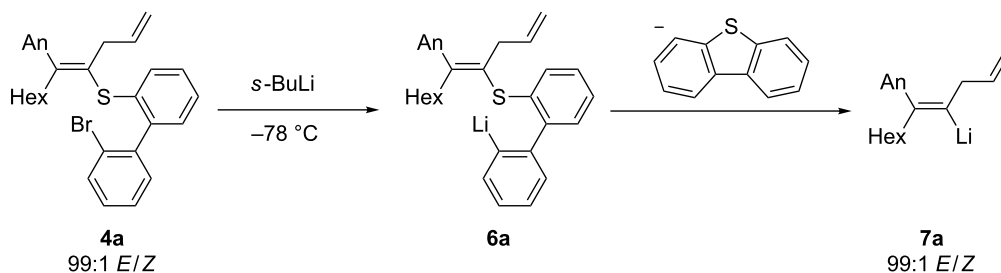
(1.1 equiv, –78 °C, 15 min) furnishes the corresponding unsaturated ethylester **5b** in 55% isolated yield and an *E/Z* ratio of 95:5. Finally, a copper-catalyzed allylation with ethyl 2-(bromomethyl)acrylate [37] (1.5 equiv, –78 to 0 °C, 2 h) affords the triene **5c** in 55% yield and an *E/Z* ratio of 99:1 (Scheme 6).

These quenching experiments demonstrate that this new method based on a successive carbocupration and sulfur–lithium exchange allows the stereoselective preparation of various tetrasubstituted alkenes. Since Normant has shown that various alkylcopper species add to alkynyl thioethers [38–40], the use of a bromobiphenyl substituent (R^2) on the sulfur may allow a general stereoselective synthesis of tetra-substituted alkenes.

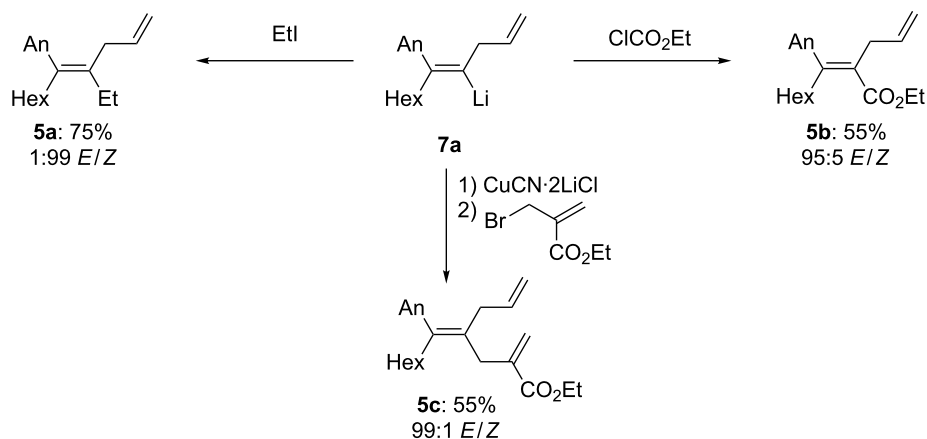
In order to prove that this new sulfur–lithium exchange has further applications in the stereoselective synthesis of alkenes, we prepared the *Z*-alkenyl thioether **12** starting from 2,2'-dibromobiphenyl. Thus, the performance of a double bromine–lithium exchange with BuLi (1.1 equiv, –78 °C, 0.25 h) followed by a quenching with tetramethylthiuram disulfide (1.1 equiv, –78 to 25 °C, 12 h) furnishes the dithiocarbamate **13** in 82% yield. Since the reduction to the free thiol is hard to achieve due to dibenzothiophene formation [41], we performed an in situ deprotection and stereoselective addition to phenylacetylene [42] (1.5 equiv, 1.25 equiv NaOEt, EtOH,



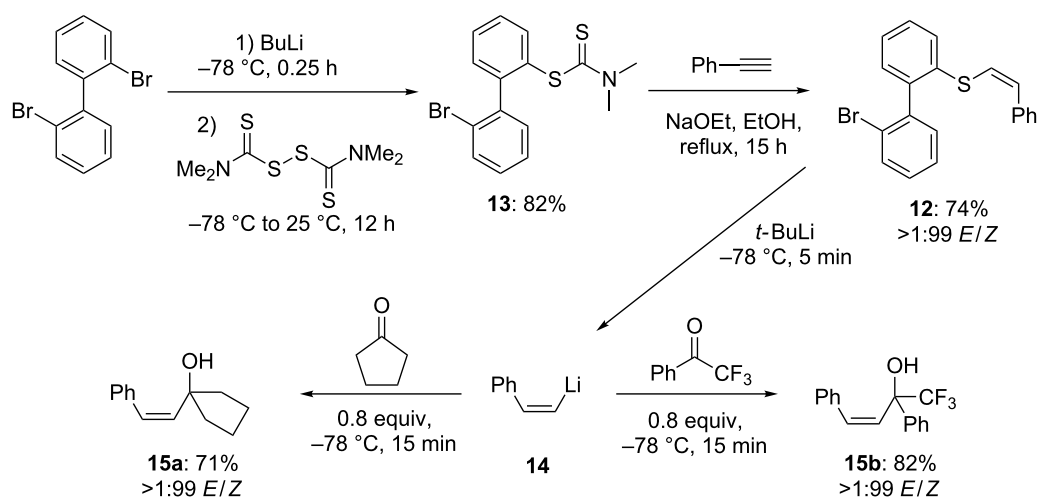
Scheme 4: Carbocupration of the thioether **1a** leading to the tetrasubstituted alkene **4a**.



Scheme 5: Synthesis of the alkenyllithium reagent **7a** by an S–Li exchange.



Scheme 6: Quenching of the alkynyllithium **7a**. (Product ratios and diastereoselectivities were determined by ^1H - and 2D-NMR.)



Scheme 7: Synthesis and quenching of *Z*-styryllithium.

reflux, 15 h) yielding the *Z*-alkenyl thioether **12** in 74% yield (Scheme 7).

Treatment of **12** with *t*-BuLi (1.6 equiv, $-78\text{ }^\circ\text{C}$, 10 min) provides directly the *Z*-styryllithium **14**, which stereoselectively adds to α,α,α -trifluoroacetophenone (0.8 equiv, $-78\text{ }^\circ\text{C}$, 0.5 h) and cyclopentanone (0.8 equiv, $-78\text{ }^\circ\text{C}$, 0.5 h) to afford the expected tertiary allylic alcohols **15a–b** in 71–82% yield and *E/Z* ratios of >1:99.

Conclusion

In summary, we have reported tetrasubstituted olefins with excellent *E/Z* ratios using a sequential carbocupration and a new sulfur–lithium exchange involving an alkenyl thioether bearing a 2'-bromobiphenyl substituent, which triggers efficiently the

sulfur–lithium exchange. Extension to the stereoselective preparation of *Z*-styryllithium was shown.

Supporting Information

Supporting Information File 1

Experimental details and characterization data of new compounds.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-248-S1.pdf>]

Acknowledgements

We thank the Fonds der Chemischen Industrie and the European Research Council (ERC) for financial support. We also

thank BASF SE (Ludwigshafen), Heraeus Holding GmbH (Hanau) and Rockwood Lithium GmbH (Frankfurt) for the generous donation of chemicals.

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