Abstract
We have designed a new sequential carbocupration and sulfur–lithium exchange that leads stereo- and regioselectively to trisubsti-
tuted 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 carbometalation
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 carbometalation 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 alkyn unit to facilitate the carbometalation step. Recently, we studied the chemistry of alkenyl sulfides and their use for carbometalation 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 bromo-
biphenyl 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·LiCl [29-35] followed by iodolysis leading to the iodide 10 in 93% yield. Treatment of 1,2-dibromobenzene with iPrMgCl·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).
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 (An2Zn: 2a) according to a procedure previously developed by us [36]. Thus, the reaction of 1a (1.0 equiv) with An2Zn (1.5 equiv, THF) in the presence of CuCN·2LiCl (1.5 equiv) at 25 °C for 8 h produces the intermediate copper reagent 3a, which, after alkylation 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 alkylation 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 (R2) 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 6: Quenching of the alkynyllithium 7a. (Product ratios and diastereoselectivities were determined by $^1$H- 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, $-78$ °C, 10 min) provides directly the $Z$-styryllithium 14, which stereoselectively adds to $\alpha,\alpha,\alpha$-trifluoroacetophenone (0.8 equiv, $-78$ °C, 0.5 h) and cyclopentanone (0.8 equiv, $-78$ °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]

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References

2. Das, J. P.; Chechik, H.; Marek, I. Nat. Chem. 2009, 1, 128. doi:10.1038/ncchem.131

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