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Diastereoselective Copper-Mediated Cross-Couplings between Stereodefined Secondary Alkylcoppers with Bromoalkynes

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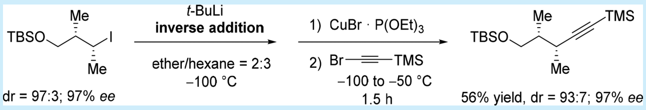
Supporting Information



ABSTRACT: A copper(I)-mediated cross-coupling of stereodefined secondary alkyllithiums with bromoalkynes provided stereodefined alkynes with high diastereoselectivity (dr up to 98:2). This cross-coupling was extended to various secondary alkyllithiums bearing a remote oxygen functionality, and the alkyne synthesis was also performed with optically enriched alkyl iodides (up to 99% *ee*) providing, after cross-coupling, alkynes bearing two stereocenters (dr = 93:7; up to 99% *ee*).

Cross-coupling reactions have been successfully used to prepare polyfunctional alkynes. Thus, the Sonogashira[1] and Negishi[2] cross-couplings allow linking alkynyl moieties with C_{sp^2}-unsaturated halides in the presence of copper[3] or palladium[4] catalysts. The alkyne acts as a nucleophile in these reactions. Alternatively, 1-halogenoalkynes react with zinc organometallics or mixed copper−zinc reagents,[5] providing alkylated alkynes. The use of catalytic amounts of copper salts[6] or palladium catalysts[7] in such cross-couplings has been reported. However, the preparation of alkynes bearing chiral centers in the α-position is still a challenge.[8]

Recently, we have reported that secondary alkyl iodides such as **1** undergo an I/Li exchange, leading to the corresponding secondary alkyllithium reagents of type **2** with retention of configuration using *t*-BuLi (2.5 equiv, inverse addition).[9] We have shown that these secondary alkyllithium reagents undergo a stereoretentive transmetalation to the corresponding alkylcopper reagents of type **3**. The use of $CuBr{\cdot}P(OEt)_3$[10] as a soluble copper salt was essential for achieving high stereoselectivity.[11] These secondary alkylcopper reagents react with activated alkynes, allylic halides, and epoxides with retention of configuration.[9d,11]

Herein, we report a successful cross-coupling reaction of stereodefined secondary alkylcopper reagents of type **3** with 1-bromoalkynes (**4**), leading to alkylated alkynes of type **5** bearing a chiral side chain with high retention of configuration (up to 98:2; Scheme 1).

In preliminary experiments, we have studied the thermal and configurational stability of such alkylcopper species **3**. Thus, we have treated the diastereomerically enriched secondary alkyl iodide (*anti*-**1a**; dr = 1:99) with *t*-BuLi (hexane−ether, −100 °C, 1 min) followed by the addition of $CuBr{\cdot}P(OEt)_3$ (2 equiv, −100 °C), leading to the corresponding alkylcopper reagent *anti*-**3a** (Table 1). After stirring the solution at −70 °C for 10 min or for 1 h, benzoyl chloride (3.0 equiv)[12] was added at −70 °C, leading to the desired ketone *anti*-**6** in 59% yield (dr = 3:97; entry 1) and 38% yield (dr = 6:94; entry 2), respectively. This result indicated the high configurational stability of *anti*-**3a** at −70 °C.

Scheme 1. Enantioselective Synthesis of Stereodefined Alkynes Starting from Optically Enriched Iodides via I/Li-Exchange, Transmetalation to Copper Reagents, and Quench with 1-Bromoalkynes

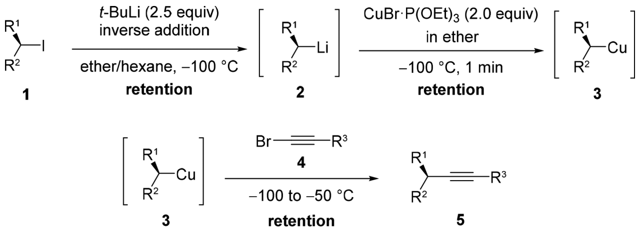
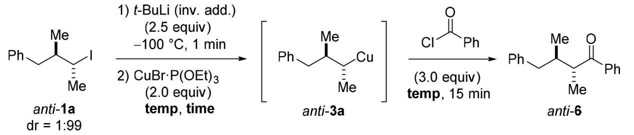


Table 1. Effect of Temperature and Time on the Stability of Secondary Alkylcopper Reagent *anti*-3a



entry	temp (°C)	time (min)	yield (%)[a]	dr[a]
1	−70	10	59	3:97
2	−70	60	38	6:94
3	−50	10	50	5:95
4	−50	60	37	7:93
5	−30	10	41	6:94
6	−30	60	26	50:50

[a] The diastereoselectivity (dr; *syn*/*anti* ratio) and yield were determined by capillary GC using undecane as internal standard.

Stirring the copper intermediate (*anti*-**3a**) at −50 °C (for 10 min or 1 h, entries 3 and 4) or at −30 °C for 10 min (entry 5) led, after benzoylation, to a yield decrease of *anti*-**6**, but only to a marginal loss of diastereoselectivity. However, stirring *anti*-**3a**

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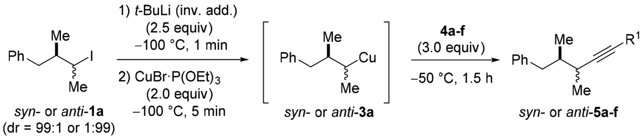
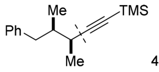
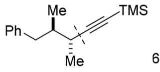
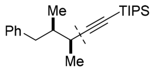
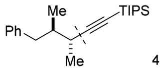
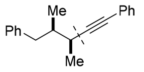
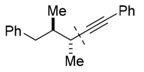
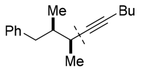
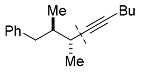
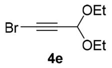
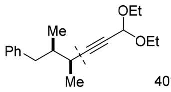
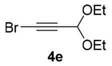
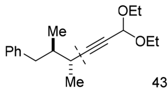
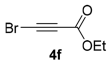
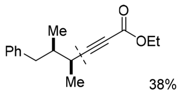
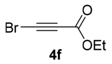
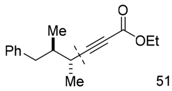
Table 2. Stereoselective Preparation of Secondary *syn*- and *anti*-Alkylated Alkynes (5) Obtained by the Cross-Coupling of *syn*- and *anti*-Alkylcopper (3a) with 1-Bromoalkynes of Type 4



entry	alkylcopper	electrophile	product of type 5 [a,b]
1	*syn*-**3a**	$Br-C\equiv C-TMS$ **4a**	 *syn*-**5a**: 42%; dr = 93:7
2	*anti*-**3a**	$Br-C\equiv C-TMS$ **4a**	 *anti*-**5a**: 66%; dr = 2:98
3	*syn*-**3a**	$Br-C\equiv C-TIPS$ **4b**	 *syn*-**5b**: 29%, dr = 98:2
4	*anti*-**3a**	$Br-C\equiv C-TIPS$ **4b**	 *anti*-**5b**: 46%; dr = 4:96
5	*syn*-**3a**	$Br-C\equiv C-Ph$ **4c**	 *syn*-**5c**: 43%; dr = 93:7
6	*anti*-**3a**	$Br-C\equiv C-Ph$ **4c**	 *anti*-**5c**: 51%; dr = 4:96
7	*syn*-**3a**	$Br-C\equiv C-Bu$ **4d**	 *syn*-**5d**: 44%; dr = 97:3
8	*anti*-**3a**	$Br-C\equiv C-Bu$ **4d**	 *anti*-**5d**: 46%; dr = 8:92
9	*syn*-**3a**	 **4e**	 *syn*-**5e**: 40%; dr = 97:3
10	*anti*-**3a**	 **4e**	 *anti*-**5e**: 43%; dr = 8:92
11	*syn*-**3a**	 **4f**	 *syn*-**5f**: 38%; dr = 89:11
12	*anti*-**3a**	 **4f**	 *anti*-**5f**: 51%; dr = 4:96

[a]Isolated yield. [b]dr (*syn*/*anti* ratio) was determined by ^{1}H and ^{13}C NMR analysis.

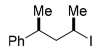
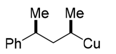
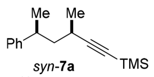
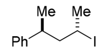
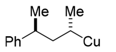
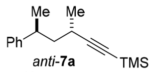
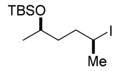
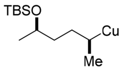
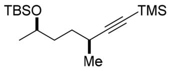
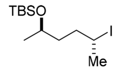
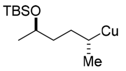
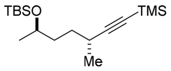
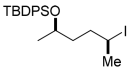
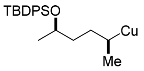
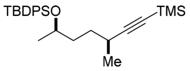
at −30 °C for 1 h led to a complete epimerization, as well as to a significant yield decrease (entry 6). This indicated that secondary alkylcoppers of type **3** are configurationally stable at −30 °C for only a short time.

After having determined the configurational stability of the alkylcopper reagents **3**, we have performed a cross-coupling of the diastereomerically defined *syn*- and *anti*-secondary alkylcopper reagents (**3a**) with a range of alkynyl bromides of type **4**, leading to the corresponding *syn*- and *anti*-alkynes of type **5**.

Typically, the secondary alkylcopper reagent (*syn*- or *anti*-**3a**) was generated as described above and treated with a bromoalkyne of type **4** (3.0 equiv) at −100 °C. The reaction mixture was allowed to warm to −50 °C within 10 min and was stirred at this temperature for 1.5 h to ensure complete conversion. After workup, the alkynes **5a−f** were isolated in 29−66% yields (Table 2). In most cases, a high retention of configuration between the two adjacent centers was observed, and only the cross-coupling of **4f** with *syn*-**3a** led to more than 10% epimerization (entry 11).

This cross-coupling was extended to a range of secondary alkylcopper reagents of type **3** prepared by an I/Li-exchange reaction of the secondary alkyl iodides **1**. Thus, the reaction of the *syn*- and *anti*-alkyl iodides (*syn*-**1b** and *anti*-**1b**) with *t*-BuLi (2.5 equiv, −100 °C), followed by the addition of CuBr·P(OEt)$_3$ (2.0 equiv, −100 °C, 5 min), provided the intermediate alkylcopper reagents (*syn*- and *anti*-**3b**), which underwent a smooth cross-coupling with 1-bromo-2-(trimethylsilyl)ethyne (**4a**), leading to the expected alkynes *syn*- and *anti*-**7a** in 48−53% yield with a dr of 89:11 and 9:91, respectively (entries 1 and 2, Table 3). Similarly, the *syn*- and *anti*-alkyl iodides (*syn*- and *anti*-**1c**) were converted to the corresponding copper reagents and gave, after cross-coupling with **4a**, the diastereomerically enriched alkynes *syn*-**7b** (58% yield; dr = 87:13; entry 3) and *anti*-**7b** (51% yield; dr = 15:85; entry 4). The use of a more bulky silyl protecting group such as TBDPS (**1d**) improved the diastereoselectivity and yield of the cross-coupling reaction with **4a**, leading to the *syn*-product *syn*-**7c** in 67% yield (dr = 91:9, entry 5).

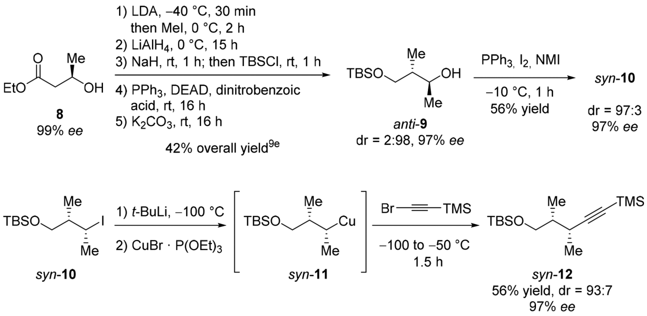
Table 3. Scope of Diastereoconvergent Quenching of Secondary *syn*- and *anti*-Alkylcoppers (3) with 1-Bromoalkyne (4a) Leading to Alkylated Alkynes of Type 7

entry	alkyliodide of type **1**	alyklcopper of type **3**	product of type **5** [a,b]
1	 *syn*-**1b**, dr = 98:2	 *syn*-**3b**	 *syn*-**7a** 53%; dr = 89:11
2	 *anti*-**1b**, dr = 1:99	 *anti*-**3b**	 *anti*-**7a** 48%; dr = 9:91
3	 *syn*-**1c**, dr = 99:1	 *syn*-**3c**	 *syn*-**7b** 58%, dr = 87:13
4	 *anti*-**1c**, dr = 2:98	 *anti*-**3c**	 *anti*-**7b** 51%; dr = 15:85
5	 *syn*-**1d**, dr = 99:1	 *syn*-**3d**	 *syn*-**7c** 67%; dr = 91:9

[a]Isolated yield. [b]dr (*syn*/*anti* ratio) was determined by ^{1}H and ^{13}C NMR analysis.

We have also performed such a cross-coupling with an optically enriched alkyl iodide *syn*-**10** (see Scheme 2). Starting from the commercially available (+)-*R*-hydroxybutyrate **8** (99%

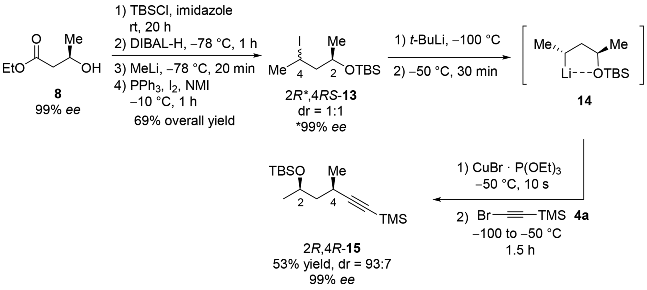
Scheme 2. Preparation of the Chiral Alkyne *syn*-**12** Starting from Optically Enriched Alcohol *anti*-**9**



ee), we have prepared the alcohol *anti*-**9** (dr = 2:98) in 5 steps and 42% overall yield.[9e] This alcohol was converted to the corresponding iodide (*syn*-**10**) with complete inversion of configuration (dr = 97:3) using an Appel reaction.[9] An I/Li exchange, followed by a transmetalation with CuBr·$P(OEt)_3$, furnished the intermediate copper reagent *syn*-**11**, which was converted, after a cross-coupling with **4a**, to the *syn*-alkyne *syn*-**12** in 56% yield and dr = 93:7 (97% *ee*[13]).

Furthermore, the 1,3-functionalized secondary alkyl iodide 2*R*,4*RS*-**13** was prepared starting from **8** in 4 steps[9c] and 69% overall yield (see Scheme 3). The addition of 2*R*,4*RS*-**13** to a solution of *t*-BuLi (inverse addition, 2.5 equiv, −100 °C) led, after epimerization (−50 °C, 30 min),[9c] to the chelate-stabilized lithium reagent **14**. Subsequent transmetalation with CuBr·$P(OEt)_3$ led to the corresponding alkylcopper reagent, which underwent a smooth cross-coupling reaction with **4a**, leading to the enantiomerically enriched alkyne 2*R*,4*R*-**15** in 53% yield and dr = 93:7 (99% *ee*[13]).

Scheme 3. Preparation of the Chiral Alkyne *syn*-**15** Starting from Optically Enriched Alkyl Iodide (**13**)



In summary, we have shown that α-chiral alkynes are readily obtained with high diastereoselectivity using a stereoselective I/Li exchange at −100 °C, followed by a retentive transmetalation with CuBr·$P(OEt)_3$ and further cross-coupling with various bromoalkynes. This method allows preparation of α-chiral alkynes with two stereocontrolled centers in up to 99% *ee*. Extensions of this method are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00699.

Full experimental details; ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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