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Stereoselective Retentive Domino Transmetalations of Secondary Alkyllithium Compounds to Functionalized Secondary Alkylcopper Reagents

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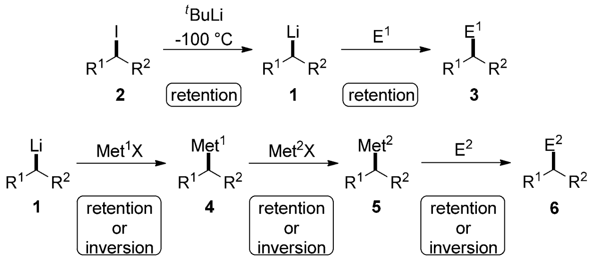
Dedicated to Professor Stephen L. Buchwald on the occasion of his 60th birthday

Abstract: *Functionalized secondary alkyllithium reagents obtained by I/Li exchange from the corresponding secondary alkyl iodides undergo two successive transmetalations with* $Me_3SiCH_2ZnBr{\cdot}LiBr$ *and* $CuBr{\cdot}2\,LiCl{\cdot}Me_2S$ *to provide functionalized secondary alkylcopper compounds with high retention of configuration. These alkylcopper derivatives react further with electrophiles such as alkynyl esters, acid chlorides, allylic chlorides, ketals, ethylene oxide, and 3-iodocyclopentanone with high retention of configuration. A related sequence of transmetalations with MeMgI and* $LaCl_3{\cdot}2\,LiCl$ *allows a retentive addition of secondary alkyllithium reagents to acetone. The influence of the solvent on the configurational stability of secondary alkylzinc reagents is described.*

Organolithium compounds are key intermediates for organic synthesis.[1] Stereoselective transformations involving chiral organolithium compounds, generally α-heteroatom-substituted alkyllithium reagents,[2] have been used for the stereoselective synthesis of various organic molecules. As shown in Scheme 1, we recently developed experimental conditions that allow the stereoselective preparation of nonstabilized functionalized secondary alkyllithium reagents of type **1** from the corresponding alkyl iodides of type **2** through a retentive I/Li exchange. After the addition of an electrophile (E^1), a range of products of type **3** were obtained with an overall retention of configuration.[3] Unfortunately, only limited classes of electrophiles (E^1) can be used with these highly reactive lithium reagents. To expand the synthetic utility of this method, we envisioned performing successive stereoselective transmetalations[4,5] of the alkyllithium reagents **1** with metallic salts (Met^1-X, Met^2-X) to give intermediate organometallic compounds **4** and **5** and then products of type **6** after quenching with a new set of electrophiles (E^2; Scheme 1).[6,7]



Scheme 1. Stereoselective domino transmetalations of nonstabilized secondary alkyllithium reagents.

Although the use of only one stereoselective transmetalation is desirable, previous work in our laboratory as well as stereoselective transmetalations of stabilized alkyllithium reagents performed by the groups of Taylor,[5b] Dieter,[5c] and Coldham[5e] indicated that a first transmetalation from lithium to zinc, followed by a second transmetalation from zinc to copper may give the best results. Furthermore, transmetalations of nonstabilized alkyllithium reagents may be difficult to realize stereoselectively, since Hoffmann has reported that transmetalations of Grignard reagents to alkylcopper or alkylmanganese reagents are complicated by single electron transfer (SET) processes which depend on the nature of the metallic salts or of the electrophiles used.[8] Therefore, we have examined in detail the domino transmetalation[9] of the secondary alkyllithium reagent *anti*-**1a** generated by I/Li exchange from the corresponding functionalized secondary alkyl iodide *anti*-**2a** (Table 1).

A preliminary experiment showed that the carbolithiation of ethyl propiolate (**7a**) with *anti*-**1a** did not provide the expected *anti*-**6a** (Table 1, entry 1). However, the addition of the alkyl iodide *anti*-**2a** (d.r. = 99:1) to a solution of *t*BuLi (2.5 equiv, −100 °C, 1 min; inverse addition[3,10]) in Et_2O followed by the addition of $CuBr{\cdot}2\,LiCl{\cdot}Me_2S$ (2.5 equiv, −100 to −78 °C, 30 min) and ethyl propiolate (**7a**, 5.0 equiv, −78 to −30 °C, 12 h) provided the acrylate (*anti*-**6a**) in 40 % yield, but unfortunately with d.r. = 65:35 (entry 2). This result shows that the direct transmetalation from lithium to copper is not stereoselective under these conditions. This may be explained by an unselective transmetalation step or by an unselective addition reaction of *anti*-**5a** to ethyl propiolate as a consequence of the nature of the copper species or a SET process. Better results were obtained by using domino transmetalations, first with the soluble stabilized zinc organometallic Me_3SiCH_2ZnI[11] (2.5 equiv, −100 °C, 20 min) followed by $CuCl{\cdot}2\,LiCl{\cdot}Me_2S$. In this case, the diastereoselectivity jumped to 83:17 (entry 3). Interestingly, this diastereo-

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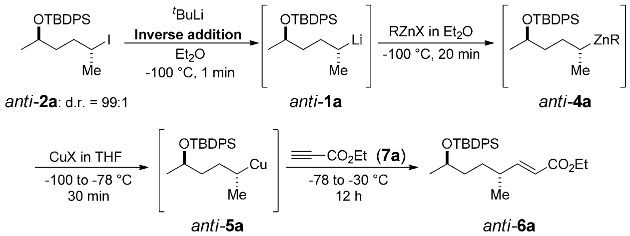
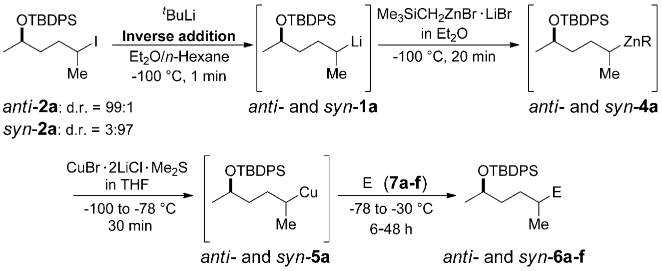
Table 1: Optimization of the domino transmetalations of a secondary alkyllithium reagent *anti*-**1a** to an alkylcopper reagent *anti*-**5a** via an alkylzinc reagent *anti*-**4a**.

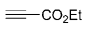
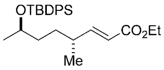
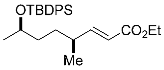
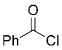
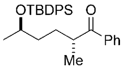
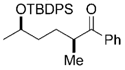
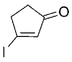
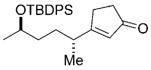
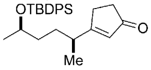
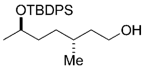
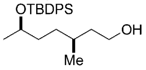
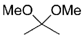
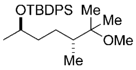
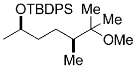
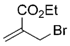
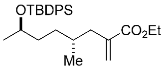
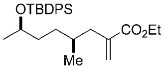


Entry	RZnX	CuX	Yield [%][a]	d.r.[b]
1	–	–	0	–
2	–	$CuBr\cdot Me_2S\cdot 2\,LiCl$	(40)	65:35
3	Me_3SiCH_2ZnI	$CuCl\cdot Me_2S\cdot 2\,LiCl$	(40)	83:17
4	Me_3SiCH_2ZnI	$CuBr\cdot Me_2S\cdot 2\,LiCl$	44	87:13
5	Me_3SiCH_2ZnI	$CuI\cdot Me_2S\cdot 2\,LiCl$	(46)	73:27
6	$Me_3SiCH_2ZnBr\cdot LiBr$	$CuBr\cdot Me_2S\cdot 2\,LiCl$	46	91:9
7	$Me_3SiCH_2ZnCl\cdot LiCl$	$CuBr\cdot Me_2S\cdot 2\,LiCl$	(51)	87:13
8[c]	$Me_3SiCH_2ZnBr\cdot LiBr$	$CuBr\cdot Me_2S\cdot 2\,LiCl$	52	94:6

[a] Yield of isolated diastereomers of **6a**. NMR spectroscopic yields in parentheses. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H and ^{13}C NMR spectroscopy. [c] Et_2O/*n*-hexane = 2:3 was used as solvent mixture. TBDPS = *tert*-butyldiphenylsilyl.

Table 2: Scope of electrophiles for the trapping reaction with alkylcopper reagents (*anti*- and *syn*-**5a**) prepared by domino transmetalations of secondary alkylithium reagents (*anti*- and *syn*-**1a**).



Entry	E	From *anti*-**1a**[a,b]	From *syn*-**1a**[a,b]
1	 **7a**	 *anti*-**6a** 52 %, d.r. = 94:6	 *syn*-**6a** 48 %, d.r. = 9:91
2	 **7b**	 *anti*-**6b** 62 %, d.r. = 94:6	 *syn*-**6b** 65 %, d.r. = 6:94
3	 **7c**	 *anti*-**6c** 63 %, d.r. = 94:6	 *syn*-**6c** 59 %, d.r. = 7:93
4	 **7d**	 *anti*-**6d** 37 %, d.r. = 93:7	 *syn*-**6d** 37 %, d.r. = 9:91
5[c]	 **7e**	 *anti*-**6e** 43 %, d.r. = 91:9	 *syn*-**6e** 44 %, d.r. = 9:91
6	 **7f**	 *anti*-**6f** 62 %, d.r. = 85:15	 *syn*-**6f** 63 %, d.r. = 15:85

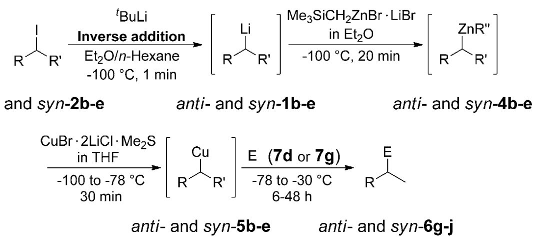
[a] Yield of isolated diastereomers of **6**. [b] Diastereoselectivity (d.r. = *anti*/*syn*) was determined by ^{1}H and ^{13}C NMR spectroscopy. [c] In the presence of $BF_3\cdot Et_2O$.

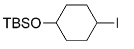
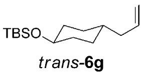
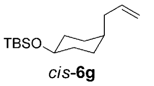
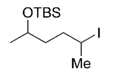
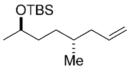
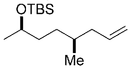
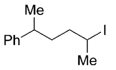
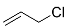
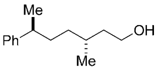
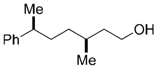
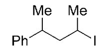
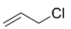
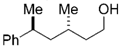
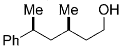
selectivity was found to depend on the counterion of the copper species. The corresponding bromide ($CuBr\cdot 2\,LiCl\cdot Me_2S$) led to a slightly increased d.r. value of 87:13 (entry 4), but the copper iodide ($CuI\cdot 2\,LiCl\cdot Me_2S$) afforded only d.r. = 73:27 (entry 5). These results led us to examine the influence of the halide of the organozinc reagents used (Me_3SiCH_2ZnX), and we found that $Me_3SiCH_2ZnBr\cdot LiBr$[12] gave an enhanced d.r. value of 91:9 (entry 6). We also noticed that the corresponding chloride $Me_3SiCH_2ZnCl\cdot LiCl$[12] did not improve the diastereoselectivity (entry 7). Switching the solvents from pure diethyl ether to a 2:3 mixture of diethyl ether and *n*-hexane allowed this diastereoselectivity to be further improved to 94:6 (entry 8). Me_3SiCH_2ZnBr was found to be a much better zinc halide source for the Li/Zn transmetalation than $ZnCl_2$ or related zinc halides and lithium complexes.[12]

These conditions proved to be broadly applicable. Thus, a secondary alkyl iodide *syn*-**2a** (d.r. = 3:97) underwent the same reaction sequence to provide the expected acrylate *syn*-**6a** in 48 % yield and d.r. = 9:91 (Table 2, entry 1). The domino transmetalations allowed not only carbocuprations[13] to be performed, but also a range of typical reactions of organocopper derivatives.[14] Thus, whereas secondary alkyllithium reagents required the use of Weinreb amides,[3b] the acylation with benzoyl chloride (**7b**) provides the 5-hydroxy ketone derivatives *anti*- and *syn*-**6b** with excellent overall retention of the configuration (d.r. = 94:6; entry 2). An addition-elimination reaction on 3-iodocyclopentenone (**7c**)[15] furnished both *anti*- and *syn*-cyclopentenones (*anti*-**6c**: d.r. = 94:6 and *syn*-**6c**: d.r. = 7:93; entry 3). The intermediate copper reagents of type **5** also opened ethylene oxide to provide the corresponding hydroxyethylated compounds.[16] Thus, the alkyllithium reagents *syn*- and *anti*-**1a** were converted through a domino transmetalation sequence using ethylene oxide (**7d**) to the selectively protected *syn*- and *anti*- 1,6-diols (*syn*-**6d**: d.r. = 93:7 and *anti*-**6d**: d.r. = 9:91). BF_3-mediated acetal opening by organocopper reagents, as pioneered by Normant and coworkers,[17] proceeded with 2,2-dimethoxypropane (**7e**) to give the 1,5-diol derivatives (*anti*-**6e**: d.r. = 91:9 and *syn*-**6e**: d.r. = 9:91; entry 5). The highly reactive allylic reagent, ethyl (2-bromomethyl)acrylate (**7f**)[18] underwent a moderately selective allylation, thus showing that in this case SET pathways may compete with the nonradical substitution.[19]

This analysis was confirmed, as shown in Table 3, by delineating the reaction scope by varying the secondary alkyl iodides of type **2**. Thus, when using allyl chloride[20] as the electrophile, the allylation reaction had much less tendency to undergo SET reactions, as shown by Hoffmann and Hölzer.[19] Starting from either a cyclic secondary alkyl iodide *trans*- and *cis*-**2b** (*trans*-**2b**: d.r. = 98:2 and *cis*-**2b**: d.r. = 1:99) or an

Table 3: Scope of substrates for domino transmetalations of secondary alkyllithium reagents.



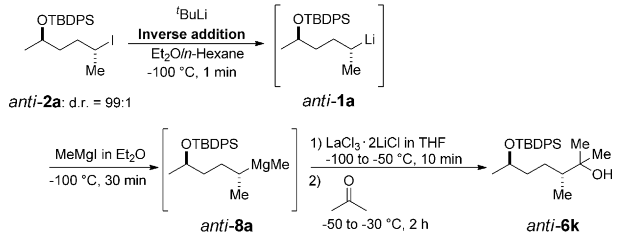
Entry	Substrate	E	From *anti* or *trans*[a,b]	From *syn* or *cis*[a,b]
1	 *trans*-**2b**: d.r. = 98:2 *cis*-**2b**: d.r. = 1:99	 **7d**	 *trans*-**6g** 84%, d.r. = 98:2	 *cis*-**6g** 75%, d.r. = 7:93
2	 *anti*-**2c**: d.r. = 98:2 *syn*-**2c**: d.r. = 1:99	 **7d**	 *anti*-**6h** 55%, d.r. = 92:8	 *syn*-**6h** 60%, d.r. = 8:92
3	 *anti*-**2d**: d.r. = 93:7 *syn*-**2d**: d.r. = 5:95	 **7g**	 *anti*-**6i** 37%, d.r. = 89:11	 *syn*-**6i** 40%, d.r. = 11:89
4	 *anti*-**2e**: d.r. = 98:2 *syn*-**2e**: d.r. = 3:97	 **7g**	 *anti*-**6j** 40%, d.r. = 94:6	 *syn*-**6j** 35%, d.r. = 5:95

[a] Yield of isolated diastereomers of **6**. [b] Diastereoselectivity (d.r. = *trans*/*cis* or *anti*/*syn*) was determined by ^1H and ^{13}C NMR spectroscopy.

acyclic iodide *anti*- and *syn*-**2c** (*anti*-**2c**: d.r. = 98:2 and *syn*-**2c**: d.r. = 1:99), we obtained high retention of the configuration in the allylation sequence that leads to the allylated products (*trans*-**6g**: d.r. = 98:2 and *cis*-**6g**: d.r. = 7:93 as well as *anti*-**6h**: d.r. = 92:8 and *syn*-**6h**: d.r. = 8:92; entries 2 and 3). Unfunctionalized secondary alkyl iodides bearing a phenyl substituent either at position 4 or 3 (*anti*-**2d**: d.r. = 93:7 and *syn*-**2d**: d.r. = 5:95 as well as *anti*-**2e**: d.r. = 98:2 and *syn*- **2e**: d.r. = 3:97) behaved as expected, and the diastereomerically enriched alcohol *anti*- and *syn*-**6i,j** were produced in 35–40% yield and good retention of diastereoselectivity.

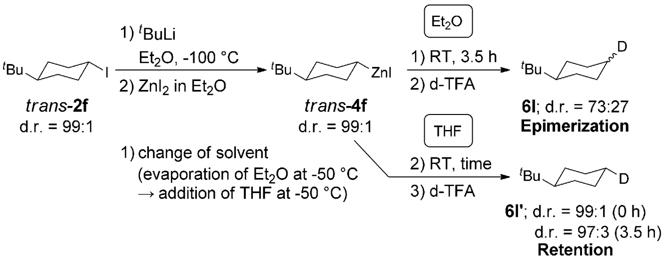
Domino transmetalations also proved to be efficient for undergoing additions to the carbonyl group of an enolizable ketone. Thus, we briefly examined the diastereoselectivity obtained in the conversion of a diastereomerically pure secondary alkyl iodide into the corresponding lanthanum reagent (Table 4).[21] The secondary alkyllithium reagent *anti*-**1a** was generated from the corresponding alkyl iodide *anti*-**2a** (d.r. = 99:1) by known methods. A direct transmetalation to the corresponding alkyllanthanum reagent by using $LaCl_3 \cdot 2LiCl$[22] followed by the addition of acetone provided the tertiary alcohol *anti*-**6k** in 54% yield, but low diastereoselectivity (d.r. = 55:45; entry 1). Repeating this reaction by transmetalating the intermediate alkyllithium reagent *anti*-**1a** to the magnesium derivative *anti*-**8a** and subsequent addition of acetone led to a lower yield and still lower diastereoselectivity (d.r. = 60:40; entry 2). However, transmetalation of alkyllithium reagent *anti*-**1a** to the corresponding alkylmagnesium reagent *anti*-**8a** followed by the addition of $LaCl_3 \cdot 2LiCl$[22] and acetone led to the desired product *anti*-**6k** with an excellent diastereoselectivity (30% yield, d.r. = 95:5; entry 3). These examples (Table 2–4) demonstrated that sequential highly retentive transmetalations of secondary alkyllithium reagents can be achieved with high diastereoselectivity under appropriate reaction conditions. The degree of retention in transmetalations depends on the nature of the metallic salt used (Table 1), as well as the solvent polarity and, therefore, of the solvent mixture used.[3a,7c,23,24] The influence of the nature of the solvent on the epimerization rate of a secondary alkylzinc reagents is demonstrated by the case of cyclohexylzinc iodide *trans*-**4f** obtained by an I/Li exchange and subsequent transmetalation with ZnI_2 (Scheme 2).

Table 4: Domino transmetalations of a secondary alkyllithium reagent *anti*-**1a** to a tentative alkyllanthanum reagent via an alkylmagnesium reagent *anti*-**8a**.



Entry	Conditions	Yield[a]	d.r.[b]
1	without MeMgI	54%	55:45
2	without $LaCl_3 \cdot 2LiCl$	15%	60:40
3	with MeMgI/$LaCl_3 \cdot 2LiCl$	30%	95:5

[a] Yield of isolated diastereomers of **6k**. [b] Diastereoselectivity (d.r. = *anti*/*syn*) was determined by ^1H and ^{13}C NMR spectroscopy.



Scheme 2. Effect of solvent on the stability of the configuration of cyclohexylzinc reagent *trans*-**4f**.

Under these conditions, the secondary alkylzinc reagent *trans*-**4f** was generated in Et_2O with good diastereoselectivty (d.r. = 99:1), but we noticed that it has only a limited configurational stability in this solvent at 25 °C, and significant epimerization to a diastereomeric mixture (d.r. = 73:27) was observed after 3.5 h at 25 °C. The epimerization rate was monitored by deuterolysis of the reaction mixture with deuterated trifluoroacetic acid. Interestingly, removal of the Et_2O and dissolution in THF resulted in a high configurational stability of *trans*-**4a** (d.r. = 97:3 after 3.5 h).

In summary, we have developed sequential retentive domino transmetalations of nonstabilized functionalized secondary alkyllithium compounds prepared from the corresponding secondary alkyl iodides by stereoselective I/Li exchange. We found reaction conditions that allow two successive transmetalations from Li to Zn and from Zn to Cu to be performed, thereby leading to secondary alkylcopper reagents with high retention of configuration. This domino transmetalation sequence allows trapping with a new set of electrophiles to afford various polyfunctionalized products with predictive diastereoselectivity.[25] A related domino transmetalation involving successive Li, Mg, and La organometallic intermediates affords the new possibility to access diastereomerically defined tertiary alcohols.

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Keywords: configurational stability · copper · diastereoselectivity · lithium · zinc

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[24] Experiments on the configurational stability of acyclic secondary alkylzinc reagents did not show the same behavior, for example, we observed a higher configurational stability in Et_2O than in THF.

[25] We realized that the overall yields in Tables 2 and 3 lay mostly between 40 and 65%, despite full conversion of the starting iodides. However, these overall yields include four reaction steps: the first is the I/Li exchange, which under our optimized conditions is $>80\%$ yield, the next two reactions involve transmetalations Li/Zn and Zn/Cu, and the last is the trapping reaction. Thus, an overall yield of 37% corresponds to a yield of ca. 77% yield per reaction step. Similarly, an overall yield of 65% corresponds to a yield of ca. 90% yield per step. Although transmetalations are usually high yielding, the requirement to prepare the transmetalation reagents ($Me_3SiCH_2ZnBr\cdot LiBr$, $CuBr\cdot 2\,LiCl\cdot Me_2S$) may lower the efficiency of these transmetalations. We observed mainly hydrolysis of the organometallic reagents as typical side products for the reaction sequence.

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