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Asymmetric Carbolithiation of Conjugated Enynes: A Flow Microreactor Enables the Use of Configurationally Unstable Intermediates before They Epimerize

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Supporting Information

ABSTRACT: We found that a flow microreactor system enables the generation of a configurationally unstable chiral organolithium intermediate and allows for its use in a reaction with an electrophile before it epimerizes. Based on this method, the enantioselective carbolithiation of conjugated enynes followed by the reaction with electrophiles was accomplished to obtain enantioenriched chiral allenes.

Chiral organometallics[1,2] provide powerful intermediates for the synthesis of enantioenriched compounds. In general, configurationally stable organometallics are used for highly enantioselective transformations because the use of configurationally unstable organometallics[3] usually leads to rapid epimerization before they can react with electrophiles, even if such intermediates are produced enantioselectively. In this communication, we report that flow microreactor systems,[4−7] on the basis of high-resolution control of the residence time,[8] enable the rapid generation of configurationally unstable organometallics and allow their reaction with electrophiles before they epimerize. Our flow microreactor method[9] opens up new possibilities in asymmetric synthesis.

Asymmetric carbolithiation[10] is an attractive reaction in asymmetric synthesis, because carbon−carbon bond formation leads to the formation of chiral organolithium intermediates,[11] which can be used for further transformations.[12] In particular, asymmetric carbolithiation of conjugated enynes has received significant research interest, because the reactions of the resulting chiral organolithium intermediates with electrophiles give chiral allenes,[13] which serve as versatile building blocks. However, to the best of our knowledge, no such study has yet been reported in the literature, presumably because of the configurational instability of organolithium intermediates.

Recently, we proposed the concept of flash chemistry,[14] involving fast chemical synthesis using flow microreactors. On the basis of high resolution control of the residence time, flash chemistry enables the use of highly reactive intermediates before they decompose.[15] We envisioned that the concept could also be applied to epimerization of reactive intermediates. Thus, we examined the addition of organolithium species to conjugated enynes bearing an appropriate directing group (**2**) in the presence of a chiral ligand (**1**) to generate chiral organolithium

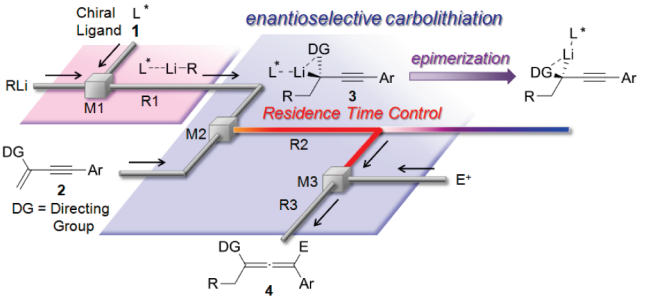

Figure 1. Flow microreactor system for enantioselective carbolithiation followed by trapping with electrophiles.

intermediates, and the subsequent reaction with electrophiles using a flow microreactor system consisting of three T-shaped micromixers (M1, M2, and M3) and three microtube reactors (R1, R2, and R3) (Figure 1). The reaction of *n*-BuLi and the chiral ligand **1** forms a complex *n*-BuLi/**1** (M1 and R1). Carbolithiation of **2** with *n*-BuLi/**1** gives the chiral organolithium intermediate **3** (M2 and R2), which is trapped with MeOH as an electrophile (M3 and R3) to give product **4** (R = Bu, *E* = H).

We began by searching for a suitable ligand and directing group. The reaction of conjugated enyne **2a**, having a carbamoyloxy group as the directing group, with *n*-BuLi in the presence of (−)-sparteine **1a** as the ligand, followed by trapping with MeOH gave the desired allene **4a** in a high yield with a high enantioselectivity (Table 1, entry 1). The use of a slight excess of (−)-sparteine increased the enantioselectivity (entry 2). In contrast, the reaction of **2b**, having no directing group, gave the desired allene **4b** in a low enantioselectivity, presumably because the enantiofacial selectivity in the addition of *n*-BuLi was low (entry 3, see the Supporting Information [SI] for details). Moreover, the reaction of **2b** also formed a significant amount of 1-phenyl-1-octyne as a byproduct (14%). In the case of **2c**, having a methoxymethoxy group, the desired product **4c** was not obtained at all, and **2c** was quantitatively recovered (entry 4). In the case of other ligands **1b**−**1e**[16] the enantioselectivity and the yield were low (entries 5−8). Thereafter, we used the carbamoyloxy group as the directing group and (−)-sparteine **1a** as the ligand. To best of our knowledge, this is the first example of the synthesis of enantioenriched chiral allenes via asymmetric carbolithiation.

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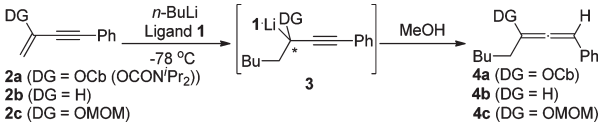
Table 1. Enantioselective Carbolithiation of 2 with *n*-BuLi in the Presence of Various Ligands in a Flow Microreactor System[a]



entry	substrate	ligand	product	% yield of product[b] (enantiomeric ratio)	% recovery of substrate
1	**2a**	**1a**	**4a**	91 (88:12)	4
2[c]	**2a**	**1a**	**4a**	82 (93:7)	10
3[c]	**2b**	**1a**	**4b**	83 (61:39)	1
4[c]	**2c**	**1a**	**4c**	0	91
5	**2a**	**1b**	**4a**	57 (52:48)	36
6	**2a**	**1c**	**4a**	<1 (45:55)	88
7	**2a**	**1d**	**4a**	<1 (34:66)	98
8	**2a**	**1e**	**4a**	0	>99

[a] Reaction condition: *n*-BuLi (0.40 M in toluene/hexane, 3.0 mL/min), ligand (0.40 M in toluene, 3.0 mL/min), **2** (0.40 M in toluene, 1.5 mL/min), and MeOH (neat, 3.0 mL/min). Temperature in M1 and R1 (0 °C) and M2−4 and R2−4 (−78 °C). Residence time in R2 (13 s). [b] Determined by chiral HPLC. Enantiomeric ratio (er) is shown in parentheses. [c] **1a** (0.67 M in toluene, 3.0 mL/min).

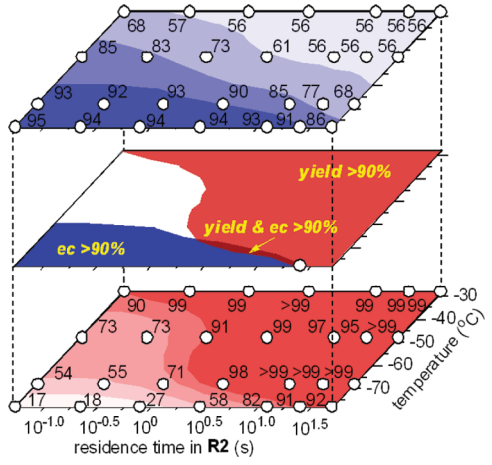
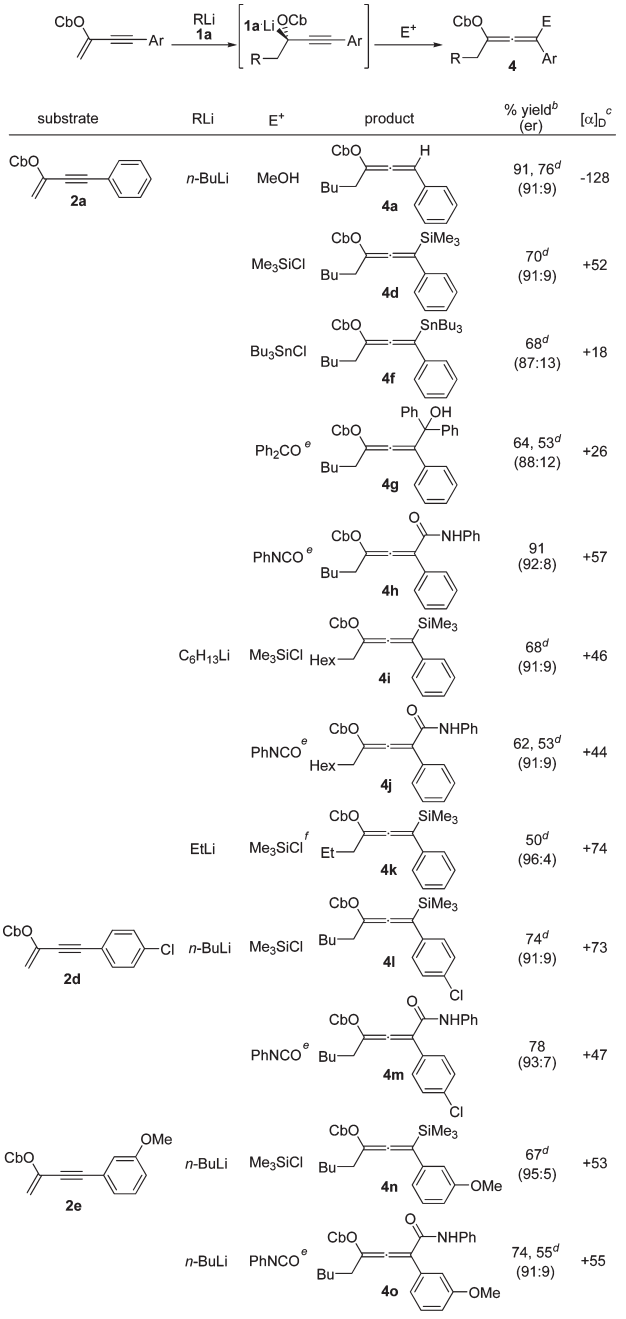


Figure 2. Temperature−residence time (in **R2**) map for the reaction of **2a** in the presence of **1a**. Contour plot with scatter overlay of enantiomeric composition (ec) of **4a** (upper), contour plot with scatter overlay of the yield of **4a** (lower), and the domain that gave the highest yield (>90%) and highest ec (>90%) (middle).

To obtain a deeper insight into the features of the reaction, we next carried out the reaction varying the residence time in R2 (t^R) at various temperatures (Figure 2, also see the SI for details). As profiled in Figure 2, the yield increased with increasing t^R and temperature. In contrast, the enantiomeric composition (ec)[17] decreased with increasing t^R and temperature, presumably because of epimerization of the intermediate **3a**.[18] This result means that the decrease of enantiomeric composition resulted from epimerization of the lithiated species rather than its formation step. The residence time−temperature domain that gave both a high yield (>90%) and a high ec (>90%) was very small. However, it is noteworthy that, when we carried out the reaction in this domain (e.g., t^R = 25 s, T = −78 °C), the desired

Table 2. Carbolithiation of Conjugated Enynes Followed by the Reaction with Electrophiles[a]



[a] Reaction condition: substrate (0.40 M in toluene, 1.5 mL/min), *n*-BuLi (0.40 M in toluene/hexane, 3.0 mL/min), HexLi (0.40 M in toluene/hexane, 3.0 mL/min), EtLi (0.10 M in toluene/benzene/cyclohexane, 3.0 mL/min), (−)-sparteine (0.67 M in toluene, 3.0 mL/min), MeOH (neat, 3.0 mL/min), Me_3SiCl (2.0 M in toluene, 3.0 mL/min), Bu_3SnCl (0.80 M in THF, 3.0 mL/min), Ph_2CO (0.80 M in toluene/HMPA, 3.0 mL/min), and PhNCO (0.80 M in toluene/HMPA, 3.0 mL/min). [b] Determined by chiral HPLC. Enantiomeric ratio (er) is shown in parentheses. [c] c = 0.57−2.3, in CH_2Cl_2. [d] Isolated yield. [e] Concentrations of RLi, **1a**, and **2a** were one-half of the standard ones. [f] Concentrations of **1a**, **2a**, and Me_3SiCl were one-fourth of the standard ones.

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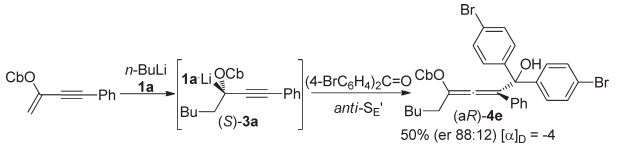
Scheme 1. Determination of Absolute Configuration of 3a



product **4a** was obtained in a high yield (91%) with a high selectivity (91% ec). In contrast, the reaction using a batch macro reactor (reaction time: 25 s, $T = -78$ °C) gave **4a** in 99% yield with a low selectivity (61% ec). Batch reactions under several conditions also led to low ec (See SI for details). These results show that a flow microreactor system is a powerful tool for enantioselective reactions.

Reactions with various electrophiles were examined under the optimized conditions, and the results are summarized in Table 2. Chlorotrimethylsilane, tributylchlorostannane, benzophenone, and phenyl isocyanate were effective as electrophiles and gave the corresponding allenes (**4d**, **4f**−**4h**) with a high enantioselectivity. The reactions of **2a** with other organolithium compounds, such as hexyllithium (HexLi) and ethyllithium (EtLi), and the reactions of other conjugated enynes bearing a carbamoyloxy group (**2d** and **2e**) were also examined, and the corresponding products (**4i**−**4o**) were obtained in good yields and high enantioselectivity.

The absolute configuration of the major stereoisomer of **4e**, which was obtained from **2a** and 4,4′-dibromobenzophenone, was determined as *R* using X-ray analysis employing an anomalous dispersion technique. Since the similar propargyllithium/**1a** complex has been shown to proceed in an *anti*-S_E' manner,[20] the absolute configuration of the organolithium intermediate **3a** was estimated to be *S* (Scheme 1).

In conclusion, we have developed a method for asymmetric synthesis based on suppressing the epimerization of a configurationally unstable chiral organolithium intermediate based on high-resolution control of the residence time using a flow microreactor system. Enantioenriched allenes were synthesized from the asymmetric carbolithiation of conjugate enynes using this method, demonstrating its potential. Thus, our method adds a new dimension to asymmetric synthesis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data of compounds, and complete ref 6n. This material is available free of charge via the Internet at http://pubs.acs.org.

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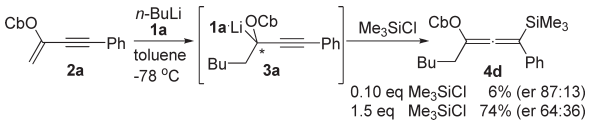
(16) **1b**: (*R*,*R*)-(−)-2,3-Dimethoxy-1,4-bis(dimethylamino)butane; **1c**: 2,2-bis((4*S*)-(−)-4-isopropyloxazoline)propane; **1d**: (*S*)-(−)-*N*,α-dimethylbenzylamine; **1e**: (*S*)-(−)-1-methyl-2-pyrrolidine methanol.

(17) Enantiomeric composition, that enantiomeric ratio normalizes to a percent, proposed by Kagan. Kagan, H. B. *Recl. Travl. Chim. Pays-Bas* **1995**, *114*, 203.

(18) To verify that the enantioselectivity was determined by the epimerizaiton, Hoffman[19] test was carried out using Me_3SiCl as an electrophile in a batch macro reactor. The enantiomeric ratio of **4d** obtained with 0.10 equiv of Me_3SiCl was different from that obtained with 1.5 equiv of Me_3SiCl. The result indicates that the activation enegies for the reactions of **3a** and *epi*-**3a** (epimer of **3a**) with an electrophile are different. It also indicates that the activation energy for the epimerization of **3a** and *epi*-**3a** is much higher than those for the reactions with an electrophile. This means that the enantiomeric ratio of the allene product reflects the ratio of organolithium intermediates **3a** and *epi*-**3a**, if a stoichiometric amount of an electrophile is used.



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