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# α-Arylation of α-Amino Acid Derivatives with Arynes via Memory of Chirality: Asymmetric Synthesis of Benzocyclobutenones with Tetrasubstituted Carbon

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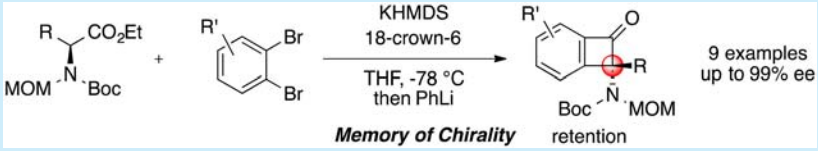
Supporting Information

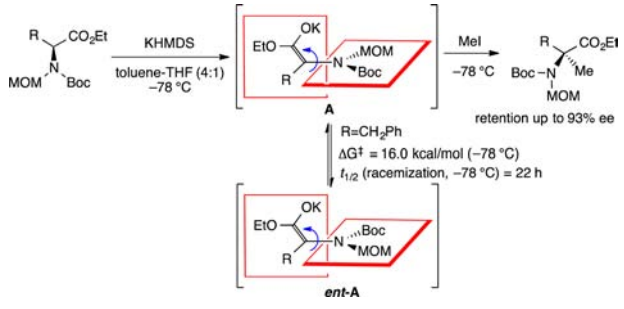



**ABSTRACT:** A method for asymmetric α-arylation of α-amino acid derivatives via memory of chirality has been developed. Addition of axially chiral enolates, generated from α-amino acid derivatives, to in situ generated arynes, followed by intramolecular C-acylation of the resulting aryl metallic species, gave benzocyclobutenones with a tetrasubstituted carbon with retention of configuration in up to 99% ee.

Benzocyclobutenones (BCBs) have been used as versatile synthetic intermediates in various molecular transformations,[1] including in the total synthesis of complex natural products.[2] Numerous efficient methods for the preparation of BCBs have been developed.[3] To the best of our knowledge, however, the asymmetric construction of BCBs with an α-tetrasubstituted stereocenter has never been reported. Here we report highly enantioselective synthesis of α-tetrasubstituted BCBs via memory of chirality (MOC).

We have studied asymmetric synthesis via MOC.[4−6] A characteristic feature of MOC strategy is that asymmetric reactions take place via chiral enolate intermediates that have limited half-lives of racemization, and the reactions of these chiral enolates with electrophiles compete with enolate racemization (Scheme 1). Therefore, the reactions are usually performed at low temperatures to minimize the enolate racemization. Under such conditions, intermolecular MOC reactions that include asymmetric alkylation,[5a] aldol reactions,[5b] and conjugate addition[5c] have been successfully developed. On the other hand, intramolecular MOC reactions can be performed at higher temperatures, because the intermediary chiral enolates can react immediately, after they have been generated. Thus, intramolecular alkylation,[6a−c] conjugate addition,[6d] acyl migration,[6e] and α-arylation[6f] have been

**Scheme 1. Asymmetric α-Alkylation of Amino Acid Derivatives via MOC**




**Scheme 2. Strategy for Asymmetric Synthesis of BCBs with Tetrasubstituted Carbon**

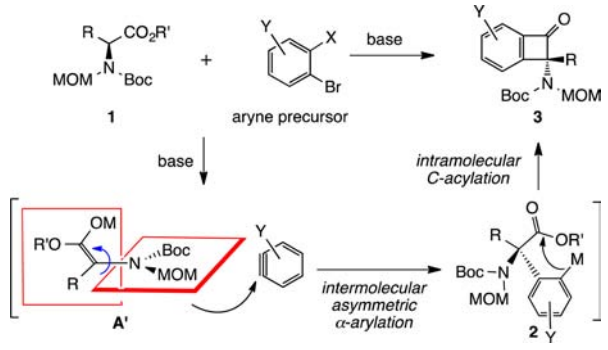



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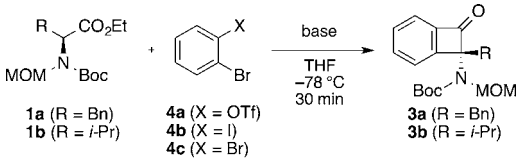
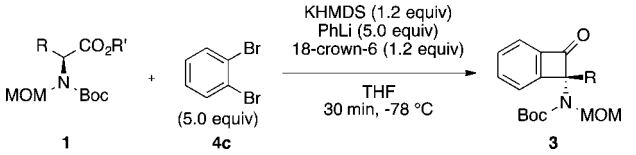
**Table 1. Asymmetric α-Arylation of α-Amino Acid Derivatives 1**[a]

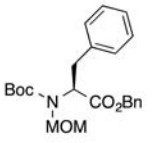
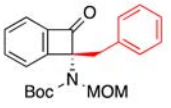
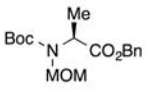
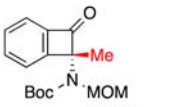
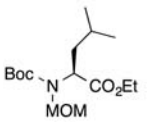
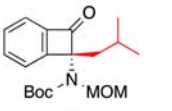



| entry | R | X | base | procedure[b] | yield | ee[c] |
|---|---|---|---|---|---|---|
| 1 | Bn (**1a**) | OTf (**4a**) | *t*-BuLi | **I** | 42[d] | 23 |
| 2 | Bn (**1a**) | OTf (**4a**) | LiHMDS then *t*-BuLi | **II** | 22[d] | 31 |
| 3 | Bn (**1a**) | OTf (**4a**) | NaHMDS then *t*-BuLi | **II** | 22[d] | 28 |
| 4 | Bn (**1a**) | OTf (**4a**) | KHMDS then *t*-BuLi | **II** | 28[d] | 49 |
| 5 | *i*-Pr(**1b**) | OTf (**4a**) | KHMDS then *t*-BuLi | **II** | 18[d] | 92 |
| 6 | *i*-Pr (**1b**) | **I** (**4b**) | KHMDS then *s*-BuLi | **III** | 21[d] | 87 |
| 7 | *i*-Pr (**1b**) | Br (**4c**) | KHMDS then *s*-BuLi | **III** | 22 (31)[e] | 88 |
| 8 | *i*-Pr (**1b**) | Br (**4c**) | KHMDS then MeLi | **III** | 22 (29)[e] | 83 |
| 9[f] | *i*-Pr (**1b**) | Br (**4c**) | KHMDS then *i*-PrMgCl·LiCl | **III** | 15 (18)[e] | 15 |
| 10 | *i*-Pr (**1b**) | Br (**4c**) | KHMDS then PhLi | **III** | 56 (80)[e] | 84 |
| 11[g] | *i*-Pr (**1b**) | Br (**4c**) | KHMDS then PhLi | **III** | 53 (78)[e] | 95 |

[a]All reactions were run at the substrate concentration of 0.1 M. [b]**I**: A solution of **1a** (0.10 mmol) and **4a** (2.0 equiv) was added to a solution of the base (6.0 equiv) at −78 °C. **II**: A solution of **1** (0.10 mmol) and **4a** (5.0 equiv) was added to a solution of the metal amide base (1.2 equiv). After the mixture was stirred for 10 min, the organolithium reagent (10.0 equiv) was added to the reaction mixture. **III**: A solution of **1** (0.10 mmol) and **4** (5.0 equiv) was added to a solution of the metal amide base (1.2 equiv). After stirring for 10 min, the organometallic reagent (5.0 equiv) was added to the reaction mixture. [c]Ee was determined by HPLC analysis with a chiral stationary phase. [d]Isolated yield. [e]Yield was determined by $^1$H NMR of the crude reaction mixture using an internal standard. Numbers in the parentheses indicate the yields based on recovered **1**. [f]The reaction was run at −78 °C to room temperature. [g]Run in the presence of 18-crown-6 (1.2 equiv).

**Table 2. Substrate Scope of Asymmetric α-Arylation of α-Amino Acid Derivatives 1**[a]




| entry | 1 | product | yield[b] | ee[c] |
|---|---|---|---|---|
| 1 |  **1c** |  **3a** | 60 | 82 |
| 2[d] |  **1d** |  **3c** | 55 | 74 |
| 3 |  **1e** |  **3d** | 57 | 71 |

[a]All reactions were run at the substrate concentration of 0.1 M. [b]Isolated yield. [c]Ee was determined by HPLC analysis with a chiral stationary phase. [d]Run in toluene−THF (4:1).

developed via MOC. An extreme example of the MOC reaction involves asymmetric intramolecular alkylation via a C−O axially chiral enolate whose racemization barrier was roughly estimated to be 11.5 kcal/mol, which corresponds to a half-life of racemization of ca. 1 s even at −78 °C.[6g] Our long-standing objective in the MOC study is to develop an asymmetric intermolecular α-arylation of α-amino acid derivatives. This has been unsuccessful because general methods for the α-arylation of enolates often require long reaction times at high temperature,[7] which can cause significant racemization of the chiral enolates. For example, the half-life of racemization of chiral enloate **A** can be estimated as >0.1 s at 20 °C from the racemization barrier. Given this background, we focused on arynes as reactive electrophilic aryl species at low temperatures[3c,e,8] and have successfully developed an asymmetric α-arylation of α-amino acid derivatives via MOC.

We envisioned that arynes could be prepared *in situ* and immediately reacted with the chiral enolate **A′** generated from α-amino acid derivatives **1** with a base (Scheme 2). The resulting aryl metallic species **2** would undergo intramolecular acylation with the ester moiety to give BCB **3**.

Asymmetric α-arylation was first examined with *N*-Boc-*N*-MOM-Phe-OEt **1a** as a substrate (Table 1). 2-Bromophenyl triflate **4a** was chosen as a benzyne precursor because **4a** was expected to be readily converted to benzyne at −78 °C by halogen−lithium exchange followed by β-elimination.[3c,9a] Other methods for aryne generation employing deprotonation[9b] or fluorine-mediated desilylation[9c] were not effective for this purpose when performed at −78 °C (data not shown). We first examined *t*-BuLi as a base because of the expected roles of *t*-BuLi as a base for both enolate formation and benzyne generation. Treatment of a solution of **1a** and **4a** in THF with *t*-BuLi at −78 °C for 0.5 h gave BCB **3a** in 42% yield and 23% ee (entry 1). While the use of LiHMDS as a base for enolate formation resulted in a decrease in the yield, the enantioselectivity was slightly increased (22% yield and 31% ee, entry 2). Use of NaHMDS or KHMDS gave **3a** in 28% ee or 49% ee, respectively (entries 3 and 4). The reaction of valine-derived **1b** gave BCB **3b** in 18% yield and 92% ee (entry 5). Since the low yields were assumed to be resulting from inefficient benzyne formation as well as product decomposition caused by excess *t*-BuLi, other methods for benzyne formation were examined (entries 6−11). The use of 2-bromoiodobenzene (**4b**) or 1,2-dibromobenzene (**4c**) did not improve the yield when *s*-BuLi or MeLi was used as a base for the benzyne formation (21−22% yields, 83−88% ee: entries 6−8). Use of *i*-PrMgCl·LiCl, well-known as a mild reagent for metal−halogen exchange,[10] led to the decrease in both the yield and enantioselectivity due to the higher reaction temperature (room temperature) required for the benzyne formation (15% yield and 15% ee: entry 9). PhLi was found to be the best reagent to improve the mass balance, and its use gave **3b** in 56% yield (80% brsm) and 84% ee (entry 10). BCB **3b** was obtained from **1b** in 53% yield



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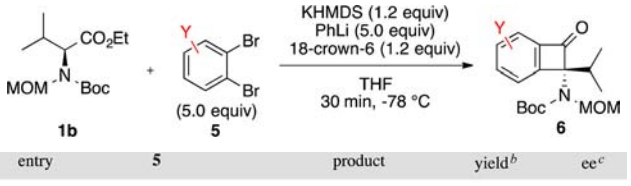
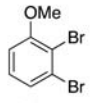
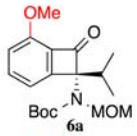
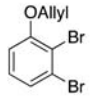
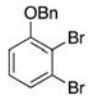
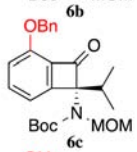
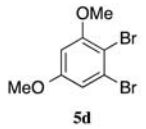
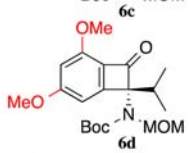
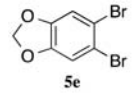
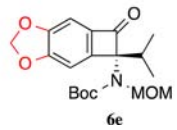
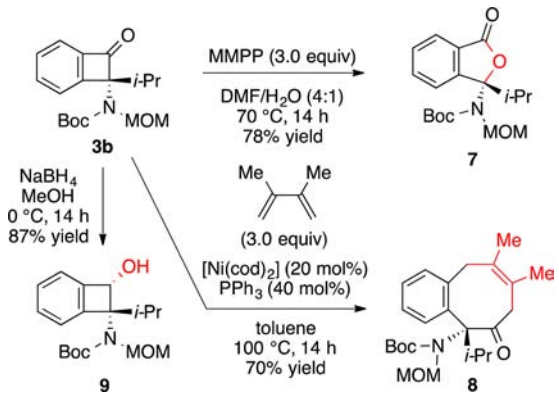
**Table 3. Substrate Scope of Asymmetric α-Arylation of 1b with Various Aryne Precursors 5[a]**




| entry | 5 | product | yield[b] | ee[c] |
|---|---|---|---|---|
| 1 |  5a |  6a | 63 | 90 |
| 2 |  5b |  6b | 53 | 77 |
| 3 |  5c |  6c | 40 | 80 |
| 4 |  5d |  6d | 47 | 99 |
| 5 |  5e |  6e | 55 | 83 |

[a]All reactions were run at the substrate concentration of 0.1 M. [b]Isolated yield. [c]Ee was determined by HPLC analysis with a chiral staionary phase.

**Scheme 3. Synthetic Application of BCB 3b**




(78% brsm) and 95% ee in the presence of 18-crown-6 (entry 11).

The absolute configuration of **3b** was assigned by vibrational circular dichromism (VCD) spectroscopy and electronic circular dichroism (ECD) spectroscopy supported by theoretical calculations (see Supporting Information). On the basis of the agreement in both VCD and ECD, the absolute configuration of the **3b** was determined to be *R*. This indicated that α-arylation of **1b** proceeded with retention of configuration at the newly generated tetrasubstituted carbon center of BCB.

The scope of this reaction was explored with a few *N*-Boc-*N*-MOM-amino acid derivatives under the optimized conditions (Table 1, entry 11) (Table 2). The reaction of phenylalanine benzyl ester derivative **1c** with **4c** gave **3a** in 60% yield and 82% ee (entry 1). Upon treatment of alanine-derived **1d** with the bases and **4c** in a 4:1 toluene−THF mixture gave **3c** in 55% yield and 74% ee (entry 2). Similarly, the leucine-derived **1e** gave **3d** in 57% yield and 71% ee (entry 3).

The asymmetric α-arylation was further examined with various aryne precursors (Table 3). The reactions of **1b** with aryne precursor **5a** possessing a methoxy substituent at C(3) gave a single regioisomer **6a** in 63% yield and 90% ee (entry 1) (Regiochemistry was determined by NOE and HMBC studies, see Supporting Information). The reactions of **1b** with arynes derived from 3-allyloxy and 3-benzyloxy dibromobenzene, (**5b**) and (**5c**), respectively, gave the corresponding BCBs **6b** (53% yield, 77% ee) and **6c** (40% yield, 80% ee), respectively (entries 2 and 3). The regiochemistry of the addition of the enolate to arynes was assumed to be controlled by the inductive effect of the alkoxy group on the aromatic ring.[3c] Similarly, the reactions of **1b** with 3,5-dimethoxy-substututed aryne precursor **5d** and 4,5-methylenedioxy-substituted aryne precursor **5e** gave **6d** (47% yield, 99% ee) and **6e** (55% yield, 83% ee), respectively (entries 4 and 5).

The synthetic utility of the BCBs obtained by the present method was explored. Baeyer−Villiger oxidation[1c] of **3b** gave a five-membered lactone with a tetrasubstituted carbon **7** in 78% yield (Scheme 3). Benzo-fused eight-membered ketone **8** could be obtained by Ni-catalyzed intermolecular (4 + 4)-cycloaddition[1e] between 2,3-dimethylbutadiene and **3b** in 70% yield. Densely functionalized cyclobutanol derivative **9** was also obtained as a single diastereomer by reduction of **3b** in 87% yield.

In summary, we have developed a method for asymmetric intermolecular α-arylation of amino acid derivatives via memory of chirality to afford BCBs with a tetrasubstituted carbon.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03533.

Synthetic details; HPLC data; $^{1}H$ and $^{13}C$ NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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