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# Asymmetric Synthesis of α-Aryl Amino Acids; Aryne-Mediated Diastereoselective Arylation

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## ABSTRACT


**An aryne-mediated α-arylation reaction of Schöllkopf's bis-lactim ether is described. Arynes were generated *via* an *ortho*-lithiation approach, affording *syn*-arylated products in up to 94:6 dr with moderate to good yields and excellent regioselectivities. Hydrolysis provided a variety of substituted arylglycines containing a range of functional groups without racemization.**

The ability to synthesize unnatural aryl amino acids has facilitated their application in multiple areas of organic chemistry, not only as fragments in the preparation of natural products but also in their incorporation into glycopeptide antibiotics and as building blocks in medicinal chemistry.[1] Replacement of a natural amino acid side chain with a more hydrophobic aryl analogue has been shown to have wide implications on the biological structure and activity of the corresponding molecules.[2]

Methods to generate chiral arylglycines have previously involved starting materials already containing the crucial carbon−aryl bond[3] and/or late stage resolution approaches due to the high acidity of the α-aryl proton.[4] An alternative strategy employing metal-catalyzed C−H activation of protected amino acids has recently been developed by Hartwig and Buchwald,[5,6] but the asymmetric variant has yet to be reported.

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(3) For a review on the asymmetric synthesis of arylglcines, see: Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889 and references within. For a recent review on asymmetric Streker reactions, see: (b) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875.

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(5) For a review, see: Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676.

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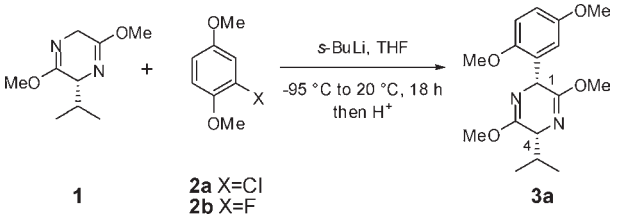
**Table 1.** α-Arylation Optimization




**1** **2a** X=Cl **2b** X=F **3a**

| entry | 2 | equiv base | equiv 2 | proton source[b] | dr[c] | yield[e] (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | 2.1 | 1 | $H_2O$ | 88:12 | 45 |
| 2 | **a** | 2.5 | 1.25 | $H_2O$ | 91:9 | 38 |
| 3 | **a** | 3.0 | 1.75 | $H_2O$ | 89:11 | 63 |
| 4 | **a** | 3.0 | 1.75 | citric acid | 89:11 | 69 |
| 5 | **a** | 3.0 | 1.75 | *t*-BuOH | 92:8 | 60 |
| 6 | **a** | 3.0 | 1.75 | BHT[d] | 94:6 | 75 |
| 7[a] | **b** | 3.0 | 1.75 | BHT | 94:6 | 56 |

[a] *n*-BuLi was added at −78 °C for precursor **2b**. [b] Reactions were quenched at room temperature by water, citric acid, *tert*-butanol, or BHT. [c] As determined by integration of $^1$H NMR spectra. [d] BHT = 2,6-di-*tert*-butyl-4-methylphenol. [e] Isolated yield.

We have previously demonstrated multiple component coupling reactions of arynes in order to synthesize the natural products clavilactone B[7] and dehydroaltenuene B.[8] Arynes are extremely attractive candidates for the α-arylation reaction of ketones, esters, and other enolizable starting materials. Their intrinsic electrophilicity should allow for nucleophilic addition by a suitably protected glycine enolate to provide diverse derivatives of phenylglycine. Attracted by the simplicity of approach, we began our studies.

Since additions of enolates to arynes have been reported to result in the formation of adducts derived by the intramolecular cyclization of the resultant aryl anion onto the carbonyl group,[9] we chose Schöllkopf's bis-lactim ether **1**[10] as the protected glycine equivalent, due to the reduced nucleophilicity of the ring nitrogen atoms[11] and the lack of electrophilic carbonyl groups. Deprotonation of bis-lactim **1** and aryne precursor **2a**[12] at low temperature using *sec*-butyllithium, followed by warming to room temperature and quenching with water, afforded adduct **3a** as an inseparable (88:12) mixture of diastereoisomers in a combined 45% yield (entry 1, Table 1). Interestingly, the major diastereoisomer was determined to be the *syn*-adduct by observation of a larger $H_1-H_4$ coupling constant ($J$ = 6.3 Hz) than that for the *anti*-adduct ($J$ = 3.1 Hz) as reported for similar compounds, as well as by NOE analyses (Figure 1).[13] Increasing the number of equivalents of chloride **2a** to 1.75 and base to 3.0 (entries 2 and 3) resulted in improved yields of adduct **3a** to 63%.

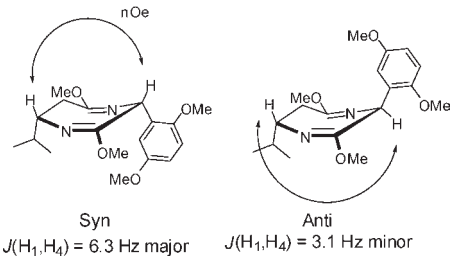
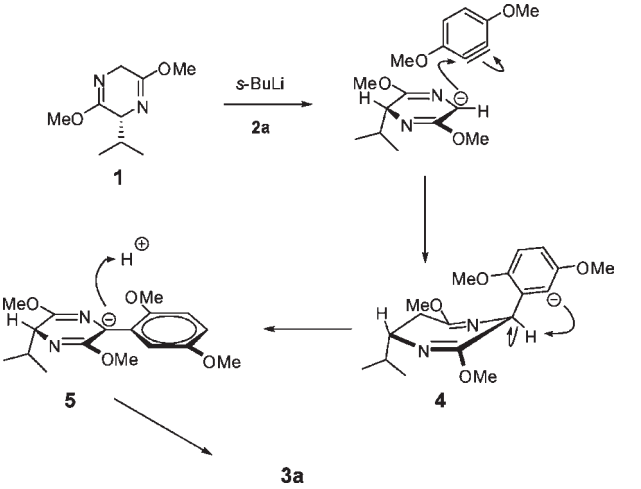



**Figure 1.** $J$ values and nOes for *syn*- and *anti*- diastereomers.

To rationalize the stereochemical outcome, a mechanism was proposed in which initial attack of lithiated **1** onto the aryne occurs as expected, on the opposite face to the *iso*-propyl group. Subsequent inter- or intramolecular proton transfer to the α-aryl position with the newly formed carbanion **4** gave the planar species **5**. Subsequent diastereoselective protonation occurred on the less hindered face to give *syn*-adduct **3a** (Scheme 1).

**Scheme 1.** Proposed Mechanism




Based on this model, we examined bulkier weak acids, with the aim of improving the dr (entries 4−6). To our delight the use of 2,6-di-*tert*-butyl-4-methylphenol (BHT)[14] gave an excellent dr of 94:6. Benzyne generation from

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(10) (a) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085 and references therein. (b) Schöllkopf, U.; Grüttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem.* **1987**, *99*, 717.

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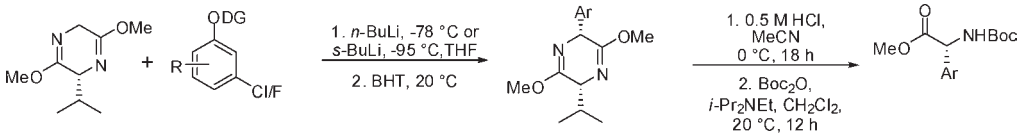
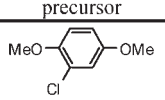
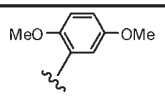
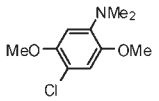
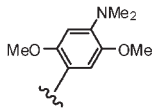
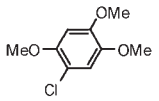
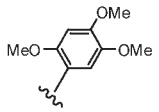
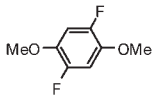
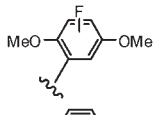
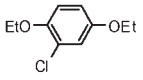
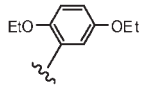
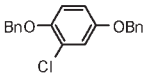
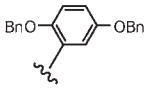
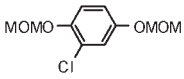
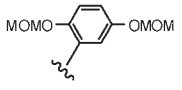
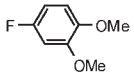
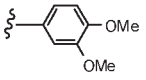
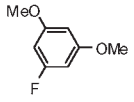
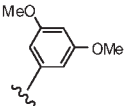
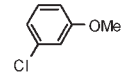
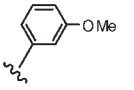
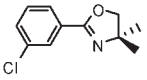
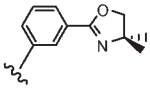
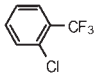
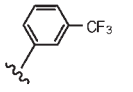
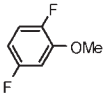
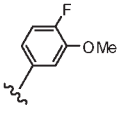
(14) Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2009**, *65*, 9944.

**Table 2.** Scope of α-Arylation Reaction with Different Benzyne Precursors




**1** **2a-o** **3a-o** **8a-o**

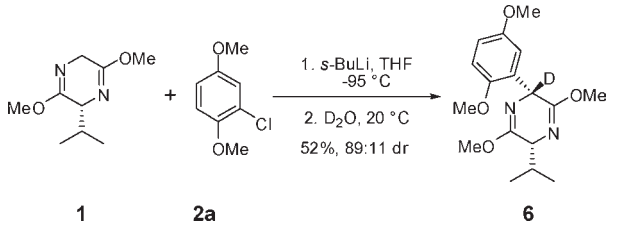
| entry | benzyne precursor | | base[a] | Ar | | yield of **3**[b] (%) | dr[c] | yield of **8**[b, d] (%) | |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | **2a** | *s*-BuLi |  | **3a** | 75 | 94:6 | 89 | **8a** |
| 2 |  | **2c** | *s*-BuLi |  | **3c** | 41 | 92:8 | 96 | **8c** |
| 3 |  | **2d** | *s*-BuLi |  | **3d** | 37 | 94:6 | 59 | **8d** |
| 4 |  | **2e** | *n*-BuLi |  | **3e** | 57[e] | 91:9 | 48 + 46[f] | **8e+8f** |
| 5 |  | **2g** | *s*-BuLi |  | **3g** | 72 | 92:8 | 98 | **8g** |
| 6 |  | **2h** | *s*-BuLi |  | **3h** | 33 | 90:10 | 79 | **8h** |
| 7 |  | **2i** | *s*-BuLi |  | **3i** | 52 | 89:11 | 66 | **8i** |
| 8 |  | **2j** | *n*-BuLi |  | **3j** | 62 | 76:24 | 92 | **8j** |
| 9 |  | **2k** | *n*-BuLi |  | **3k** | 72 | 74:26 | 70 | **8k** |
| 10 |  | **2l** | *s*-BuLi |  | **3l** | 67 | 70:30 | 67 | **8l** |
| 11 |  | **2m** | *n*-BuLi |  | **3m** | 55 | 71:29 | 41 | **8m** |
| 12 |  | **2n** | *n*-BuLi |  | **3n** | 61 | 50:50 (>99:1)[g] | 93 | **8n** |
| 13 |  | **2o** | *n*-BuLi |  | **3o** | 53 | 73:27 | 62 | **8o** |

[a] General Procedure: To a solution of **1** (1 equiv, 1 mmol) and halide **2** (1.75 equiv) in THF (0.2 M) at either −78 °C (for *n*-BuLi) or −95 °C (for *s*-BuLi) was added a base (3.0 equiv). After stirring for 1 h, the reaction was allowed to warm to room termperature over 18 h and then BHT (4 equiv) was added. [b] Isolated yield. [c] Determined by $^1$H NMR integration. [d] HPLC analysis of a representative number of compounds **3** determined that they undergo negligible racemization upon hydrolysis to the corresponsing amine; this indicates that the er's of **8** are the same as the dr's of **3**. See Supporting Information. [e] Isolated as a 1:1 mixture of regioisomers. [f] Separable by chromatography. [g] After separation by chromatography.

fluoride **2b**[15] also gave **3a** with a comparable diastereoselectivity.

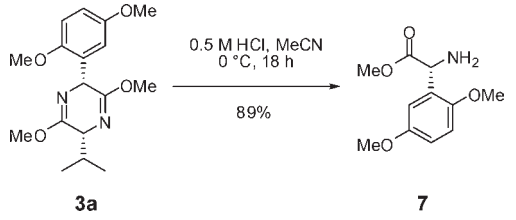
To support the mechanistic hypothesis, a deuterium labeling experiment was undertaken. Quenching the reaction with $D_2O$ as opposed to water gave deuterium incorporation only in the $C_1$ position to give **6**, indicating that that the second deprotonation had occurred as expected (Scheme 2).

**Scheme 2.** Deuterium Labelling Experiment




Hydrolysis of adduct **3a** under mild acidic conditions[10] provided the desired amine **7** in 89% yield (Scheme 3). Chiral HPLC analysis confirmed that negligible prior epimerization of adduct **3a** occurred under the reaction conditions.[16]

**Scheme 3.** Hydrolysis of **3a**




The scope of the reaction was investigated to ascertain which substitution patterns and functionality were tolerated on the aryl unit. Benzyne precursors **2** containing *ortho*-directing groups (ODG) and either a chloride or fluoride leaving group were employed (Table 2). Following hydrolysis, the amines were protected immediately as the corresponding *tert*-butyl carbamates **8** for ease of handling. Dimethylamino, methoxy, and fluoride analogues gave adducts **3c**−**d** (entries 2−4) with excellent diastereoselectivity and as single regioisomers except for **2e** which exhibited no regioselectivy and gave fluoride adduct **3e** as a 1:1 mixture of arene regioisomers. Fortunately upon hydrolysis and *N*-Boc protection, the two isomeric carbamates **8e** and **8f** were separable. The low yield for **3c** can be rationalized by competing lithiation at the 5-position. Changing the nature of the directing groups to ethyl, benzyl, or MOM ethers (entries 5−7) gave adducts **3g**−**i**, again in good diastereoselectivities and yields except for in the case of the sterically demanding benzyl precursor **2h**. It is worth noting that, under these mild hydrolysis conditions, no deprotection of the MOM ether in adduct **3i** was observed. Altering the position of the *para*-methoxy groups in **2a** to the *ortho*-**2j** and *meta*-**2k** dimethoxy percursors[17] provided adducts **3j** and **3k** in good yields (entries 8−9), again with complete arene regioselectivity.[18] The diastereoselectivity for formation of these adducts was dramatically reduced to around 75:25. 3-Chloroanisole **2l** reacted without a problem to give adduct **3l** (entry 10). The nature of this single directing group was varied from an ether to oxazoline precursor[19] **2m** and 1-chloro-2-(trifluoromethyl)benzene[20] **2n**, affording their respective adducts **3m** and **3n** in respectable yields (entries 11 and 12). Although there was no diastereoselectivity in the formation of adduct **2n**, the two diastereoisomers were easily separable, and hence the methyl ester **8n** was obtained in high enantiopurity. A fluorine on the anisole ring was also tolerated, giving adduct **3o** (entry 13). It is clear that, for all aryne precursors without a chelating substituent in the *ortho*-position to the Schöllkopf glycine (entries 8−13), the diastereoselectivity of the reaction noticeably decreased. It is possible that without this substituent, there is twisting of the linked 6-membered rings out of plane, hence decreasing facial selectivity.

Hydrolysis and *N*-Boc protection were high yielding in all cases, except for oxazoline **3m**, which is most likely due to the acid-sensitive nature of this directing group.

In conclusion, a general approach has been developed for the synthesis of enantiomerically enriched α-arylglycines, using arynes as electrophilic arylation reagents. Further extension of this research, involving the formation of quaternary arylglycine derivatives, is in progress and will be reported in due course.

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**Supporting Information Available.** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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