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Development of a Method for the *N*-Arylation of Amino Acid Esters with Aryl Triflates

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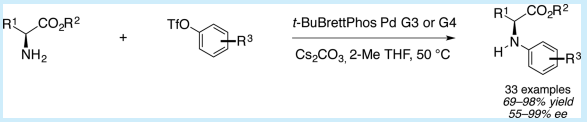
Supporting Information

ABSTRACT: A general method for the *N*-arylation of amino acid esters with aryl triflates is described. Both α- and β-amino acid esters, including methyl, *tert*-butyl, and benzyl esters, are viable substrates. Reaction optimization was carried out by design of experiment (DOE) analysis using JMP software. The mild reaction conditions, which use *t*-BuBrettPhos Pd G3 or G4 precatalyst, result in minimal racemization of the amino acid ester. This method is the first synthetic application of the *t*-BuBrettPhos Pd G4 precatalyst. Mechanistic studies show that the observed erosion in enantiomeric excess is due to racemization of the amino acid ester starting material and not of the product.



The functionalization of amino acids is of great importance for the pharmaceutical and agrochemical industries (Figure 1).[1] Derivatives of natural amino acids can be employed as inexpensive chiral building blocks in these and other fields.[2] Moreover, the incorporation of functionalized amino acids in peptides and proteins has been crucial for advances in chemical biology, as they allow the development of new methods to study protein structure and function.[3] Among the many variations of functionalized amino acids, *N*-arylated amino acids and their esters are desirable compounds in these contexts, and a general and straightforward synthesis of these compounds in enantioenriched form is of substantial synthetic utility.

The *N*-arylation of amino acids and esters through nucleophilic aromatic substitution[4] or hypervalent iodine chemistry[5] has been reported, along with other more indirect methods for the preparation of arylated amino acids.[6] Transition metal catalyzed *N*-arylation of amino acids and esters using aryl (pseudo)halides constitutes another direct approach to these compounds. However, many reported methods for this transformation to date result in partial or complete racemization of the α stereocenter. In other instances, the stereochemical integrity of the product was not rigorously established. A general and robust protocol for the enantioretentive *N*-arylation of amino acids and esters remains to be developed and would be a useful addition to the current methods for amino acid functionalization.

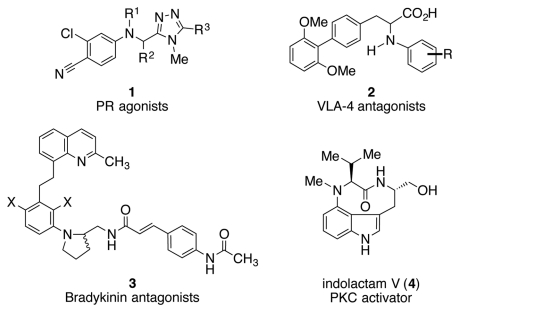


Figure 1. Medicinal agents containing an *N*-aryl amino acid core.

Previous efforts toward the development of a method for the *N*-arylation of amino acids have primarily focused on Cu-catalyzed Ullmann-type coupling reactions. Ma's seminal work constituted the first report in this field, and their conditions are generally applicable to the coupling of hydrophobic amino acids with aryl bromides.[7] More recently, methods with aryl iodides have been developed, but the stereochemical integrity of the product was only verified for a few substrates.[8] Other Cu-catalyzed methods employ harsh reaction conditions that likely result in racemization of the amino acid.[9] Comparatively little work has been done on the development of Pd-catalyzed *N*-arylation methods.[4,10] The reported conditions suffer from limited substrate scope, and significant racemization is observed for a majority of amino acids examined as substrates.[11] Methods for the stereoretentive coupling of amino acid esters tend to be even narrower in scope due to their greater propensity to racemize compared to amino acids themselves. Thus, the development of a general method for the *N*-arylation of these derivatives would be especially desirable. Over the past several years, our group has developed palladacycle precatalysts and demonstrated their advantages in challenging cross-coupling reactions.[12] In light of the mild conditions under which these precatalysts undergo activation, we believed that our third (G3)[13] and fourth (G4)[14] generation of precatalysts would be well suited for the *N*-arylation of amino acid esters without concomitant racemization. Herein, we report the development of a general, enantioretentive method for the *N*-arylation of amino acid esters.

N-Arylation of phenylalanine *tert*-butyl ester (**5a**) with bromobenzene was chosen as a model system for reaction development. Table 1 summarizes initial studies for which *t*-BuBrettPhos Pd G3 (**P1**) was selected as the precatalyst. Additional optimization results are presented in the Supporting

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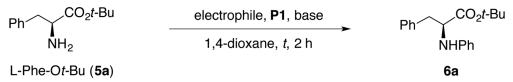
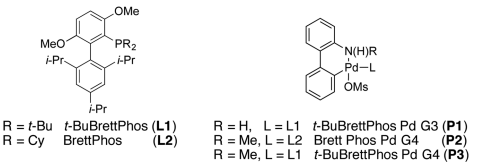
Table 1. Initial *N*-Arylation Experiments[a]



entry	electrophile	base	*t* (°C)	yield (%)[b]	ee (%)[c]
1	PhBr	NaO*t*-Bu	rt	29	0
2	PhBr	NaOPh	70	9	72
3	PhBr	Cs_2CO_3	70	19	73
4	PhCl	Cs_2CO_3	70	12	78
5	PhOTf	Cs_2CO_3	70	61	84



[a]Reaction conditions: phenylalanine *tert*-butyl ester free base (**5a**, 1.2 equiv), electrophile (1 equiv), **P1** (1 mol %), base (1.2 equiv). [b]Isolated yields. [c]Enantiomeric excess (ee) was determined by HPLC analysis using chiral stationary phases.

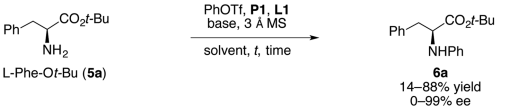
Information (SI, Figure S1). At the outset of our studies, we were aware that a strong base could readily racemize amino acid esters. Indeed, the *N*-arylation of **5a** using sodium *tert*-butoxide proceeded in 29% yield and resulted in complete racemization (entry 1). Thus, to maintain the stereochemical integrity of the amino acid ester, our efforts focused on identification of a weaker base suitable for the reaction. The use of sodium phenoxide and cesium carbonate afforded the *N*-arylation product **6a** in low yields but with an encouraging level of enantioretention (9% yield, 72% ee, entry 2 and 19% yield, 73% ee, entry 3, respectively). The conditions with cesium carbonate (entry 3) served as a suitable starting point for additional optimization. Further studies revealed that use of phenyl trifluoromethanesulfonate as the electrophile in place of bromobenzene resulted in greatly improved yield and enantioretention (entry 5).

At this point, reaction optimization was finished by Design of Experiment (DOE) analysis with the aid of JMP software.[15] For a single iteration of DOE analysis, several reaction variables served as input for the software, including both continuous (temperature and concentration) and categorical variables (base and solvent). Calculations then provided the least number of reactions necessary to run to determine whether each variable had a statistically significant effect on the reaction output (yield and enantioretention). After running these reactions and recording the output, calculations reported the effect of each variable. In this way, multiple iterations of DOE analysis led to the optimized reaction conditions.

Initial DOE analysis of the *N*-arylation of phenylalanine ester **5a** with phenyl trifluoromethanesulfonate and precatalyst **P1** examined 11 reaction variables (Table 2A). The effect of these variables on both the yield and enantiomeric excess of **6a** was evaluated. Three variables (ligand additive, treatment of base by grinding, and the ratio of amino acid ester to phenyl trifluoromethanesulfonate) did not exhibit a statistically significant effect on either the yield or enantiomeric excess of **6a**. Four additional variables (precatalyst loading, reaction time, concentration, and solvent) had a significant effect on either the yield or enantiomeric excess of **6a** but not both at the same time. However, the final four variables (temperature, quantity of the base, presence of 3 Å molecular sieves, and identity of the base) had significant but contrasting effects on the yield and enantiomeric excess of **6a**. For example, higher reaction temperatures resulted in isolation of **6a**

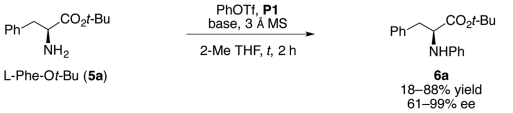
Table 2. Summary of Reaction Optimization by DOE:[a] **(A) Initial Analysis of 11 Reaction Variables; (B) Subsequent Analysis of Four Reaction Variables**

A.



variable	effect on yield	effect on ee	conclusion
ligand additive	0	0	omit
base treatment	0	0	omit
ratio **5a**:PhOTf	0	0	1:1
precatalyst loading	+	0	2 mol %
time	0	–	2 h
solvent (mL)	–	0	0.5 M
solvent	THF, 2-Me THF	dioxane, 2-Me THF	2-Me THF
t (°C)	+	–	optimize further
equiv base (to **5a**)	+	–	optimize further
3 Å MS	–	+	optimize further
base	Cs_2CO_3 (minor)	K_3PO_4 (minor)	optimize further

B.



variable	effect on yield	effect on ee	conclusion
t (°C)	+	–	optimize further
equiv base (to **5a**)	+	–	optimize further
3 Å MS	–	+ (minor)	omit
base	Cs_2CO_3	0	Cs_2CO_3

[a]For categorical variables, highest yield/ee obtained with listed entry. For continuous variables: 0 = variable has no effect on yield/ee, + = highest yield/ee obtained at highest value of variable, – = highest yield/ee obtained at lowest value of variable.

in higher yield but lower enantiomeric excess. These four variables were further examined in a second round of DOE analysis.

In this second iteration (Table 2B), the first seven variables were set to the conclusion value from the first analysis. This subsequent analysis showed that reaction temperature and quantity of base again had significant but contrasting effects on the yield and enantiomeric excess of **6a**. Thus, the optimal value of these two variables required reaching a compromise between acceptable yield and enantiopurity. The addition of 3 Å molecular sieves led to a significant decrease in the yield of **6a** and only a minor positive effect on stereoselectivity and was subsequently omitted from the optimized reaction conditions. The use of cesium carbonate as base provided an increase in the yield of **6a** while minimally affecting the enantiomeric purity of the product. With the results of this second DOE analysis taken into consideration, optimal results (69% yield of **6a** in 89% ee) were obtained when the reaction was conducted at 50 °C with 3 equiv of cesium carbonate. Increasing the loading of **P1** in this reaction from 2 mol % to 5 mol % increased the yield of **6a** without affecting the enantiomeric purity (93% yield, 91% ee). These conditions were used for investigations into the substrate scope of the arylation protocol.

The scope of amino acid ester substrates for this *N*-arylation reaction was first explored (Scheme 1). The optimized conditions were suitable for the *N*-arylation of a wide range of amino acid esters, including methyl, *tert*-butyl, and benzyl esters. The *N*-arylation of hydrophobic amino acid esters (glycine, alanine,

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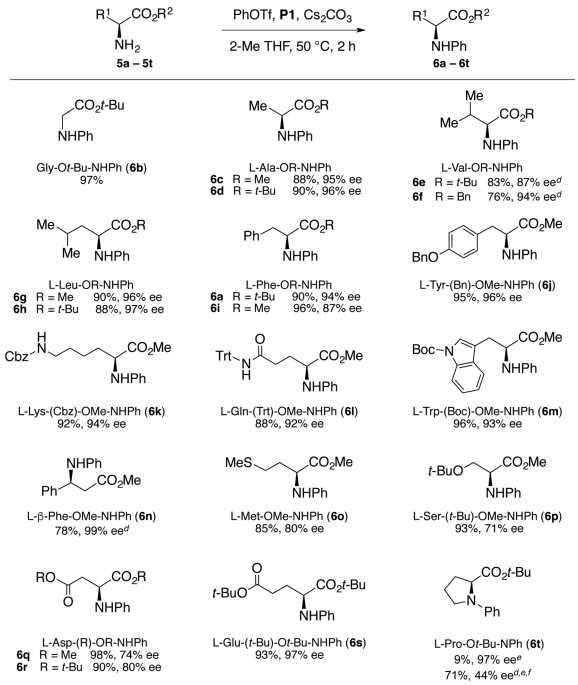
Scheme 1. Substrate Scope of the Amino Acid Ester[a,b,c]

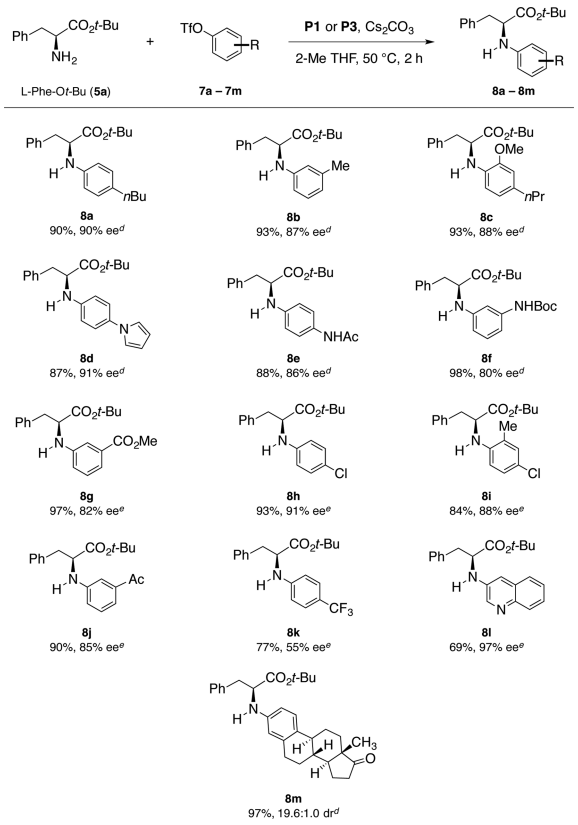


[a]Reaction conditions: amino acid ester (1 mmol), phenyl trifluoromethanesulfonate (1 mmol), **P1** (5 mol %), cesium carbonate (3 mmol), 2-methyltetrahydrofuran (2.0 mL). [b]Isolated yields (average of two runs). [c]Enantiomeric excess (ee) was determined by HPLC analysis using chiral stationary phases. [d]Reaction was run for 14 h. [e]**P2** (5 mol %) was used as the precatalyst. [f]Reaction was run at 80 °C.

valine, leucine, and phenylalanine esters) provided desired products **6a**–**6i** in high yield and good to excellent levels of enantioretention. A number of protected aromatic and polar amino acid esters were also transformed to the *N*-arylated products with low levels of enantioerosion and high synthetic efficiency, including tyrosine (benzyl protected, **6j**), lysine (Cbz protected, **6k**), glutamine (trityl protected, **6l**), tryptophan (Boc protected, **6m**), and glutamic acid (Boc protected, **6s**) esters. The *N*-arylation of some protected amino acid esters with other heteroatom-containing side chains, such as methionine, serine, and aspartic acid esters **5o**–**5r**, provided the expected products **6o**–**6r** in high yield but with a greater degree of erosion of enantiomeric purity. Proline was unreactive under standard conditions, although by employing precatalyst **P2**, the desired coupling product **6t** was obtained with minimal loss of enantiomeric purity, albeit in low yield. At higher temperature and longer reaction time, *N*-aryl proline **6t** was obtained in good yield but modest enantiomeric excess. Various protected cysteine, arginine, and histidine esters were found to be incompatible substrates for this reaction.

We next evaluated the aryl triflate substrate scope (Scheme 2). The previously optimized reaction conditions were deemed suitable for the *N*-arylation of the phenylalanine *tert*-butyl ester **5a** with electron-neutral and electron-rich substrates. For electron-poor aryl triflate substrates, the use of *t*-BuBrettPhos Pd G4 (precatalyst **P3**) in place of **P1** was found to facilitate conversion of the amino acid ester, leading to higher yields of the *N*-arylation product without eroding the enantiopurity. It is worthwhile to note that these cases represent the first synthetic applications of precatalyst **P3**. A range of aryl triflate substrates was then explored as substrates. *N*-Arylation of **5a** with aryl triflates with aliphatic

Scheme 2. Substrate Scope of the Aryl Triflate[a,b,c]



[a]Reaction conditions: phenylalanine *tert*-butyl ester (**5a**, 1 mmol), aryl triflate (1 mmol), cesium carbonate (3 mmol), 2-methyltetrahydrofuran (2.0 mL). [b]Isolated yields (average of two runs). [c]Enantiomeric excess (ee) was determined by HPLC analysis using chiral stationary phases. [d]**P1** (5 mol %) was used as the precatalyst. [e]**P3** (5 mol %) was used as the precatalyst.

substituents, such as **7a** and **7b**, provided the coupling products **8a** and **8b** in high yield and enantiomeric excess. The presence of *ortho* substituents on the aryl triflate was likewise tolerated, providing **8c** and **8i** with similarly high levels of efficiency and enantioretention. Functionalized aryl triflates containing a pyrrole (**8d**), a quinoline (**8l**), an acetamide (**8e**), or chloro substituents (**8h**, **8i**) all proved to be suitable substrates for this coupling process. Additionally, the *N*-arylation of **5a** with estrone triflate **7m** afforded the expected product (**8m**) in 98% yield and 19.6:1.0 dr. However, the presence of electron-withdrawing substituents, including an ester (**8g**), a ketone (**8j**), or a trifluoromethyl group (**8k**), led to higher levels of racemization.

We subsequently investigated the mechanism of racemization in this cross-coupling protocol. First, the *N*-arylation of phenylalanine *tert*-butyl ester **5a** with phenyl trifluoromethanesulfonate was conducted under the optimized conditions but stopped when the reaction proceeded to roughly 50% conversion (Scheme 3A). The enantiomeric excess of remaining **5a** and *N*-arylation product **6a** were determined in the crude reaction mixture. Racemization of the recovered starting material (**5a**) was observed (81% ee). In contrast, product **6a** was obtained in 97% ee. To test further for racemization of the product, the same experiment was performed with exogenous *N*-arylation product **9** (93% ee, Scheme 3B). Chromatographic purification of **9** from the crude reaction mixture demonstrated that the enantiomeric excess of **9** was unchanged, suggesting that product racemization

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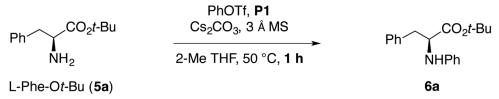
Scheme 3. (A) Experiment Determining the ee before and after the Reaction; (B) Experiment to Test for Product Racemization with Exogenous Product Added

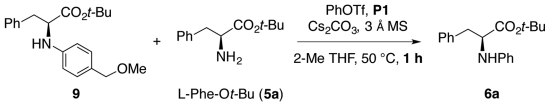
A.



L-Phe-O*t*-Bu (**5a**) **6a**

	ee before reaction	ee after reaction[a]
5a	99%	81%
6a	–	97%

B.



9 L-Phe-O*t*-Bu (**5a**) **6a**

	ee before reaction	ee after reaction[b]
9	93%	93%
5a	99%	81%
6a	–	93%

[a]Enantiomeric excess (ee) was determined directly from the crude reaction mixture by HPLC analysis using chiral stationary phases. [b]Enantiomeric excess (ee) was determined after purification by silica gel chromatography.

does not occur to a significant extent. In an additional experiment, the *N*-arylation of phenylalanine *tert*-butyl ester **5a** was conducted under the optimized reaction conditions, and the yield and enantiomeric excess of the product **6a** were monitored as a function of reaction time (see SI, Table S5). The enantiomeric excess of **6a** decreased as a function of time, which is consistent with our understanding that racemization in this reaction is mainly due to racemization of the starting material **5a** and not of the product.

In summary, we have developed a general method for the *N*-arylation of amino acid esters with aryl triflate electrophiles. Key to the development of this method was the use of (1) DOE analysis for reaction optimization and (2) *t*-BuBrettPhos Pd G3 (**P1**) and G4 (**P3**) precatalysts, which enabled the use of mild reaction conditions and resulted in minimal racemization of the amino acid ester. Given the importance of the *N*-aryl amino acid core structure in medicinal agents, we anticipate the adoption of this protocol in diverse contexts as a practical and improved method for their synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02082.

Experimental procedures along with experimental and spectroscopic data for new compounds (PDF)

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Notes

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands and precatalysts described in this work from which S.L.B. as well as former or current co-workers receive royalty payments.

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