Organic LETTERS

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Pd-Catalyzed Dimethylation of Tyrosine-Derived Picolinamide for Synthesis of (*S*)-*N*-Boc-2,6-dimethyltyrosine and Its Analogues

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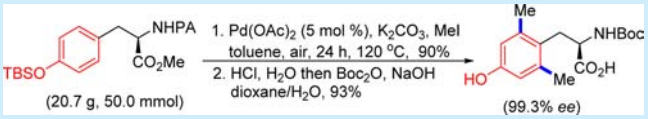
Supporting Information

ABSTRACT: A short and efficient synthesis of (*S*)-*N*-Boc-2,6-dimethyltyrosine utilizing palladium-catalyzed directed C−H functionalization is described. This represents the first general method for the *ortho*-dimethylation of tyrosine derivatives and offers a practical approach for preparing this synthetically important building block. Notably, throughout the reaction sequence no racemization occurs at the susceptible α-chiral centers.



The H-Tyr-Tic-OH dipeptide **1a** (Figure 1, Tic: (*S*)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid) is the smallest peptide fragment that still retained potent δ-opioid receptor antagonist properties.[1] Replacement of the tyrosine residue in this dipeptide with (*S*)-2,6-dimethyltyrosine (DMT), a conformationally restricted unnatural amino acid, gave improved δ-opioid affinity and selectivity.[2] Since the discovery of H-Dmt-Tic-OH (**1b**),[2] thousands of its analogues have been designed and synthesized for developing drugable opioid receptor modulators.[3] This campaign has resulted in the discovery of Eluxadoline (**2**), an orally administered, first-in-class drug for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D) in adults.[4]

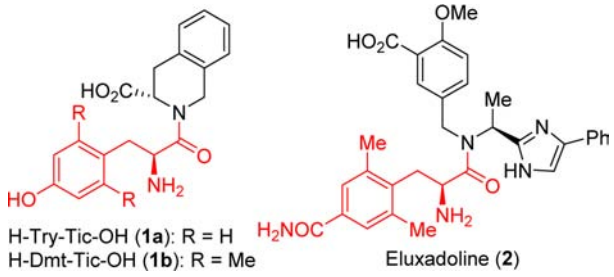
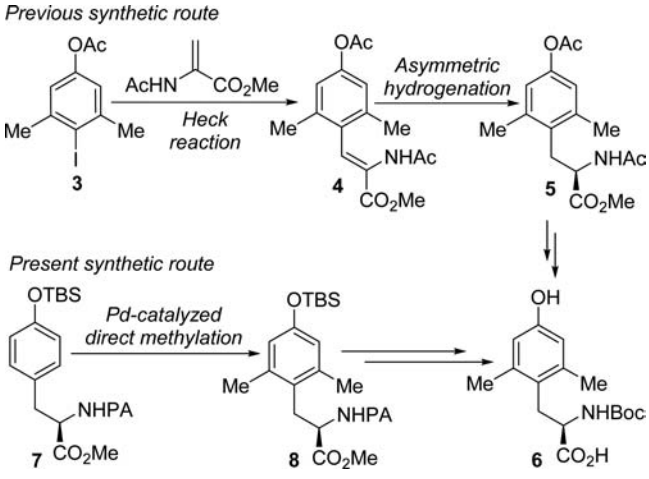


Figure 1. Structures of some potent δ-opioid receptor antagonists.

Although the structure of (*S*)-2,6-dimethyltyrosine is simple, its 2,6-dimethyl substituents make the assembly of this unnatural amino acid to be rather challenging.[5] To date, two major approaches have been developed for preparing (*S*)-2,6-dimethyltyrosine and its derivatives. One is alkylation of protected (2,6-dimethyl-4-hydroxy)benzyl halides with glycine-derived chiral synthons,[5a,b] while another one is asymmetric hydrogenation of (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate **4** to afford enantioenriched **5** (Scheme 1).[5c,d] In both approaches, tetra-substituted benzene starting materials are not conveniently available, and expensive reagents or catalysts are required to achieve asymmetric control. Although the asymmetric hydrogenation approach allows for the synthesis of (*S*)-*N*-Boc-2,6-dimethyltyrosine (**6**) on a large scale,[5c] the required catalyst is expensive, which results in high costs. During the studies on direct functionalization of conveniently available amino acid derivatives to obtain high value-added products via metal catalyzed C−H bond activation,[6] we found that Pd-catalyzed dimethylation of tyrosine derivative **7** could give **8** in

Scheme 1. Previous and Present Routes for Assembling (*S*)-*N*-Boc-2,6-dimethyltyrosine



Received: November 28, 2016
Published: December 27, 2016

DOI: 10.1021/acs.orglett.6b03548
Org. Lett. 2017, 19, 246−249

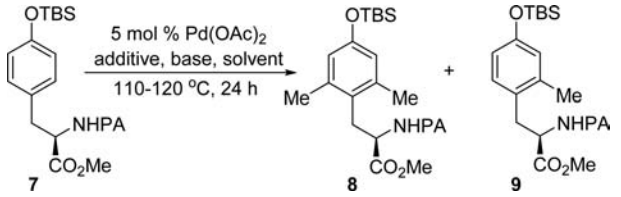
about 90% yield, and thereby providing an inexpensive method for synthesizing **6**. Herein we wish to detail our results.

The *ortho*-alkylation of acetanilides under the action of stoichiometric amounts of palladium acetate was initially reported by Tremont and Rahman in 1984.[7] In this reaction the acetoamido group was believed to coordinate with Pd and thereby serve as a directing group. In recent years, this idea was refreshed by employing more powerful picolinamide (PA) directing group.[8] Under the assistance of this group, direct *ortho*-alkylation of the amides generated from a number of benzylamines proceeded under the catalysis of 10 mol % $Pd(OAc)_2$.[8a] The key for this reaction was using NaOTf as the additive, *t*-AmylOH as the solvent, and oxygen as the oxidant.[8a] The major drawback of this transformation is it can not completely stop at the monoalkylation stage, and therefore, only *ortho*- and *meta*-substituted substrates gave single monoalkylation products. This problem may result from that monoalkylation products are more reactive than the corresponding substrates toward Pd-catalyzed C−H bond activation, which has been seen in several metal-catalyzed *ortho*-functionalizations of benzylamine-derived amides.[9−12] We envisioned that this special feature could turn to be an advantage for assembling (*S*)-2,6-dimethyl-tyrosine derivatives. Indeed, in their subsequent study Chen group has discovered that $Pd(OAc)_2$-catalyzed double methylation of a phenylalanine-derived picolinamide could be achieved under the action of 2 equiv of Ag_2CO_3.[8b] However, direct use of these conditions to prepare the (*S*)-*N*-Boc-2,6-dimethyltyrosine **6** from the tyrosine derivative **7** would not be cost-effective, mainly because using 2 equiv of silver salt not only increases the cost but also gives difficulty for recovery of more expensive Pd catalyst. Thus, we planned to discover more practical conditions for double methylation.

As demonstrated in Table 1, we started our investigation by conducting *ortho*-methylation of the amide **7** (preparing from (*S*)-tyrosine in 3 steps and 88% overall yield) under Chen's conditions.[8a] It was found that reaction occurred at 110 °C, but gave poor conversion and monomethylation product **9** as the major product (entry 1). Removal of the additive NaOTf gave a similar result (entry 2). Interestingly, a great improvement was observed by using mixed toluene and *t*-AmyOH as the reaction media. The similar phenomenon has been observed in Chen's study.[8b] In this case, reaction completed and gave the desired dimethylation product **8** as the major product (entry 3). Changing oxygen to air provided a similar but reproducible result (entry 4). It seemed that oxygen is important to this reaction because under Ar the conversion was significantly decreased (entry 5). After having failed to increase the yield of **8** by changing the bases (entries 6−9), we further explored the solvent effect. While 1,2-dichloroethane gave complete conversion (entry 10), dioxane and acetonitrile led to incomplete conversions (entries 11 and 12). Changing the ratio of toluene and *t*-AmyOH gave a worse result (entry 13). However, using toluene alone could slightly improve the yield of **8** (entry 14). The best result was observed when the reaction was carried out at 120 °C in toluene, which led to exclusive formation of **8** in about 95% yield (entry 15). Under the same conditions, an unsatisfactory result was obtained if the catalytic loading was reduced to 2.5 mol % (entry 16).

We then proceeded to investigate the effect of directing group on the efficiency of the reaction. Accordingly, amides **10**, **12**, **14**, and **16** that were generated from quinaldic acid,[10] 2-pyrazinecarboxylic acid,[11] 2-[bis(1-methylethyl)-amino]-2-oxo-acetic acid,[12] and 2-methoxyiminoacetic acid,[6a,b] respectively, were tested under the standard conditions (Scheme 2). Unfortunately, none of them gave improved results in either toluene or 1,2-dichloroethane.

Table 1. Pd-Catalyzed *ortho*-Methylation of Amide 7 under Different Reaction Conditions[a]



entry	atmosphere	base	solvent	yield (%)[b] 7/8/9
1[c]	O_2	K_2CO_3	*t*-AmyOH	60/1/13
2	O_2	K_2CO_3	*t*-AmyOH	65/2/15
3	O_2	K_2CO_3	toluene/*t*-AmyOH (9:1)	0/86/12
4	air	K_2CO_3	toluene/*t*-AmyOH (9:1)	0/85/12
5	Ar	K_2CO_3	toluene/*t*-AmyOH (9:1)	36/25/37
6	air	$KHCO_3$	toluene/*t*-AmyOH (9:1)	7/50/42
7	air	KOAc	toluene/*t*-AmyOH (9:1)	78/5/17
8	air	K_3PO_4	toluene/*t*-AmyOH (9:1)	75/5/18
9	air	Na_2CO_3	toluene/*t*-AmyOH (9:1)	42/9/48
10	air	K_2CO_3	$ClCH_2CH_2Cl$	0/80/9
11	air	K_2CO_3	dioxane	33/11/26
12	air	K_2CO_3	MeCN	60/5/27
13	air	K_2CO_3	toluene/*t*-AmyOH (1:1)	67/8/25
14	air	K_2CO_3	toluene	0/88/10
15[d]	air	K_2CO_3	toluene	0/95/0
16[e]	air	K_2CO_3	toluene	7/72/21

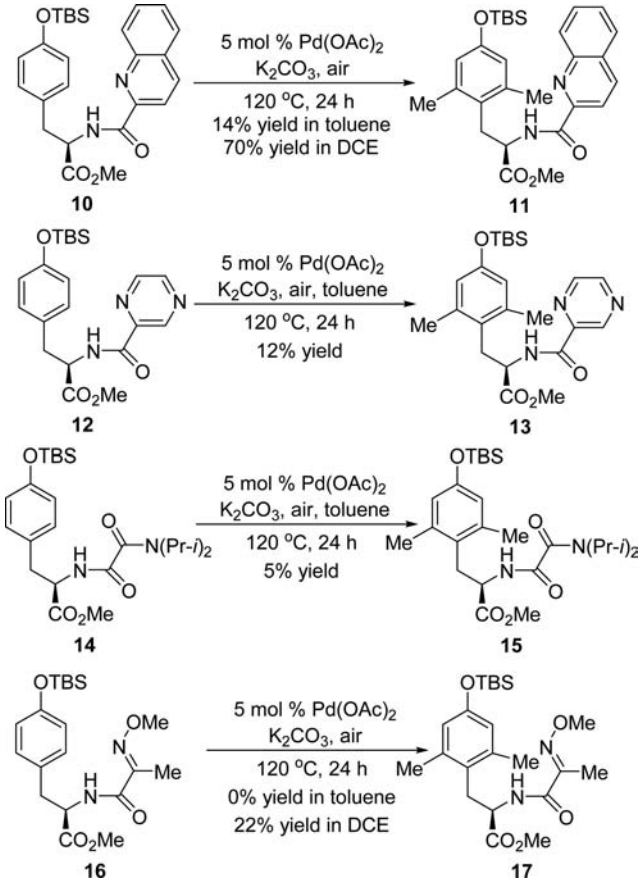
[a]General conditions: **7** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), base (0.6 mmol), 0.2 M, 110 °C, 24 h. [b]The yield was determined by ^1H NMR analysis of crude products using 1,3,5-trimethoxy-benzene as the internal standard. [c]Using NaOTf as the additive. [d]At 120 °C. [e]At 120 °C, 2.5 mol % $Pd(OAc)_2$ was used.

As outlined in Scheme 3, we also checked some analogues of **7** with different substituents at the 4-position. Benzoxyl substituted analogue **18a** gave the dimethylation product in 85% yield. However, poor yields were observed in case of chloro and ester substituted analogues **18b** and **18c** as the substrates. These results implied that electron-rich aryl compounds are more reactive toward Pd-catalyzed dimethylation. Interestingly, in the case of chloro substituted analogue **18b**, an excellent yield was obtained when 1,2-dichloroethane was used as the solvent. The chloride functionality in the products can be functionalized through a variety of transformations, thus providing a divergent route to access a library of medicinally relevant scaffolds. Furthermore, aryl chlorides can also be easily convert to the amide group, which will result in the core intermediate en route to the synthesis of Eluxadoline (**2**).[4,13]

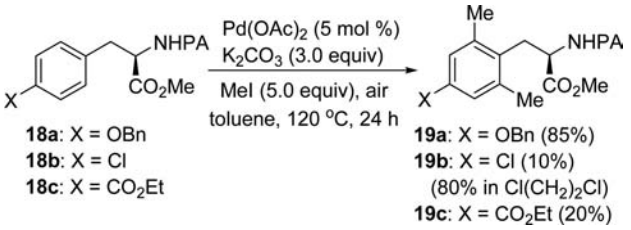
Next, we turned our attention to scaling up the dimethylation of **7** from a milligram to a multigram scale. Gratifyingly, we found that the optimized conditions were also equally effective on a large scale synthesis. When 20.7 g (50.0 mmol) of **7** was subjected to the dimethylation conditions, the desired product **8** was formed in 90% yield with 99.7% ee (Scheme 4). The deprotection of the amino and phenolic hydroxy groups using HCl, and subsequent Boc protection of the amino group with Boc anhydride, was achieved in a one-pot manner, giving **6** in a 93% yield without loss of enantiomeric excess. The overall yield, enantiomeric excess and atom-economy of this sequence was

DOI: 10.1021/acs.orglett.6b03548
Org. Lett. 2017, 19, 246−249

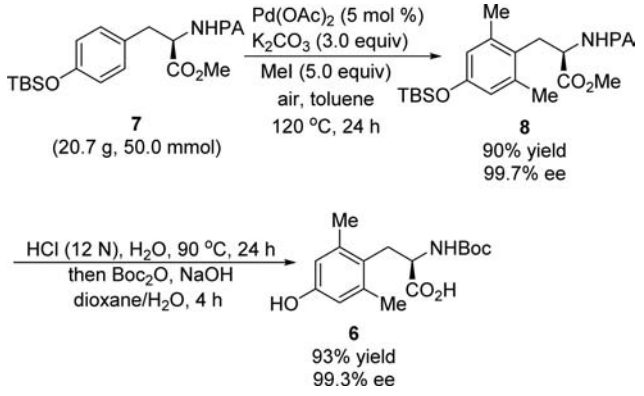
Scheme 2. Pd-Catalyzed *ortho*-Dimethylation of Other Tyrosine-Derived Amides



Scheme 3. Pd-Catalyzed *ortho*-Dimethylation of Analogues of 7



Scheme 4. Large-Scale Synthesis of 8 and Its Conversion to 6



thus better than the previously reported synthetic routes for preparing (*S*)-*N*-Boc-2,6-dimethyltyrosine.

In summary, we have demonstrated a novel, operationally simple strategy for the practical synthesis of (*S*)-*N*-Boc-2,6-dimethyltyrosine via Pd-catalyzed double C−H methylation. The present reaction sequence is very general, straightforward, easily scalable, and worked under mild reaction conditions for various tyrosine derivatives. Additionally, the use of commercially available amino acid derivatives eliminated the need of expensive reagents or catalysts, further facilitating the synthesis of these classes of molecules. Finally, this approach can also be extended to other enantiomerically pure α-substituted tyrosine derivatives, thus providing a facile route to access a library of analogues for practical application in drug discovery and development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03548.

Experimental procedures, spectra data, and copies of all new compounds (PDF)

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to Chinese Academy of Sciences (supported by the Strategic Priority Research Program, grants XDB20020200 and QYZDJ-SSW-SLH029) and the National Natural Science Foundation of China (grant 21132008) for their financial support.

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