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Design and synthesis of Fmoc-SPPS-ready iodoarene amino acid pre-catalysts and their reactivity in the catalytic oxytosylation of ketones

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ABSTRACT

A small suite of iodo-aryl amide containing amino acids were synthesized and assessed as catalysts for the hypervalent iodine(III) mediated α-oxytosylation of ketones. The efficiency of each catalyst was determined by comparing the relative rates of catalysis in the direct α-oxytosylation of propiophenone. In addition, these catalysts can be easily converted to congeners that are suitable for Fmoc-solid phase peptide synthesis for facile incorporation into a chiral peptide framework. This work facilitates the broader goal of our program to develop peptide-based enantioselective catalysts for hypervalent iodine chemistry.

Introduction

In recent years, a number of chiral materials bearing aryl iodides have emerged as versatile organocatalysts and reagents for enantioselective processes hinging on hypervalent iodine(III) intermediates [1–4]. The main attraction of utilizing hypervalent iodine catalysts arises from their ability to act as practical alternatives to heavy metals due to their inexpensive cost, environmentally benign and stable nature, and similar reactivity patterns in comparison to transition metals [3–5]. In the last decade, considerable attention has been focused on applying catalytic amounts of chiral aryl iodide precatalysts or iodine (III) stoichiometric reagents for enantioselective processes [2,5]. Many groups have demonstrated success with such systems, yet processes deploying highly modular and easily tunable catalyst scaffolds are less developed [2,6–8].

A number of investigations have validated the use of chiral peptide scaffolds in asymmetric catalysis [9–12]. The utility of peptides as catalysts stems from their facile synthesis, modular nature, and functional versatility [11–13]. We have initiated a strategy to combine the desirable features of hypervalent iodine (III) catalysis with the modularity of peptide scaffolds with the ultimate goal of developing a new class of peptide-based precatalysts that might be useful for enantioselective processes governed by hypervalent iodine(III) chemistry.

Initially, our group reported an investigation of the steric and electronic determinants that govern the reactivity of iodoarene amide catalysts in the direct α-oxytosylation of propiophenone (Scheme 1, see catalysts **1**–**3** and generic peptide **4**) [14]. In the context of our broader catalyst design strategy, the study of *N*-butyl iodoarene amides **1**–**3** was motivated by a desire to investigate the effects of the amide functional group on the catalytic performance of aryl iodide precatalysts. This line of inquiry was pursued because the amide linkage represented a logical means to incorporate the aryl iodo motif into a broader peptide framework. Nevertheless, this strategy was necessarily limited to the installation of the aryl iodo amide precatalyst to the *N*-terminus of the peptide chain (*e.g.* generic precatalyst **4**) using conventional Fmoc solid phase peptide synthesis (SPPS) [15–17]. While it was noted that the presence of an amide moiety slightly impaired the rate of the transformation, three highly reactive catalysts **1**–**3** emerged from this study, all of which positioned the iodine precatalyst in the *meta* position relative to the amide.

In the next phase of our efforts, we envisioned the incorporation of similar, highly reactive iodoarene amides into the side chain of Fmoc-SPPS-ready amino acids (*i.e.* generic scaffolds **5** and **6**, Scheme 1). Such a strategy would allow for the incorporation of the iodoarene active site anywhere along the peptide sequence by means of routine SPPS (see generic peptide **7**). Herein, we report

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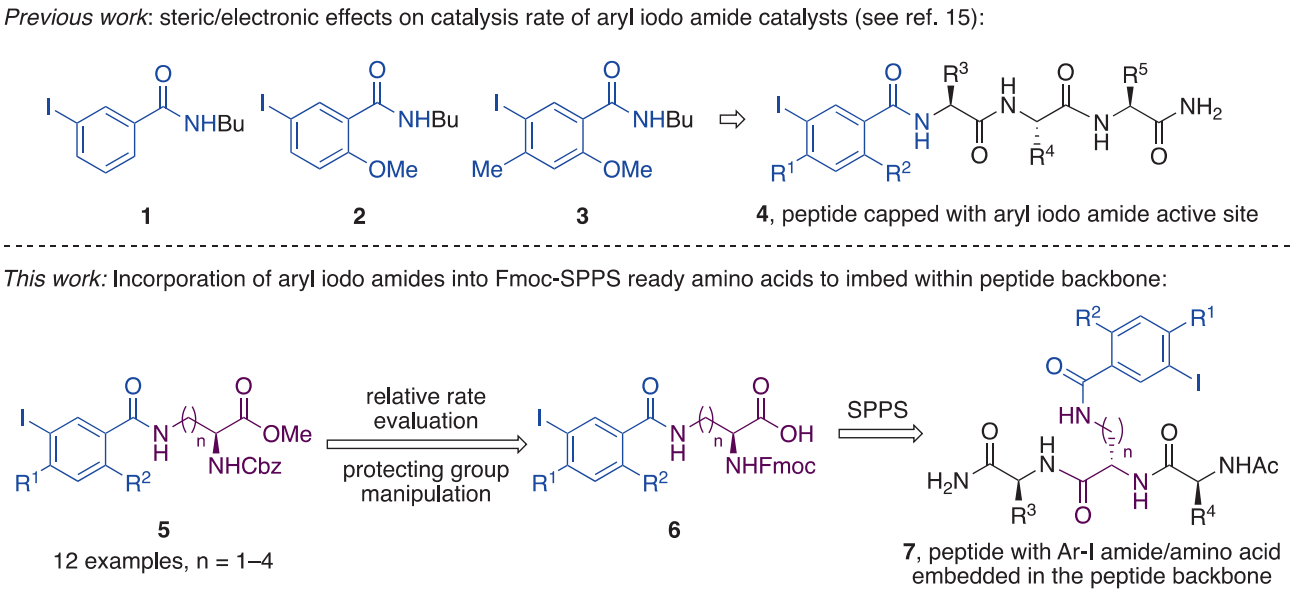


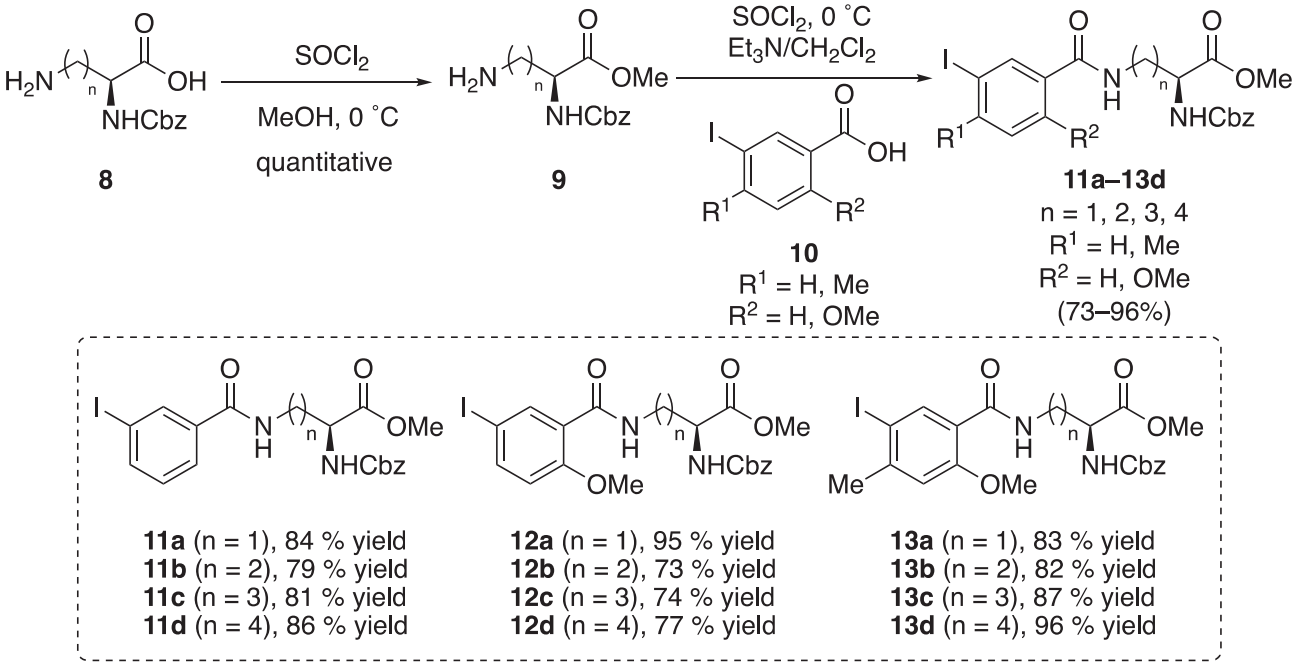
Scheme 1. Strategies for incorporating highly reactive aryl-iodo amide precatalysts into a peptide backbone for asymmetric hypervalent iodine catalysis.

the straightforward synthesis of a series of Fmoc-protected amino acids (**6**) that incorporate the critical iodoarene active site onto the amino acid side chain *via* an amide bond. Further, we demonstrate that these iodoarene containing amino acids exhibit comparable reactivity in the catalytic α-oxytosylation of ketones. Finally, we have demonstrated the feasibility of incorporating these novel amino acids into a peptide scaffold by means of conventional SPPS.

Results and discussion

We elected to install the appropriate iodoarene active site onto the side-chain of various diamino acids, through an amide coupling, resulting in a variety of iodinated amino acid catalyst analogs (**11a** – **13d**, Scheme 2). One would expect that the tether length between the free amine, slated to bear the Ar-I(III) active site, and the amino acid α-carbon might play a vital role in the design of an effective chiral catalyst, therefore we elected to probe simultaneous modification of L-diaminopropanoic acid (Dap, n = 1), L-diaminobutanoic acid (Dab, n = 2), L-ornithine (Orn, n = 3) and L-lysine (Lys, n = 4). Our syntheses began with the commercially available N_α-protected carboxybenzyl (*i.e.* Cbz or Z) diamino acids, because the Z protecting group was more suitable for conventional amidation reaction conditions than the base-labile Fmoc protecting group. Furthermore, we opted to first convert the N_α-Z-diamino acids to their methyl ester derivatives in order to avoid undesirable side-reactions during the acylation step.

The synthetic route for our small series of N_α-Z-amino methyl ester I(III)-precatalysts **11a** – **13d** is outlined in Scheme 2. To begin,



Scheme 2. Synthetic route to generate twelve aryl-iodo catalysts.

the commercially available N_α-Z-diamino acids (**8**) were converted to their corresponding acyl chlorides in the presence of thionyl chloride in methanol in order to generate the methyl esters, **9**. The desired active iodoarene sites (*i.e.* **10**) were then coupled to the free amine side-chain following traditional base-assisted amidation conditions to provide the desired iodo-arene amide containing amino acids **11a**–**13d**. Scaffold **12a** was successfully characterized by by X-ray crystallography (Fig. 1).

Catalysts **11a**–**13d** (Scheme 2) were then investigated as catalysts for the α-oxytosylation of propiophenone (**14**). All conversion rates and enantioselectivities (*i.e.* % ee) of product **15** were obtained by means of GC and chiral stationary phase HPLC analysis, respectively. The direct α-oxytosylation of propiophenone **14** was initially carried out for 24 h at room temperature in the presence of 10 mol % catalyst (Table 1).

N_α-Z-amino methyl ester I(III)-precatalysts **12b**, **12c**, **13b**, and **13c** generated the desired α-oxytosylated propiophenone product **15** in quantitative yields following the allotted 24 h (Entries 6–7 and 10–11, Table 1). Precatalyst structures **12b** and **12c** represent a 5-iodo-2-methoxy active site attached to the side-chain of Z-Dab-OMe and Z-Orn-OMe (**12b**, n = 2 and **12c**, n = 3), respectively. Precatalysts **13b** and **13c** possess a 5-iodo-2-methoxy-4-methyl iodoarene structure with amino acid side-chain lengths of n = 2 and 3. In order to discern the identity of the most active catalyst (s) in our 24 h screen, reactions promoted by the four best catalysts (**12b**, **12c**, **13b**, and **13c**) were quenched with dimethylsulfide after only 4 h. As shown in Table 2, catalyst **13c** – containing the active iodoarene site on the side-chain of the methyl ester derivative of ornithine – performed the best, followed by catalyst **12b**, with a 2-carbon tether length, providing the desired product in 49% and 46% conversions, respectively. (Entries 1 and 4, Table 2)

Catalysts **11a** and **11d**, with side chain tether lengths of n = 1 and n = 4, resulted in the lowest yields after 24 h at room temperature, with n = 4 giving the desired product **15** in only 35% yield (Entries 1 and 4, Table 1). This data suggests that there may be an ideal intermediate distance (in terms of catalyst activity) between the Ar-I site and the α-carbon of the amino methyl ester. Evidently, the most reactive catalytic framework involves the attachment of the iodoarene two or three methylene units away from the amino α-carbon. Conversely, the presence of one or four methylene units (*i.e.* modified Z-Dap-OMe and Z-Lys-OMe) results in slower conversion during the α-oxytosylation of propiophenone.

Not surprisingly, there was no significant enantioinduction observed in the preparation of **15** promoted by our library of functionalized amino methyl ester catalysts; they all resulted in essentially racemic mixtures of the α-oxytosylated product **15** regardless of side-chain tether length or the active iodoarene constituent (Tables 1 and 2).

Next, we modified the Cbz-protected amino methyl ester **11a** into an Fmoc-SPPS compatible amino acid (**16**) in order to demonstrate that the iodo-arene amide containing amino acids could be employed directly in solid phase peptide synthesis (Scheme 3). In order to accomplish this task, the methyl ester in **11a** was converted to the free carboxylic acid *via* saponification, then the Cbz-protecting group of the diamino acid was removed in the presence of trimethylsilyl iodide (TMSI) [18,19]. Subsequently, the amine was re-protected with the base-labile Fmoc carbamate [19–21]. These amino acids are accessible at gram scale as demonstrated by the preparation of Fmoc-SPPS-compatible amino acid catalyst **16** which contains an unsubstituted iodoarene active site tethered one methylene away from the α-amino acid carbon.

Further, we were able to demonstrate the successful incorporation of **16** into a simple β-turn peptide with the sequence Ac-Ile-(**16**)-Pro-D-Ala-Ala-Ala (**17**) following standard Fmoc-SPPS protocols [15–17]. Briefly, the peptide was prepared on the Rink Amide

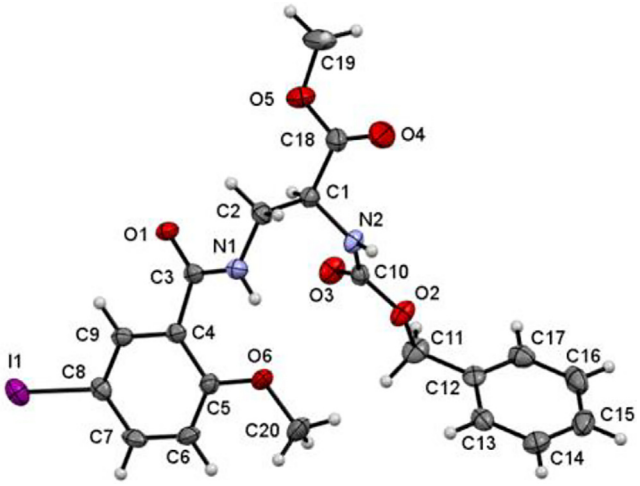
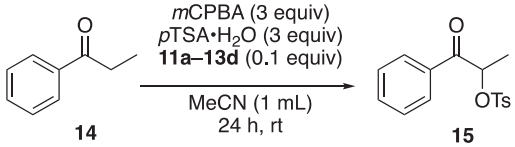


Fig. 1. X-ray structure of amino acid **12a**.

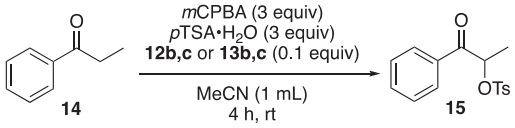
Table 1
Evaluation of catalysts **11a**–**13d** for the α-oxytosylation of propiophenone (**14**).



Entry	Catalyst	Yield of 15 (%)[a,b]	Ee of 15 (%)[c]
1	11a	47 ± 3	1.2
2	11b	82 ± 3	<1
3	11c	84 ± 1	1.6
4	11d	35 ± 2	1.5
5	12a	79 ± 3	1.7
6	12b	quant.	2.0
7	12c	quant.	3.8
8	12d	84 ± 1	<1
9	13a	93 ± 3	2.6
10	13b	quant.	2.1
11	13c	quant.	<1
12	13d	92 ± 3	<1

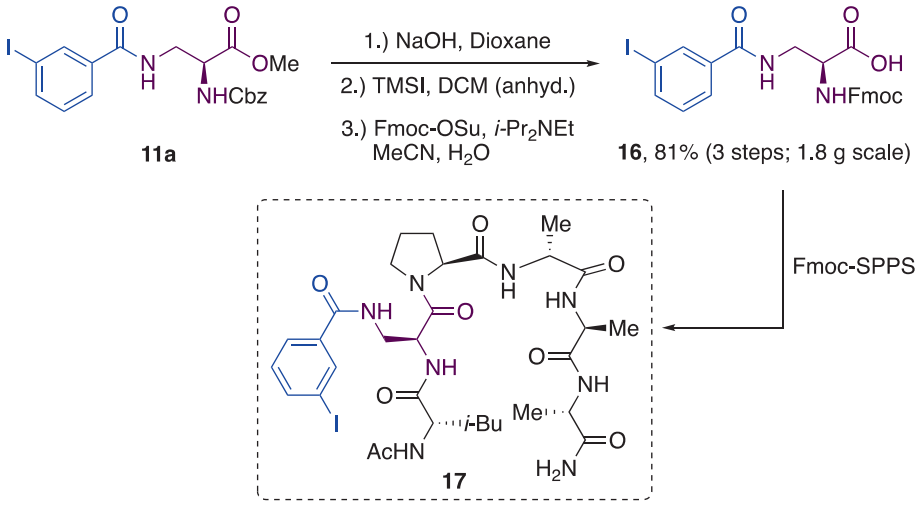
[a] GC yield (triplicate runs; ISTD: tetraglyme).
[b] 0.1 mmol scale.
[c] As judge by chiral stationary phase HPLC.

Table 2
Evaluation of catalysts **12b,c** and **13b,c** for the α-oxytosylation of propiophenone (14) over 4 h.



Entry	Catalyst	Yield of 15 (%)[a,b]	Ee of 15 (%)[c]
1	12b	46 ± 1	1.4
2	12c	42 ± 0	<1
3	13b	42 ± 1	1.3
4	13c	49 ± 1	<1

[a] GC yield (triplicate runs; ISTD: tetraglyme).
[b] 0.1 mmol scale.
[c] As judge by chiral stationary phase HPLC.



Scheme 3. Conversion of **11a** into Fmoc-SPPS ready **16** and incorporation into β-turn peptide **17**.

MBHA resin that is functionalized with an Fmoc-protected amine. Following resin swelling (CH_2Cl_2) and standard Fmoc-deprotection (20% 4-methylpiperidine in DMF) the desired amino acid residues were sequentially assembled onto the resin utilizing double treatments of HCTU as the coupling agent in the presence of diisopropylethylamine in DMF [15]. Upon coupling and deprotection of the final N-terminal amino acid (*i.e.* Ile), the N-terminus was acetylated by treatment of the resin with 5% acetic anhydride in DMF (5 mL, 5 min). The final iodoarene-containing peptide (**17**) was cleaved from the resin following standard trifluoroacetic acid (TFA) cleavage conditions (TFA/H_2O/triisopropylsilane, 95:4.5:0.5). Upon filtration from the resin, evaporation of the cleavage cocktail, and precipitation with ice cold ether a powdery, white peptide was obtained in 72% yield as judged from the resin loading. MALDI-TOF MS analysis was used to verify the success of this synthesis (See ESI for full details).

Conclusion

In conclusion, we have successfully generated a series of modified diamino acids that bear an iodoarene catalytic site (*i.e.* **11a**–**13d**) suitable for I(III) mediated transformations. We have evaluated the reactivity of these novel amino-acids in the context of the catalytic I(III) mediated α-oxytosylation of propiophenone. Further, these materials can be appropriately protected for facile incorporation into a peptide sequence by means of conventional Fmoc-SPPS. We hope to leverage these novel amino acids in the pursuit of developing an new class of peptide-based iodoarene catalysts for asymmetric hypervalent iodine chemistry. The results of these broader efforts will be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151723.

References

[1] S. Brenet, F. Berthiol, J. Einhorn, Eur. J. Org. Chem. 36 (2013) 8094–8096.
[2] A. Parra, S. Reboredo, Chem. Eur. J. 19 (2013) 17244–17260.
[3] Hypervalent Iodine Chemistry – Modern Developments in Organic Synthesis; Wirth, T., Ed.; Springer: Berlin, 2003; Vol. 224.
[4] V.V. Zhdankin, P.J. Stang, Chem. Rev. 108 (2008) 5299–5358.
[5] H. Liang, M.A. Ciufolini, Angew. Chem., Int. Ed. 50 (2011) 11849–11851.
[6] A. Yoshimura, V.V. Zhdankin, Chem. Rev. 116 (2016) 3328–3435.
[7] M. Brown, U. Farid, T. Wirth, Synlett 24 (2013) 424–431.
[8] T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, J. Am. Chem. Soc. 135 (2013) 4558–4566.
[9] S.J. Miller, Acc. Chem. Res. 37 (2004) 601–610.
[10] P.I. Dalko, L. Moisan, Angew. Chem., Int. Ed. 40 (2001) 3726–3748.
[11] E.R. Jarvo, S.J. Miller, Tetrahedron 58 (2002) 2481–2495.
[12] J. Duschmale, Y. Arakawa, H. Wennemers, Asymmetric Organocatalysis 2 (2012) 741–786.
[13] H. Togo, K. Sakuratani, Synlett (2002) 1966–1975.
[14] T.R. Lex, M.I. Swasy, D.C. Whitehead, J. Org. Chem. 80 (2015) 12234–12243.
[15] C.A. Hood, G. Fuentes, H. Patel, K. Page, M. Menakuru, J.H. Park, J. Pept. Sci. 14 (2008) 97–101.
[16] W.C. Chan, P.D. White, Fmoc Solid Phase Peptide Synthesis: A Practical Approach, Oxford University Press, Oxford, UK, 2000.
[17] G.B. Fields, R.L. Noble, Int. J. Peptide Res. 35 (1990) 161–214.
[18] S. Urwyler, P. Floersheim, B.L. Roy, M. Koller, J. Med. Chem. 52 (2009) 5093–5107.
[19] Y. Wang, L.H. Bluhm, T. Li, Anal. Chem. 72 (2000) 5459–5465.
[20] J.K. Kretsinger, J.P. Schneider, J. Am. Chem. Soc. 125 (2003) 7907–7913.
[21] V. Dzubeck, J.P. Schneider, Tetrahedron Lett. 41 (2000) 9953–9956.