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Novel Cyclic Tripeptides and Substituted Aromatic Amino Acids via Ruthenium-Activated S_NAr Reactions

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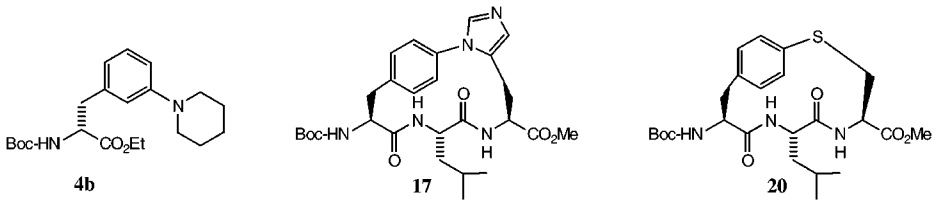
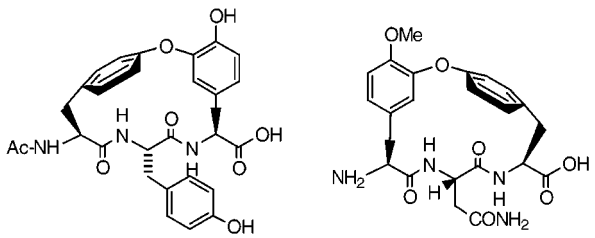
ABSTRACT



Chlorophenylalanines η^6-complexed to ruthenium undergo S_NAr reactions with a variety of nucleophiles to form substituted phenylalanines exemplified by 4b. Extension of these reactions to intramolecular ruthenium-activated S_NAr cyclizations led to three novel cyclic tripeptide systems (exemplified by 17 and 20).

Several peptide-derived natural products contain biaryl ether linkages,[1] a functionality that may be important for restricting conformational freedom.[2] While many methods are available to form biaryl ethers, the ruthenium-activated S_NAr reaction offers access to peptide-derived systems under mild conditions.[3,4] Previously, we showed that cyclic biaryl ether-containing tripeptides K-13 (**1**) and OF-4949-III (**2**) can be synthesized using a ruthenium-activated intramolecular S_NAr reaction for the macrocyclization step.[4] Here we report the expansion of this methodology to nucleophiles in amino acids histidine, cysteine, and lysine in intramolecular reactions and additional simple nucleophiles in intermolecular reactions.



Intermolecular S_NAr reaction of various nucleophiles with simple ruthenium-activated aromatic systems is well characterized.[5] We decided to investigate the utility of these reactions in more functionalized systems. Boc-3-chlorophenylalanine ethyl ester complex **3** in which the aromatic ring is η^6-complexed to cyclopentadienyl ruthenium hexa-

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(1) For reviews see: (a) Evans, D. A.; DeVries, K. M. In *Glycopeptide Antibiotics, Drugs and the Pharmaceutical Sciences*; Nagarajan, R., Ed.; Marcel Decker Inc.: New York, 1994; Vol. 63, p 63. (b) Itokawa, H.; Takeya, K. *Heterocycles* **1993**, *35*, 1467. (c) Zhu, J. *Synlett* **1997**, 133.

(2) (a) Hart, P. A.; Rich, D. H. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press Inc.: San Diego, 1996; p 393. (b) Fairlie, D. P.; Abbenante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654. (c) Veber, D.; Holly, F. W.; Nutt, R. F.; Bergstrand, S.; Brady, S. F.; Hirschmann, R.; Glitzer, M. S.; Saperstein, R. *Nature* **1979**, *280*, 512.

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(4) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488.

(5) (a) Moriarty, R. M.; Ku, Y. Y.; Gill, U. S. *Organometallics* **1988**, *7*, 660. (b) Moriarty, R. M.; Guo, L.; Ku, Y.; Gilardi, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1765. (c) Dembek, A. A.; Fagan, P. J. *Organometallics* **1996**, *15*, 1319.

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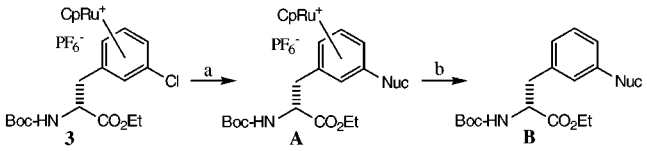
fluorophosphate was used as the model system. Displacement of chlorine by a variety of nucleophiles, followed by photolytic removal of the ruthenium complex (Scheme 1),

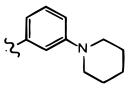
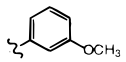
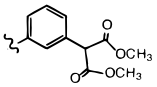
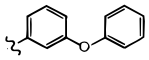
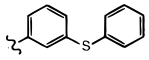
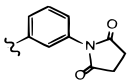
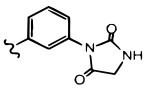
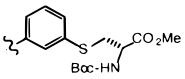
Scheme 1



(a) Nucleophile, NaH, THF (b) CH_3CN, hv

led to the substituted phenylalanines shown in Table 1. In this reaction the sodium anions of phenol, benzenethiol, dimethyl malonate, methanol, and excess neutral piperidine readily displaced chloride in typical fashion. Additionally, the sodium thiolate of Boc-Cys-OMe and weakly nucleophilic sodium anions of succinimide and hydantoin displaced chloride from **3**, although no attempts were made to optimize these three reactions.

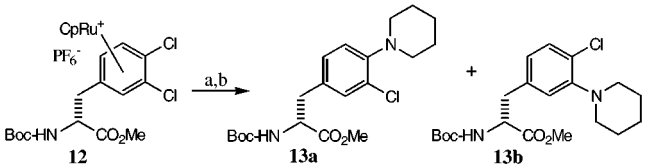
Table 1. Intermolecular S_NAr Reactions

cmpd	nucleophile	product	% yield (A)	% yield (B)
4	Piperidine[a]		88	72
5	Methanol[b]		97	70
6	Dimethyl malonate		88	55
7	Phenol		81	63
8	Benzenethiol		95	62
9	Succinimide[c]			29 (2 steps)
10	Hydantoin[c]			16 (2 steps)
11	Boc-Cys-OMe		45	33

[a] Five equivalents, no NaH for step 1. [b] Complete transesterification observed. [c] DMF as solvent for step 1.

Dichloroaromatic rings are known to undergo stepwise displacement of halogen.[6] However, displacement was not regioselective with ruthenium complex 3,4-dichlorophenylalanine **12** (Scheme 2). For example, nucleophilic attack by

Scheme 2



(a) 2.5 eq. piperidine, THF, 24 hrs. (b) CH_3CN, hv, 24 hrs. 65% (combined yield)

piperidine on **12** gave equal amounts of the 3- and 4-substituted aniline derivatives (**13a** + **13b**). However, only monosubstitution was observed, even with an excess of piperidine.

Displacement of both chlorines from **12** could be accomplished with sodium benzenethiolate. Additionally, the cyclopentadienyl ruthenium complexes of monochloro **13a** and **13b** react with sodium benzenethiolate to give the thioether and piperidine-substituted phenylalanine. Unfortunately, the present irradiation technique did not remove ruthenium from the complex, a problem previously noted with highly heteroatom-substituted aromatic rings.[5c] Further work on decomplexation is therefore required. The ease of displacement of chlorine in both mono- and dichlorinated phenylalanines and the compatibility of the protected amino acid complex with a variety of nucleophiles indicates that libraries of substituted peptides could be prepared by use of combinatorial chemistry.

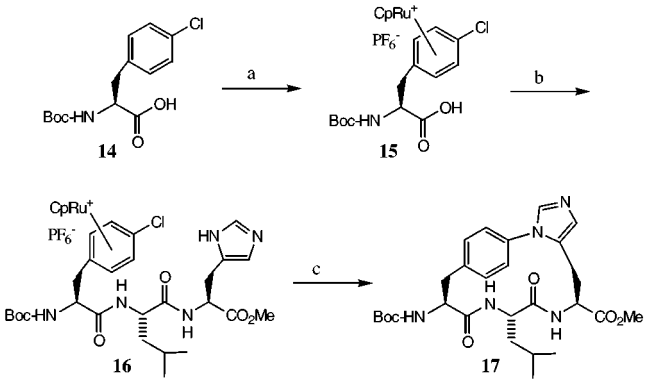
Our results with model intermolecular ruthenium-activated S_NAr reactions led us to see if an intramolecular version could be used to synthesize novel cyclic systems. Previously, only phenols[3,4] have been used as nucleophiles in the ruthenium-activated intramolecular S_NAr reaction. The nucleophilic heteroatoms sulfur and nitrogen in cysteine, histidine, and lysine containing tripeptides were chosen to explore this area of chemistry and provide entry to 14-, 15-, and 17- member ring systems, respectively.

Formation of the histidine-containing cyclic tripeptide began with complexation of ruthenium to Boc-(4Cl)Phe-OH[7] (**14**) followed by peptide coupling with Leu-His-OMe to give the ruthenium-containing linear tripeptide **16** (Scheme 3). Cyclization under high dilution conditions (c = 5 mM) followed by photolytic decomplexation of ruthenium[3] led to the novel heteroaryl cyclized tripeptide **17**.

The first attempts to synthesize the analogous cysteine and lysine cyclic peptides were disappointing due to low yields obtained in the cyclization step. Our first attempt, outlined for cysteine (Scheme 4), began with peptide coupling of **15** to the free amine derived from Fmoc-Leu-Cys(Mmt)-OMe (**18**) to give ruthenium-containing linear tripeptide **19**. Highly acid-labile protecting groups [4-methyoxytrityl (Mmt) for cysteine and 4-methyltrityl (Mtt) for lysine] were chosen for side-chain protection. The trityl group was selectively

(6) Pearson, A. J.; Park, J. G.; Zhu, P. Y. *J. Org. Chem.* **1992**, *57*, 3583.
(7) Pearson, A. J.; Park, J. G. *J. Org. Chem.* **1992**, *57*, 1744.

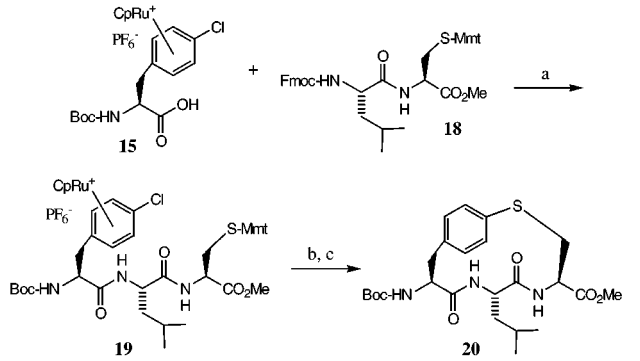
Scheme 3



(a) $RuCp(CH_3CN)_3PF_6$, DCE, Δ. 95% (b) Leu-His-OMe, EDCI, HOBt, DMF. 82%
(c) i. K O^{t}Bu, -78°C, THF, DMF, 3 days. ii. CH_3CN, hv. 24%.

removed in the presence of the Boc group by use of 94/5/1 CH_2Cl_2/TES/TFA at 0 °C for 30 min.[8] After deprotection of the thiol group, intramolecular S_NAr cyclization was accomplished by use of 40% KF on Al_2O_3 in the presence of 18-crown-6. Photolytic decomplexation afforded cyclized tripeptide **20**. When the same strategy and conditions were repeated with lysine, a very disappointing yield of 2% was obtained for the deprotection/cyclization/decomplexation sequence.

Scheme 4

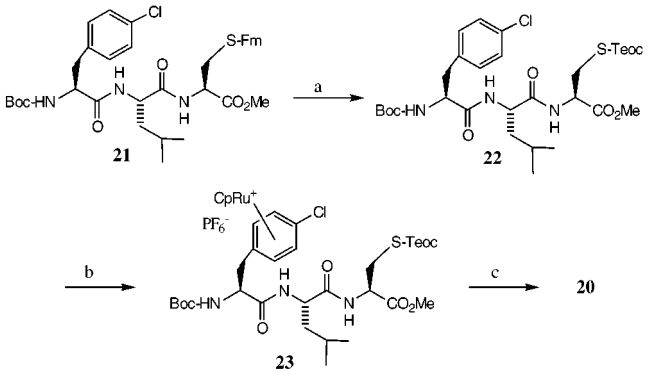


(a) i) 50% piperidine/DMF, ii) EDCI, HOBt, DMF, 75%. (b) 94/5/1 CH_2Cl_2/TES/TFA, 0°C. 56%
(c) i) 40% KF on Al_2O_3, 18-C-6, THF/DMF, ii) CH_3CN, hv, 18%

Greater success in the cyclization step for both cysteine and lysine analogues was achieved by changing the side-chain protecting group from an acid-labile trityl group to the fluoride-labile 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group. The new protecting group strategy allowed two improvements: (i) selective η^6-complexation of ruthenium to the linear tripeptide, and (ii) one-pot deprotection/cyclization conditions.

Application of the new strategy began with a protecting group switch from S-fluorenylmethyl (Fm) in tripeptide **21** to the S-Teoc group in **22** by use of the hindered guanidinium base 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]-pyrimidine (MTBD) (Scheme 5). Selective η^6 ruthenium

Scheme 5

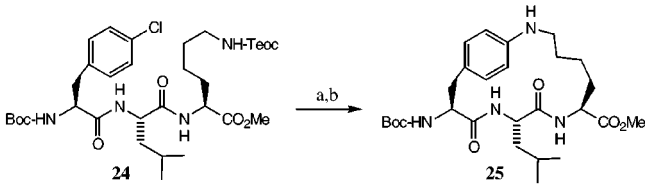


(a) MTBD, Teoc-p-nitrophenyl, 5/1 CH_3CN/DMF, -20°C, 59%
(b) $RuCp(CH_3CN)_3PF_6$, DCE, Δ, 95%
(c) i) TBAF, THF, DMF, -78°C, ii) CH_3CN, hv, 52%

complexation provided linear tripeptide **23** in excellent yield. The one-pot deprotection/cyclization was found to occur using a variety of fluoride sources, with TBAF giving the highest yields. Photolytic decomplexation provided **20** in 52% yield for the final deprotection/cyclization/decomplexation sequence.

The same protocol applied to the lysine analogue **24** (Scheme 6) also afforded the cyclic peptide. Reaction of the

Scheme 6



(a) $RuCp(CH_3CN)_3PF_6$, DCE, Δ, 99%,
(b) i) TASF, THF, DMF, -78°C, ii) CH_3CN, hv, 20%

aromatic peptide **24** with cyclopentadienyltris(acetonitrile)-ruthenium(II) hexafluorophosphate gave the η^6 ruthenium complex cleanly. Subsequent deprotection and cyclization with an alternate fluoride source, tris(dimethylamino)sulfur (trimethylsilyl) difluoride (TASF), followed by photolytic decomplexation gave the cyclic tripeptide **25**.

The overall conformation of compounds **17**, **20**, and **25** appears by molecular modeling to be β-strand in nature with differing degrees of conformational flexibility depending on ring size. The actual crystal structures for these molecules have not yet been obtained. However, several cyclic biaryl ether tripeptides previously synthesized have been shown by this lab[9] and by Still[10] to be β-strand mimetics. These mimetics inhibit metalloproteases and upon derivatization

(8) Barlos, K.; Gatos, D.; Chatzi, O.; Koutsogianni, S.; Schafer, W. In *Peptides 1992, Proc. 22nd European Peptide Symposium*; Schneider, C. H., Eberle, A. N., Eds.; ESCOM: Leiden, 1993; p 283.

with a hydroxyethylamine isostere inhibit HIV-protease.[9] The β-strand conformation is thought to play an important role in the activity of these compounds. The ability to alter the conformational flexibility of the tripeptide and thus its β-strand conformation via side-chain constraint would be an effective experiment in determining the extent to which the overall shape influences binding.

The use of the ruthenium-activated S_NAr reaction has provided ready access to several new substituted phenylalanine derivatives and three novel cyclic tripeptide systems under conditions that do not appear to affect amide bonds, esters, and epimerizable α-centers. These procedures provide a mild and general method for the formation of substituted peptide-derived phenylalanine derivatives containing a wide range of functionality and the conformationally restricted tripeptide units may find use in biological studies.

Acknowledgment. This work was supported by a research grant from the National Institutes of Health (GM 50113).

Supporting Information Available: Experimental procedures and full characterization for compounds **3**, **4b**, **5b**, **6b**, **7b**, **8b**, **17**, **20**, **23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Janetka, J. W.; Raman, P.; Satyshur, K.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 441.

(10) Hobbs, D. W.; Still, W. C. *Tetrahedron Lett.* **1989**, *30*, 5405.