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Copper-Catalyzed Synthesis of Medium- and Large-Sized Nitrogen Heterocycles via N-Arylation of Phosphoramidates and Carbamates

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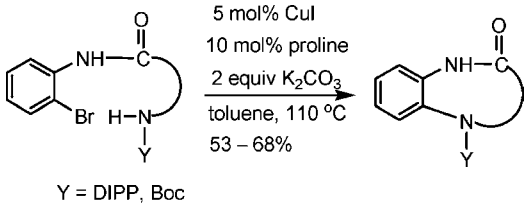
ABSTRACT



We have developed an efficient method for the preparation of medium- and large-sized nitrogen heterocycles via copper-catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates. Introduction of the phosphoryl group or *tert*-butoxycarbonyl at *N*-termini can improve intramolecular cyclization under copper catalysis, and the phosphoryl and *tert*-butoxycarbonyl can easily be removed under the mild conditions; thus, the convenient and efficient method is suitable for the preparation of medium- and large-sized nitrogen heterocycles.

Medium-sized heterocycles are very important compounds as biologically active natural products,[1] as drug candidates,[2] as materials[3] and for catalysis.[4] Direct cyclization methods are often ineffective because of enthalpic (increasing strain in the transition state) and entropic influences (probability of the chain ends meeting) unless certain conformational restraints are present in the acyclic precursor, so the generation of medium-sized nitrogen heterocycles possessing defined constitutions and configurations is still a challenge in organic synthesis.[1a] Among the various available methods, such as cycloaddition reactions, ring transformations, and cyclization reactions, the latter are probably the most commonly used because of a number of possible initiators and terminators. For example, the Staudinger ligation reaction, independently developed by the research groups of Bertozzi[5] and Raines,[6] might also serve as a powerful method for the facilitation of difficult lactamization reactions.

On the other hand, palladium-catalyzed amination/amidation of aryl halides and pseudohalides has attracted considerable attention during the past 10 years because of the

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(1) Reviews: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (c) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131. Selected examples: (d) Lindström, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94. (e) Bieräugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673. (f) Derrer, S.; Davies, J. E.; Holmes, A. B *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957. (g) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 44. (h) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(2) (a) Taunton, J.; Collins, J. L.; Schreiber,S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412. (b) Murray, P. J.; Kranz, M.; Ladlow, M.; Taylor, S.; Berst, F.; Holmes, A. B.; Keavey, K. N.; Jaxa-Chamiec, A.; Seale, P. W.; Stead, P.; Upton, R. J.; Croft, S. L.; Clegg, W.; Elsegood, M. R. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 773.

(3) (a) Sanchez-Quesada, J.; Ghadiri, M. R.; Bayley, H.; Braha,O. *J. Am. Chem. Soc.* **2000**, *122*, 11757. (b) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988.

(4) Jarvo, E. R.; Miller,S. J. *Tetrahedron* **2002**, *58*, 2481.

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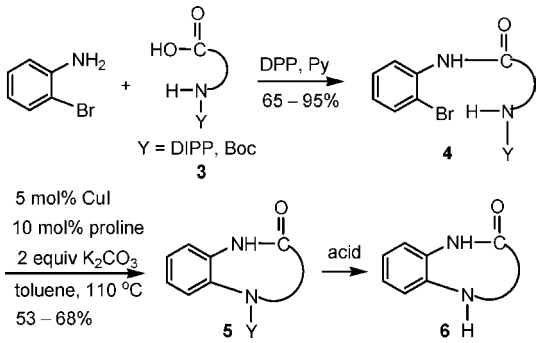
pioneering contributions by the groups of Buchwald[7] and Hartwig.[8] The copper-catalyzed Ullmann reaction (*N*-arylation of amines) and Goldberg reaction (*N*-arylation of amides) have been the subject of recent studies.[9−14] Copper-catalyzed intramolecular *N*-arylation of amines leading to a seven-membered ring has been reported from the groups of Ma[15a] and Fukuyama,[15b] respectively. Banfi and co-workers have elegantly demonstrated such a possibility for the preparation of 7-membered heterocycles employing a ring expansion of a α-lactam with a neighboring nitrogen nucleophile.[16] Both palladium- and copper-catalyzed intramolecular *N*-arylations leading to 5-, 6-, and to a lesser extent, 7-membered rings have been investigated, and various efficient catalytic systems have been developed.[15,17] However, most of the attempts to access medium- and large-sized ring systems by direct *N*-arylation were, to the best of our knowledge, unsuccessful. Recently, domino copper-catalyzed intermolecular *N*-arylation of α-lactam followed by ring expansion has been developed for the synthesis of medium-sized nitrogen heterocycles by Buchwald and co-workers.[18] Zhu and co-workers have developed a novel catalytic domino process to construct azaphenanthrenes fused to 8-, 10-, 11-, and 13-membered lactam motifs, where the bisaryl diiodide function plays the crucial role in the cyclization of amides.[19] In this paper, our copper-catalyzed results are presented on the development of novel and generally applicable methods applying *N*-arylation of phosphoramidates and carbamates to provide the closure of medium- and large-sized nitrogen heterocycles.

N-Phosphorylation of various unnatural amino acids and the peptide Ala-Pro was carried out via the Antherton−Todd method (Scheme 1).[20] Reaction of diisopropyl phosphite (**1**)

Scheme 1. Synthetic Route of Medium- and Large-Sized Nitrogen Heterocycles



with amino acids (**2a**−**f**) or peptide Ala-Pro (**2g**) in water and ethanol in the presence of carbon tetrachloride and triethylamine provided *N*-diisopropylphosphoamino acids (DIPP-AA) (**3a**−**f**) and peptide (DIPP-peptide) (**3g**) (Figure 1) in 85−89% yields. *N*-Boc-amino acids (*N*-*tert*-butoxycarbonylamino acids) (**3h** and **3i**) were also prepared according to the general procedure.[21] Coupling of *N*-phosphoamino acids and peptide or *N*-Boc-amino acids with 2-bromoaniline in pyridine using 2 equiv of diphenyl phosphite (DPP) as the coupling agent according to the reported procedure[22,23] gave phosphoramidates and *N*-Boc-peptide analogues (**4**) in 65−95% yields.

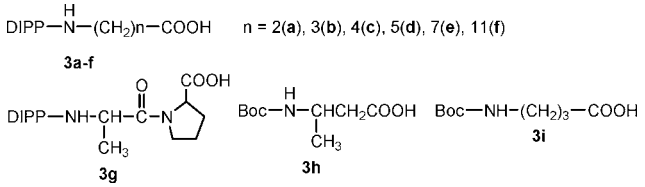


Figure 1. Synthesized compounds **3a**−**i**

The cyclization of phosphoramidates and carbamates via *N*-arylation is the key step. We first attempted the cyclization of compound **4b** in toluene under catalysis of CuI using proline as the ligand (Scheme 1). TLC showed that it transferred into the eight-membered cyclic product **5b** within 72 h, and isolation by silica gel column chromatography

(5) (a) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007. (b) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141. (c) Saxon, E.; Luchansky, S. J.; Hang, H. C.; Yu, C.; Lee, S. C.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2002**, *124*, 14893.

(6) (a) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939. (b) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2001**, *3*, 9. (c) Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Org. Chem.* **2002**, *67*, 4993.

(7) (a) Wolfe, J. P.; Wagaw; S.; Marcoux, J. F.; Buchwald, S. F. *Acc. Chem. Res*. **1998**, *31*, 805. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(8) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 7.

(9) Ley, S.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(10) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 581. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 793 and references therein.

(11) Klapars, A.; Antila, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, 123, 7727.

(12) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421.

(13) Kang, S.-K.; Kim, D.-H.; Pak, J.-N. *Synlett* **2002**, 427.

(14) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc*. **1998**, *120*, 12459. (b) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

(15) Copper-catalyzed: (a) Ma, D.; Xia, C. *Org. Lett*. **2001**, *2*, 2583. (b) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231.

(16) (a) Banfi, L.; Guanti, G.; Rasparini, M. *Tetrahedron Lett.* **1998**, *39*, 9539. (b) Banfi, L.; Guanti, G.; Rasparini, M. *Eur. J. Org. Chem.* **2003**, 1319.

(17) Palladium-catalyzed: (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451. (c) Yang, B. H.; Buchwald, S. L. *Org. Lett*. **1999**, *1*, 35. (d) Song, J. J.; Yee, N. K. *Org. Lett*. **2000**, *2*, 519. (e) Evindar, G.; Batey, R. A. *Org. Lett*. **2003**, *5*, 133. (f) Margolis, B. J.; Swidorski, J. J.; Rogers, B. N. *J. Org. Chem.* **2003**, *68*, 644. (g) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051. (h) Brain, C. T.; Steer, J. T. *J. Org. Chem*. **2003**, *68*, 6814.

(18) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc*. **2004**, *126*, 3529.

(19) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc*. **2004**, *126*, 14475.

(20) Ji, G. J.; Xue, C. B.; Zeng, J. N.; Li, L. P.; Chai, W. G.; Zhao, Y. F. *Synthesis* **1988**, 444.

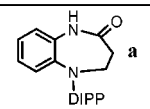
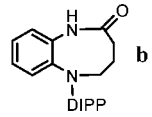
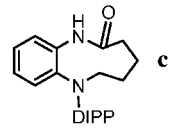
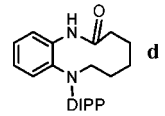
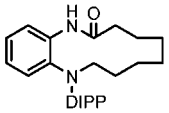
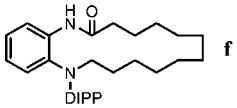
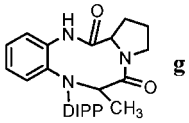
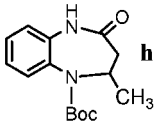
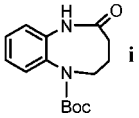
(21) Ejim, L.; Mirza, I. A.; Capone, C.; Nazi, I.; Jenkins, S.; Chee, G.-L.; Berghuisb, A. M.; Wrighta, G. D. *Bioorg. Med. Chem.* **2004**, *12*, 3825.

(22) Yamazaki, N.; Higashi, F. *Tetrahedron Lett.* **1972**, 5047.

(23) Yamazaki, N.; Higashi, F. *Tetrahedron* **1974**, *30*, 1323.

provided pure product **5b** in 68% yield. Encouraged by these results, we set out to test our proposal on the preparation of 7-, 9-, 10-, 12-, and 16-membered cyclic compounds. Fortunately, these different-sized nitrogen heterocycles also were obtained using a similar procedure in 53−64% yields (see Table 1). All of these cyclic products (**5**) were

Table 1. Yields of the Synthesized Medium- and Large-Sized Nitrogen Heterocycles under Copper Catalysis

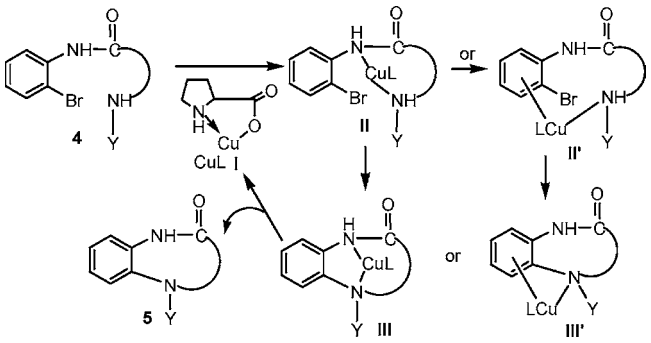
Entry	5	Isolated yield (%)	Time (h)
1	 **a**	63	60
2	 **b**	68	72
3	 **c**	64	72
4	 **d**	63	72
5	 **e**	60	72
6	 **f**	61	72
7	 **g**	53	84
8	 **h**	60	60
9	 **i**	62	72

determined by ^{31}P, ^{1}H, and ^{13}C NMR and high-resolution MS. To the best of our knowledge, this represents the first examples wherein an intramolecular direct copper-catalyzed *N*-arylation of phosphoramidates has been successfully applied to the synthesis of medium- and large-sized nitrogen heterocycles. The phosphoryl group in **5** can be deprotected in acetic acid saturated with gaseous HCl at room temperature. For example, the P−N bond of compound **5e** was completely cleaved to give product **6e** in 24 h under these conditions.

Cyclization of *N*-Boc-protected peptide analogues **4h** and **4i** was also investigated under the similar cyclization conditions, and the corresponding nitrogen heterocycles **5h** and **5i** were obtained in good yields (60 and 62%, respectively). It is well-known that Boc group can easily be removed in TFA, so it is a good protecting reagent of *N*-termini for the acyclic precursors.

We are interested in mechanistic studies of the copper-catalyzed intramolecular *N*-arylation. Deprotection of **4i** in TFA led to compound **4′i** containing free amino group at *N*-termini. We tried the CuI-catalyzed cyclization of **4′i** under similar conditions; interestingly, no 8-membered cycle product was obtained. The result showed that introduction of phosphoryl or Boc at the *N*-termini could conformationally restrain the acyclic precursor, which could be favorable for intramolecular cyclization. Thus, a simplified mechanistic view for the formation of cyclic products (**5**) from **4** is summarized in Scheme 2. First, cuprous ion reacted with

Scheme 2. Possible Copper-Catalyzed Cyclization Mechanism



proline salt to form the chelate **I**, the coordination of the copper catalyst (**I**) with the two nitrogen atoms of the amide and the DIPP-NH or Boc-NH led to the complex **II**, which makes bromine and imine of DIPP-NH or Boc-NH near the subsequent copper-catalyzed coupling produced **III**. The other possible explanation is that the coordination of the copper catalyst (**I**) with the phenylbromide ring and the nitrogen of the DIPP-NH or Boc-NH provided the π-complex **II′**. Next, intramolecular nucleophic substitution occurred at the aromatic ring, and removal of HBr by the action of potassium carbonate provided the desired nitrogen heterocycle **III′**. The removal of copper catalyst system in **III** and **III′** yielded the target products **5**.

In summary, we have developed an efficient method for the preparation of medium- and large-sized nitrogen heterocycles via copper-catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates. Introduction of the phosphoryl group or *tert*-butoxycarbonyl at *N*-termini can improve intramolecular cyclization under copper catalysis, and the

phosphoryl and *tert*-butoxycarbonyl can easily be removed under the mild conditions, so the convenient and efficient method can be suitable for the preparation of medium and large-sized nitrogen heterocycles.

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Supporting Information Available: Experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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