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Novel preparation of functionalized iodotetrahydronaphthyridine, iodoazaindoline, and iodotetrahydropyridoazepine systems

Hanh Nho Nguyen* and Zhan J. Wang†

Amgen Inc., Department of Medicinal Chemistry, One Kendall Square Bldg 1000, Cambridge, MA 02139, USA

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Abstract—A novel method, which utilizes a key halogen dance step for the preparation of iodotetrahydronaphthyridine, iodoazaindoline, and iodotetrahydropyridoazepine ring-systems is described. A variety of transformations of the iodo-functional group are also reported to demonstrate the utility of this method.
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Pyridine, pyrimidine, quinoline, and quinazoline heterocycles are common structural features in kinase inhibitors, whereby the N engages as a key H-bond acceptor with a backbone NH residing in the hinge region of the kinase.[1] This important interaction provides binding affinity between an inhibitor and the kinase and is present in the majority of protein kinases. Structure activity relationships have shown that the amino group of 2-methylaminopyridine donates a hydrogen bond to backbone carbonyl also in the hinge region. This additional interaction provides further binding affinity, which is generally reflected as a boost in inhibitory potency for 2-methylaminopyridine compared to an unsubstituted pyridine linker binding ring.[2] It was envisioned that ring-constrained versions such as azaindoline ($n = 1$), tetrahydronaphthyridine ($n = 2$), and tetrahydropyridoazepine ($n = 3$) should also provide two-point interaction with inhibitory properties (Fig. 1). In order to prepare a fully elaborated kinase inhibitor, a C4 substitution would be necessary. However, to our knowledge, these ring systems with halogen at the C4-position of the pyridine are not known. Herein, we describe a novel approach to the synthesis of iodotetrahydronaphthyridine, iodoazaindoline, and iodotetrahydropyridoazepine ring-systems, via a key halogen dance step. These iodinated heterocycles serve as versatile precursors for the preparation of novel protein kinase inhibitors.

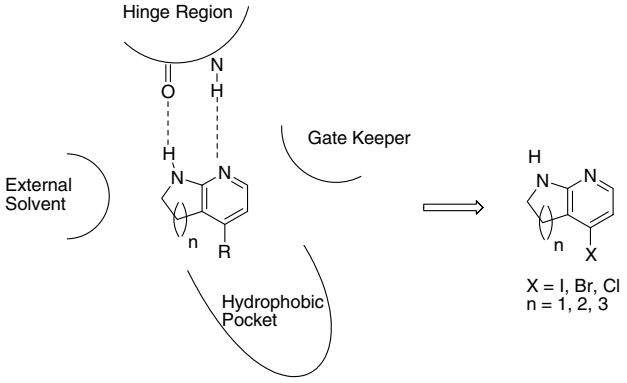

Figure 1. New hinge binding rings.

Initially, we tried to selectively hydrogenate the pyrrole ring of 4-chloro-7-azaindole and its Boc-protected analog in the presence of palladium (Scheme 1, conditions 1) or rhodium (Scheme 1, conditions 2)[3] in order to access 4-chloro-7-azaindoline. However, none of the desired product was observed. Other reduction conditions such as LAH, or BH_3 (with or without TFA) also did not provide the desired product.[4] We then turned our attention to a dianion approach that was previously reported by Bishop et al. to prepare 6-chloro-7-azaindoline.[5] However, Boc-protected 4-chloro-7-azaindoline was not observed under similar reaction conditions.

Although the dianion approach failed to provide the desired product, it provided us insight to a new method of

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* Corresponding author. Tel.: +1 617 444 5254; fax: +1 617 577 9822; e-mail: hanhn@amgen.com
† Current address: University of California, Berkeley, College of Chemistry, Berkeley, CA 94720, USA.

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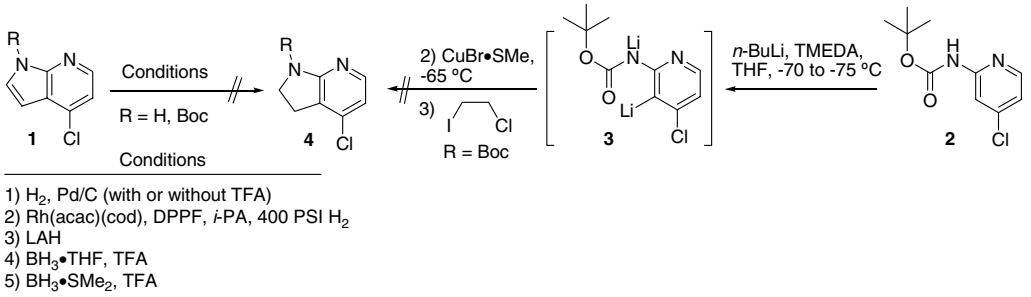
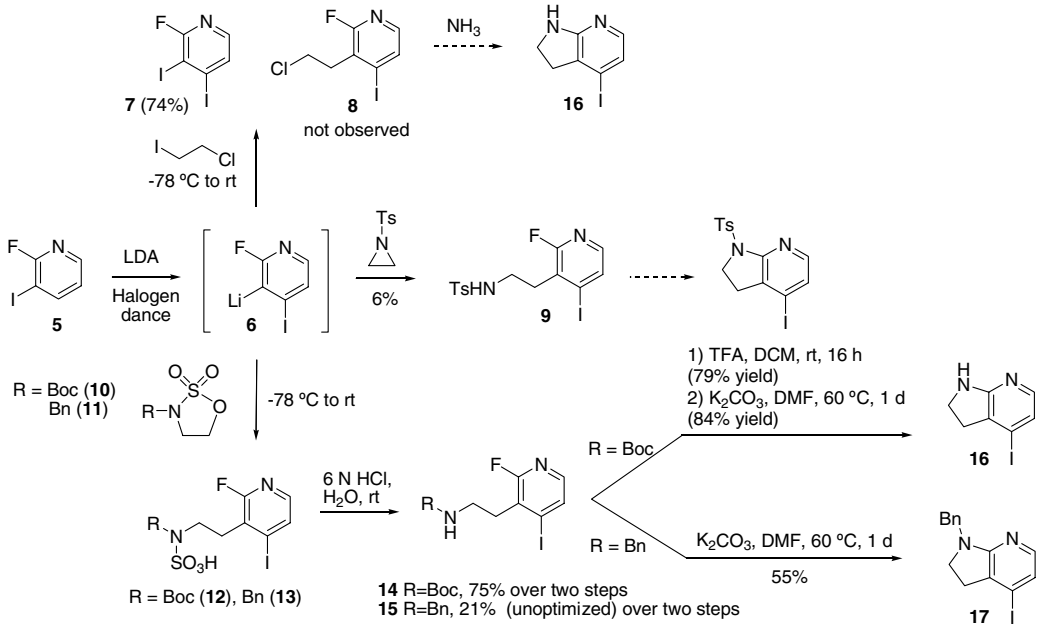


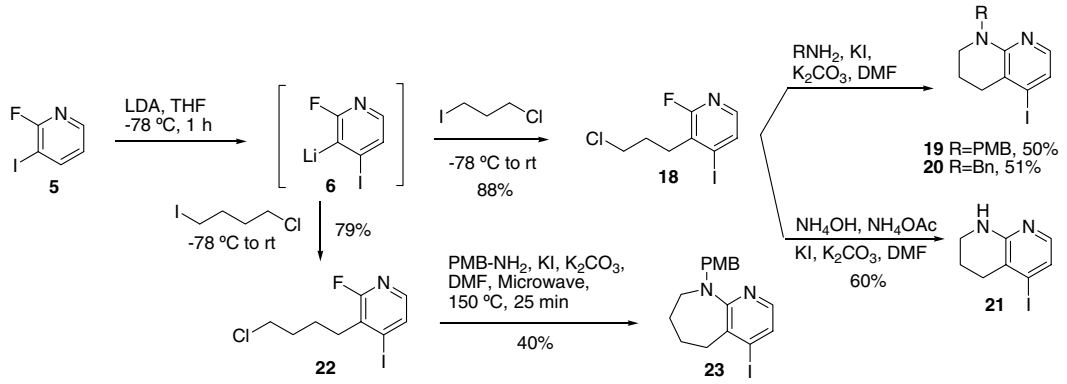
Scheme 1. Initial attempts.

obtaining the desired 4-halo-7-azaindoline system. We envisioned that a halogen dance should provide a similar anion at the C3-position as provided by the dianion approach while installing the required iodine at the C4-position of the pyridine ring (Scheme 2, transformation from **5** to **6**).[6] Attempted alkylation of the C3-anion with 1-chloro-2-iodoethane provided 1-fluoro-2,3-diiodopyridine (**7**) instead of the desired alkylation product (**8**). In this case, 1-chloro-2-iodoethane behaved as an iodinating reagent.[6] Ring-opening of activated *N*-tosylaziridine with the C3-anion provided the desired product (**9**), albeit in 6% yield. Attempts to prepare cuprate reagents from the C3-anion with different copper sources such as CuI, CuI·SMe_2, and CuCN·2LiCl prior to adding the activated *N*-tosylaziridine did not provide any desired product. We found that Boc and Bn-protected cyclic sulfamidates (**10** and **11**, respectively) were compatible electrophiles.[7] For example, ring-opening of cyclic Boc-protected sulfamidate (**10**) with the halogen dance anion (**6**) provided the desired sulfamic acid (**12**). Hydrolysis of the sulfamic acid (**12**) with aqueous HCl followed by Boc-deprotection with TFA provided the desired precursor for 4-iodo-7-azaindoline that underwent an intramolecular S_NAr reaction in the presence of potassium carbonate to furnish 4-iodo-7-azaindoline in high yield (**16**). Similarly, *N*-benzyl-4-iodo-7-azaindoline (**17**) was prepared in a similar manner.

Iodotetrahydronaphthyridine and iodotetrahydropyridoazepine were prepared in a more straightforward manner from the halogen dance approach due to the fact that 1-chloro-3-iodopropane and 1-chloro-4-iodobutane do not behave as iodinating reagents. Thus, alkylation of the C3-anion (**6**) with 1-chloro-3-iodopropane and 1-chloro-4-iodobutane provided the precursors for iodotetrahydronaphthyridine and iodotetrahydropyridoazepine, respectively (Scheme 3, compounds **18** and **22**). We found that ammonia, benzylamine, and *p*-methoxybenzylamine first underwent the S_N2 reaction under Finkelstein conditions followed by S_NAr reaction to afford the cyclized tetrahydronapthyridines. Monitoring the reaction progress by LCMS confirmed the initial appearance of the iodo-intermediate with concurrent formation of an S_N2-product resulting from amine displacement of the iodo-intermediate. A final intramolecular S_NAr cyclization afforded iodotetrahydronaphthyridines **19**–**21**. For the formation of iodotetrahydropyridoazepine (**23**), cyclization with *p*-methoxybenzylamine worked best under microwave conditions at 150 °C for 25 min. Both iodotetrahydro-



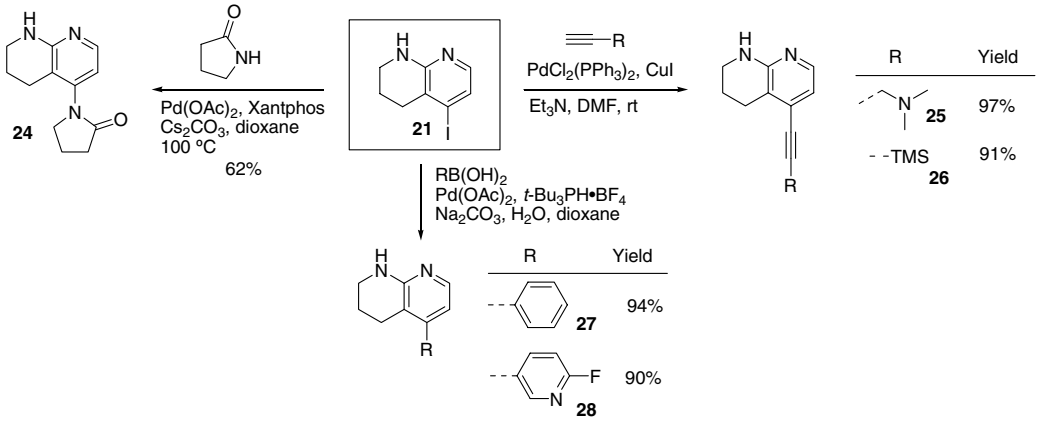
Scheme 2. Halogen dance approach to 4-iodo-7-azaindoline.



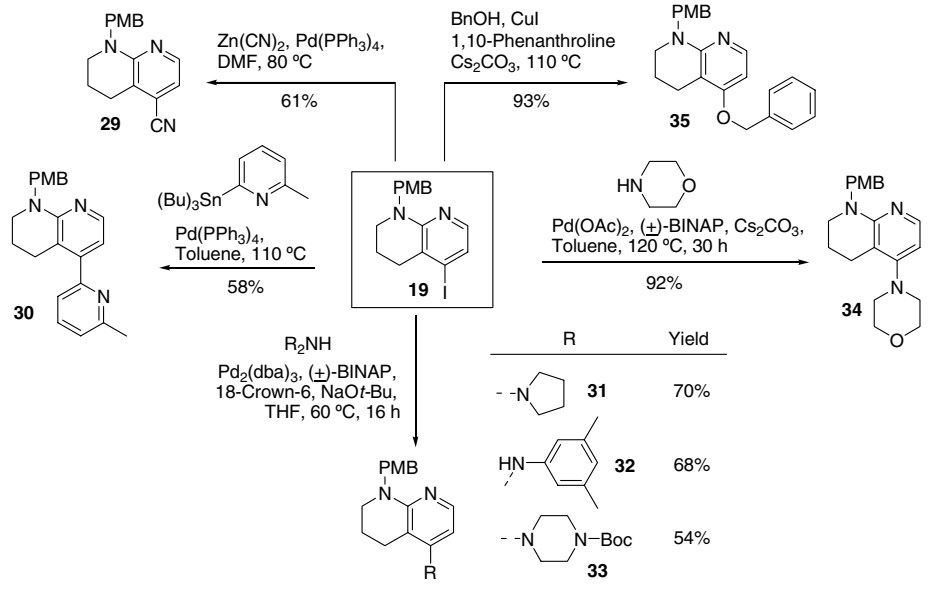
Scheme 3. Halogen dance approach to iodotetrahydronaphthyridine, and iodotetrahydropyridoazepine.

naphthyridine and iodotetrahydropyridoazepine were prepared in two steps.

Next we turned our attention to functionalize iodotetrahydronapthyridine (**21**) to demonstrate the utility of this method in the preparation of the kinase inhibitors having the tetrahydronapthyridine pharmacophore. The high reactivity of the iodo-group toward metal-catalyzed coupling reactions allowed amidation (**21**–**24**),[8] Sonogashira (**21**–**25** and **26**), and Suzuki–Miyaura (**21**–**27** and **28**) couplings[9] to occur in high yields (Scheme 4). In Scheme 5, PMB-protected



Scheme 4. Functionalization of iodotetrahydronaphthyridine.



Scheme 5. Functionalization of PMB-protected iodotetrahydronaphthyridine.

iodotetrahydronapthyridine (**19**) also underwent a variety of coupling processes such as cyanation (**19**–**29**), Stille (**19**–**30**), and Buchwald–Hartwig (**19**–**31**, **32**, **33**, and **34**) couplings,[10] and C–O bond formation (**19**–**35**).[11]

In conclusion, we have demonstrated a novel approach to synthesize functionalized hinge binding cores such as iodotetrahydronaphthyridine, iodoazaindoline, and iodotetrahydropyridoazepine ring-systems. The key step involved a halogen dance that provided the penultimate precursors to those rings. In addition, we have shown that the iodo-functional group could be transformed via a variety of metal-catalyzed coupling reactions. These rings have the potential to provide entry to new classes of kinase inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.076.

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