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Metal-Free N-H/C-H Coupling for Efficient Asymmetric Synthesis of Chiral Dihydroquinoxalinones From Readily Available α-Amino Acids

Kyalo Stephen Kanyiva,*[a] Masashi Horiuchi,[b] and Takanori Shibata,*[b]

Dedication ((optional))

Abstract: We have developed a method for the synthesis of dihydroquinoxalinones via intramolecular N-H/C-H coupling using hypervalent iodine. The starting materials were prepared from inexpensive and readily available aniline and amino acid derivatives. Various functional groups were tolerated to give multisubstituted dihydroquinoxalinones in moderate to excellent yields. The chirality of the amino acid was transferred to the desired target compound without a loss of enantiomeric excess. Preliminary mechanistic studies indicated that the reaction proceeds via an ionic mechanism.

Dihydroquinoxalinones are common structural motifs in bioactive compounds.[1] For example, bioactive dihydroquinoxalinones having anticancer, anti-HIV and absorption-inhibitory properties have been reported (Figure 1). Moreover, dihydroquinoxalinones are useful synthetic intermediates for the preparation of complex organic molecules.[2]

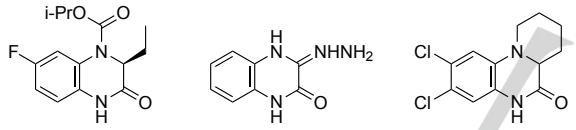
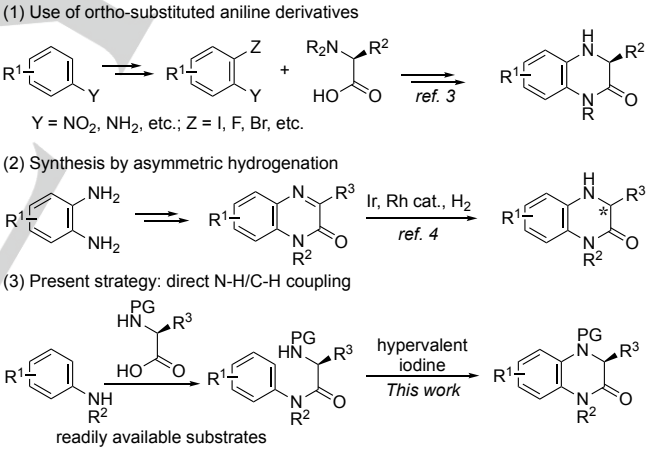


Figure 1. Examples of bioactive dihydroquinoxalinones.

Several methods have been developed for the synthesis of dihydroquinoxalinones, and these can be grouped into two major classes. One class uses *ortho*-substituted aniline derivatives, which are reacted with amino acid derivatives (Scheme 1).[1e,3] For example, Jiang and coworkers reported the copper-catalyzed Ullmann-type *N*-arylation of aliphatic amines with amino acids, followed by reduction with $SnCl_2$.[3b] Another excellent example is the copper-catalyzed synthesis of quinoxalinones by coupling of 2-bromoanilines with α-amino acids, reported by Tanimori and coworkers.[3f] This class of reaction suffers from a limited substrate scope, because the starting materials are often expensive or difficult to prepare for substituted dihydroquinoxalinones. The second major class of synthesis is the transition metal-catalyzed asymmetric hydrogenation of quinoxalinone derivatives.[4] Representative examples are the Ir- and Ir-catalyzed hydrogenations reported by Vidal-Ferran[4a] and Xu,[4b] respectively. Other approaches such as Rh-catalyzed asymmetric arylation of aldimines[2c] and the use of Jocie-type reactions have been reported. Although these methods are promising, the toxicity and cost of the transition metals, as well as the difficulty of obtaining the starting materials may limit their practical use on a large scale. Therefore, the development of new routes for the effective synthesis of substituted dihydroquinoxalinones from readily available materials is needed.



Scheme 1. Synthetic approaches to dihydroquinoxalinones.

Hypervalent iodine[6] has emerged as an effective and environmentally alternative to transition metal catalysts[7] for the construction of C-N bonds. For example, Kikugawa developed an electrophilic aromatic substitution reaction for the synthesis of dihydroquinolines,[8a] Zhao synthesized indoles,[8b] Nishiyama and Kita pioneered the synthesis of spirolactams and phenol ethers,[8c,8e] Tellitu and Domínguez achieved the synthesis of pyrrolodiazepines,[8d] and Togo synthesized sulfonamides using hypervalent iodine reagents.[8f] Moreover, recently, our group and others reported the synthesis of heteroaromatic compounds such as benzimidazoles,[8g,8i-8k] carbazoles,[8h] and azahelicenes.[8l]

Inspired by these studies and our interest in the efficient synthesis of organic compounds using amino acid derivatives,[9] we conceived that dihydroquinoxalinones could be synthesized

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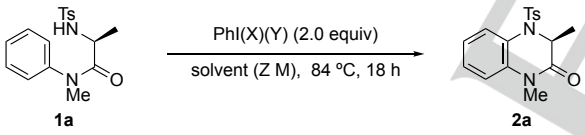
using hypervalent reagents by direct oxidative cyclization. Herein we report a metal-free method for the synthesis of dihydroquinoxalinones from commercially or readily available starting materials that do not require prefunctionalization or a directing group before the N-H/C-H coupling reaction. We also briefly discuss preliminary studies on the mechanism of intramolecular N-H/C-H coupling.

Our initial attempts to realize catalytic N-H/C-H coupling using *in situ*-generated $PhI(OAc)_2$ with or without additives such as acids, inorganic bases or Lewis acids provided the desired dihydroquinoxalinones in poor yields due to low conversion of the starting material.[10] Therefore, we turned our attention to screening stoichiometric amounts of hypervalent iodine. When substrate **1a** was treated with two equivalents of $PhI(OAc)_2$ in HFIP as a solvent at 84 ºC (oil bath temp.) for 18 h, the desired dihydroquinoxalinone **2a** was obtained in 43% isolated yield (Table 1). The reaction was carried out using a variety of organic solvents, and DCE gave the highest yield of 71% (entries 1-5). Meanwhile, other commercially available hypervalent iodines afforded lower yields, probably due to their rapid decomposition (entries 6 and 7). After further tuning of the reaction parameters such as concentration and temperature, we found that the reaction under 2.0 M concentration of **1a** at 90 ºC for 24 h afforded the desired product in 91% yield after purification using silica gel chromatography (entry 9). A reduction in the amount of $PhI(OAc)_2$ to 1.0 equivalent resulted in a significant decrease in the yield (entry 10). Notably, the reaction proceeded with perfect retention of the enantiomeric excess of the alanine derivative as confirmed by HPLC analysis using a chiral column.

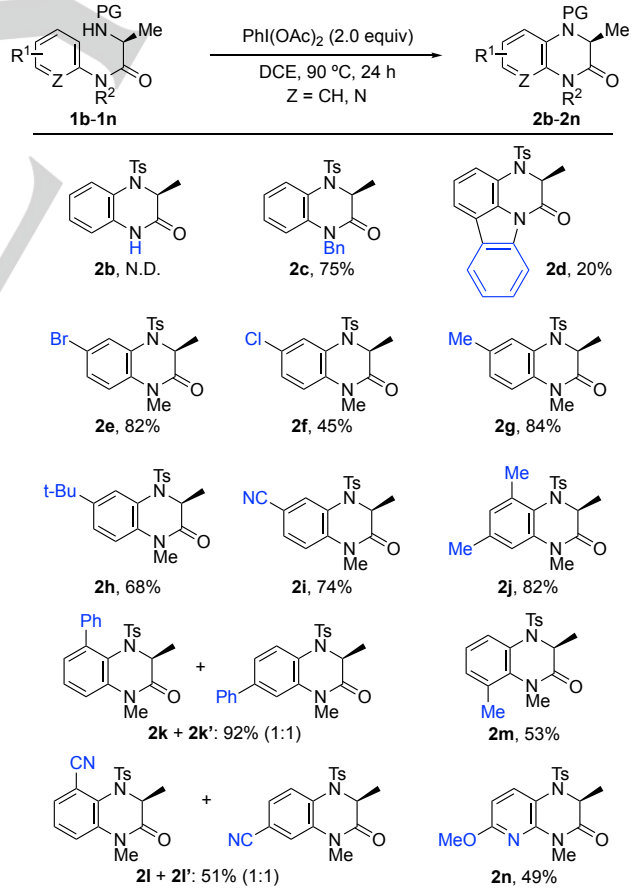
Table 1. Screening of reaction conditions for N-H/C-H coupling using **1a**.[a]



Entry	Solvent	PhI(A)(B)	X (M)	Yield (%)
1	HFIP	$PhI(OAc)_2$	1.0	43
2	DCE	$PhI(OAc)_2$	1.0	71
3	PhCl	$PhI(OAc)_2$	1.0	32
4	TFE	$PhI(OAc)_2$	1.0	49
5	MeCN	$PhI(OAc)_2$	1.0	68
6	DCE	$PhI(OTf)_2$	1.0	34
7	DCE	PhI(OH(OTs)	1.0	49
8[b]	DCE	$PhI(OAc)_2$	2.0	87
9[b,c]	DCE	$PhI(OAc)_2$	2.0	91
10[b,c,d]	DCE	$PhI(OAc)_2$	2.0	53

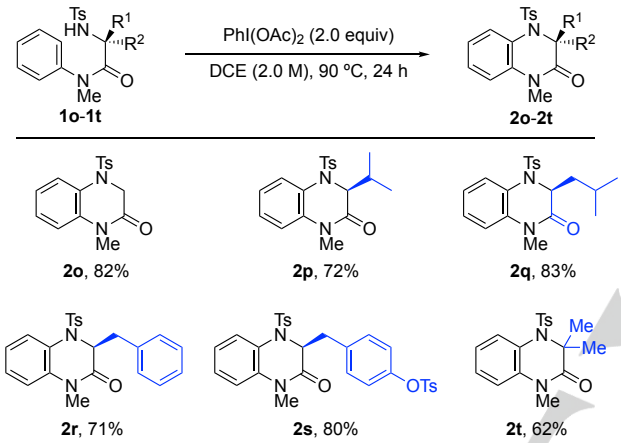
[a] Conditions: **1a** (0.20 mmol), $PhI(OAc)_2$ (0.4 mmol), solvent (0.10 mmol), [b] Run at 90 ºC. [c] Run for 24 h. [d] $PhI(OAc)_2$ (0.20 mmol, 1.0 equiv) was used. HFIP: Hexafluoroisopropanol; DCE: 1,2-dichloroethane, TFE: 2,2,2-trifluoroethanol.

Under the optimum conditions for entry 9 in Table 1, we first screened the effect of the *N*-substituent on the aryl amide (R^2). Although unprotected substrate **1b** was not tolerated in this reaction, a benzyl group gave the desired product **2c** in good yield (Scheme 2). When a *N*-phenyl substrate was used, the reaction was slow, and the product underwent further C-H bond cleavage/cyclization to give a product **2d** having a carbazole core. We next examined the effect of substituents (R^1) at the *para*, *meta* and *ortho* positions of the aryl moiety. As a result, bromo, chloro, alkyl, cyano and phenyl groups were tolerated to afford the desired dihydroquinoxalinones **2e**-**2m** in moderate to high yields. Apparently, in this N-H/C-H coupling, electron-donating groups at the *para* position gave comparatively higher yields than electron-withdrawing groups. When 3-phenyl-substituted substrate **1k** was subjected to the reaction conditions, a 1:1 mixture of regioisomers was obtained in excellent yield. A substrate containing a 3-cyano group also gave a 1:1 mixture of regioisomers in 51% yield. 2-Methyl substrate **1l** also participated in the reaction to afford **2l** in 53% yield due to moderate conversion of the starting material. Additionally, a multisubstituted dihydroquinoxalinone could also be accessed in high yield by the current metal-free synthesis, as exemplified by the synthesis of **2j**. Finally, a substrate containing a pyridyl core was also tolerated under the oxidative coupling conditions to provide **2n** in moderate yield.



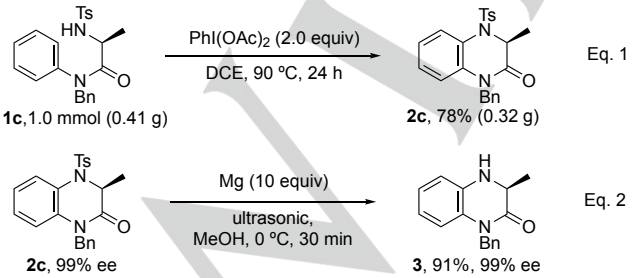
Scheme 2. Scope of *N*-arylpropanamides.

Next, we investigated the scope of amino acid derivatives (Scheme 3). When a glycine derived substrate **1o** was treated with hypervalent iodine under the standard conditions, intramolecular N-H/C-H coupling proceeded smoothly to give the corresponding product **2o** in 82% yield. Substrates **1p** and **1q** prepared from L-valine and L-leucine also reacted to give the desired dihydroquinoxalinones **2p** and **2q** in respective yields of 72% and 83%. When L-phenylalanine and tyrosine derivatives **1r** and **1s** were used, the reaction proceeded regioselectively to afford 6-membered N-H/C-H coupling product in high yields, as opposed to the formation of a 5-membered heterocycle from a phenyl ring of the respective amino acid. A substrate **1t** prepared from the unnatural amino acid 2-methylalanine also participated in the reaction to give the corresponding desired products **2t** in 62% yield.



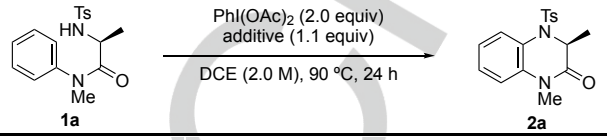
Scheme 3. Scope of amino acids.

To demonstrate the practicality of the reaction, the oxidative cyclization reaction was carried out using 1.0 mmol (0.41g) of **1c** under the standard conditions. The reaction proceeded smoothly to deliver **2c** without a decrease in yield (Eq. 1). Moreover, the tosyl group was easily removed in excellent yield using magnesium turnings under ultrasonic irradiation (Eq. 2).[11] The enantiomeric excess of the starting material was also maintained during deprotection.



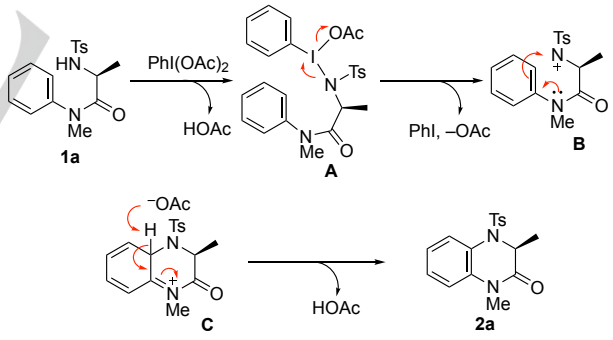
This N-H/C-H coupling may proceed through either ionic[8d,8g] or radical[8b,8j] mechanism. To elucidate the mechanism, we carried out the reaction in the presence of several radical scavengers (Table 2). Since 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 1,1-diphenylethene (DPE) had almost no effect on the yield, we considered that radical species were not generated in the reaction. In contrast, TEMPO led to a decrease of yield probably due to the competitive reaction of TEMPO with $PhI(OAc)_2$.[12]

Table 2. Addition of various radical scavengers.



Entry	Additive	Yield (%)
1	None	91
2	BHT	91
3	DPE	87
4	TEMPO	53

Based on the above mechanism studies, we propose a reaction mechanism initiated by the reaction of **1a** with $PhI(OAc)_2$ to give N-I intermediate **A**, followed by the elimination of PhI and acetate anion (Scheme 3). Aromatic nucleophilic attack of the phenyl ring to the nitrenium center of **B** gives intermediate **C**. Aromatization promoted by hydrogen abstraction using acetate anion affords the desired dihydroquinoxalinone **2a**. However, a radical mechanism can not be completely ruled out.



Scheme 3. Plausible reaction mechanism.

In summary, we have developed a metal-free synthesis of dihydroquinoxalinones from inexpensive and/or readily available aniline and amino acid derivatives. The reaction tolerates various functional groups to afford the desired multisubstituted dihydroquinoxalinones in moderate to excellent yields. The chirality of the amino acid is transferred to the desired product without a loss of enantiomeric excess. Preliminary mechanistic studies indicated that the reaction proceeded via an ionic mechanism. Further synthetic applications of amino acids as building blocks for the synthesis of potentially bioactive compounds are in progress in our laboratory.

Acknowledgements

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Keywords: dihydroquinoxalinones • C-N coupling • hypervalent iodine • amino acids • C-H functionalization

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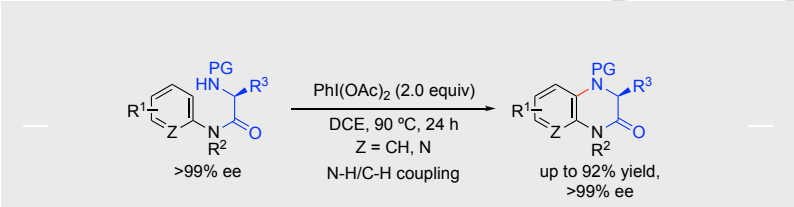

We have developed a method for the synthesis of dihydroquinoxalinones via intramolecular N-H/C-H coupling using hypervalent iodine from inexpensive and readily available aniline and amino acid derivatives. Various functional groups were tolerated to give multisubstituted dihydroquinoxalinones in moderate to excellent yields. The chirality of the amino acid was transferred to the desired target compound without loss of enantiomeric excess.

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