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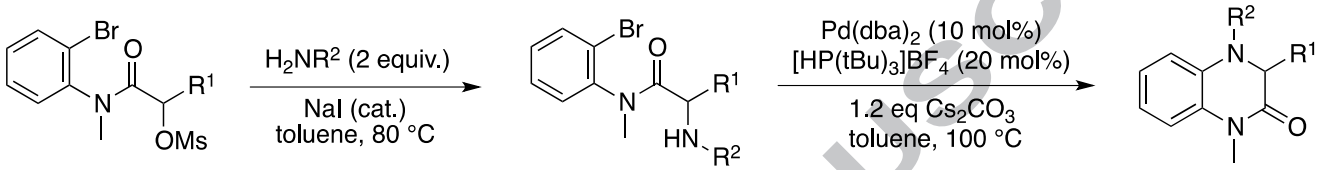

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Synthesis of dihydroquinoxaline-2(1*H*)-ones *via* palladium-catalyzed intramolecular C-N bond formation.

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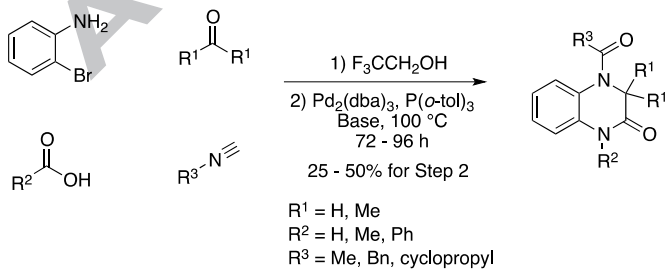
ABSTRACT

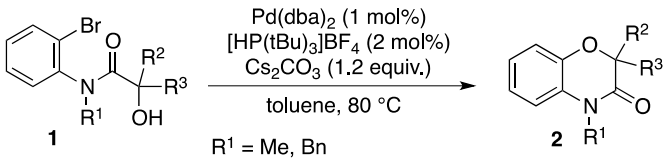
A new strategy for the preparation of highly-substituted dihydroquinoxaline-2(1*H*)-ones is reported. The strategy harnesses a divergent NaI-catalyzed amine substitution of mesylates to prepare a range of sterically hindered amidoamine substrates. These substrates are then subjected to $Pd(dba)_2/P(tBu)_3$ mediated cyclization. The preparation of amidoalcohol substrates occurs with resonable yields (40 - 84%), with lower yields being obtained with aromatic and bulky amines. Palladium-catalyzed intramolecular C-N bond formation is slow, requiring 20 mol% catalyst loadings for complete conversion in 16 hours. All substrates cyclized with reasonable yields (48 - 73%).

The synthesis of the dihydroquinoxaline-2(1*H*)-one framework, which is a derivative of the extensively biologically studied 2(1*H*)-quinoxalinone system,[1] has been the subject of recent investigations due to its prevalence in the cores of bioactive products. The dihydroquinoxaline-2(1*H*)-one core is found in compounds active against HIV,[2] potent Bradykinin B1 receptor antagonists,[3] and potential antimicrobial agents.[4] An aspect of this organic moiety that has not been fully explored is the range of substituents that can be incorporated into the molecule by varying the groups at the nitrogen and α-carbon positions. A recent strategy for preparation of dihydroquinoxaline-2(1*H*)-ones harnesses Ugi reaction[5] for one-pot substrate synthesis followed by palladium-catalyzed cyclization (Scheme 1).[6-8] This strategy is elegant, however the range of substituents at N4 is limited to amide functionalities. We have previously reported the synthesis of the related 2*H*-1,4-benzoxazin-3-(4*H*)-one framework (**2**) via palladium-catalyzed cyclization of amidoalcohols (**1**) (Scheme 2).[9] We reasoned that these palladium-catalysis methods could be adapted for the divergent preparation of highly substituted dihydroquinoxaline-2(1*H*)-one frameworks by controlled assembly of amidoamine analogues of our amidoalcohols. This route would allow introduction of a range of nitrogen substituents from a common precursor. Here we report our preliminary results in the synthesis of amidoamine substrates through NaI-catalyzed S_N2 substitution and their subsequent palladium-catalyzed cyclization.



Scheme 1: Ugi reaction approach to dihydroquinoxaline-2(1*H*)-ones.

Our synthetic strategy begins from alcohol compounds **1a** and **1b**, which are prepared by coupling 2-bromo-*N*-methylaniline[10]



Scheme 2: Preparation of 2*H*-1,4-benzoxazin-3-(4*H*)-ones.

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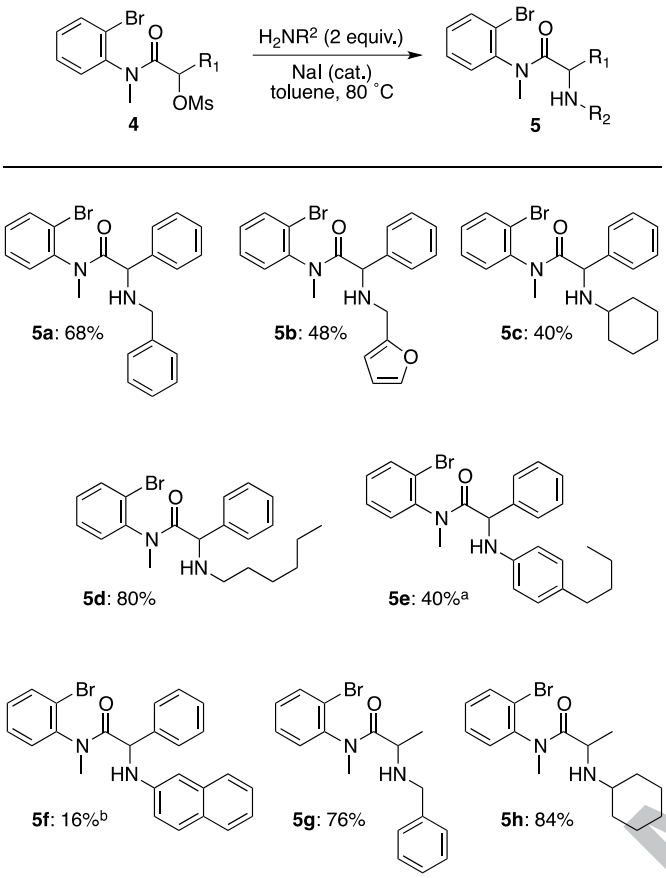
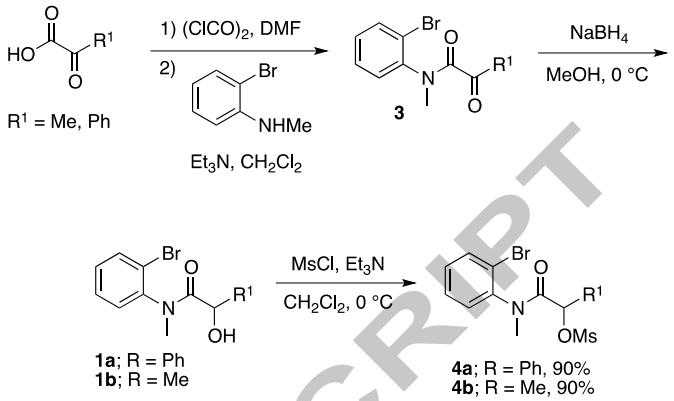
Table 1: Synthesis of amine substrates.[11]



[a] Na_2CO_3 (3 equiv.), H_2O (3 equiv.) in EtOH. [b] Na_2CO_3 (3 equiv.) in EtOH, from the 2-naphthylaminehydrochloride salt.

with either benzoylformic acid or pyruvic acid *via* the acyl halide intermediate, followed by $NaBH_4$ reduction in MeOH (Scheme 3).[9,12] The alcohol is then activated for nucleophilic substitution by conversion to the mesylate.[13] Direct substitution of the mesylate with benzylamine was not effective, with excess amine at 80 - 100 °C in toluene resulting in no conversion. This problem was circumvented through application of a Finkelstein-type process, catalyzing the S_N2 substitution with NaI (Table 1).[14,15] Finkelstein reactions are generally performed for substitution at primary positions due to the slower rate of S_N2 reactions at sterically hindered secondary positions. As can be seen from Table 1, steric hindrance plays a significant role in the substitution reaction, with the sterically hindered products **5a-c** being formed in relatively low yields (ca. 50%) when compared to the much less hindered **5g** and **5h**, where the yields are ca. 80%. The relatively unhindered n-hexylamine is a good nucleophile (**5d**, 80%), while the larger benzyl-, furfuryl-, and cyclohexylamines saw significantly lower yields (**5a-c**, ca. 50%). While the Finkelstein catalysis method was effective for substitution with aliphatic amine nucleophiles, it failed for aromatic amines. Here, we adapted a literature procedure using Na_2CO_3 in wet EtOH solvent, resulting in acceptable yields of amine products **5e** and **5f** (40 and 16%).[16]

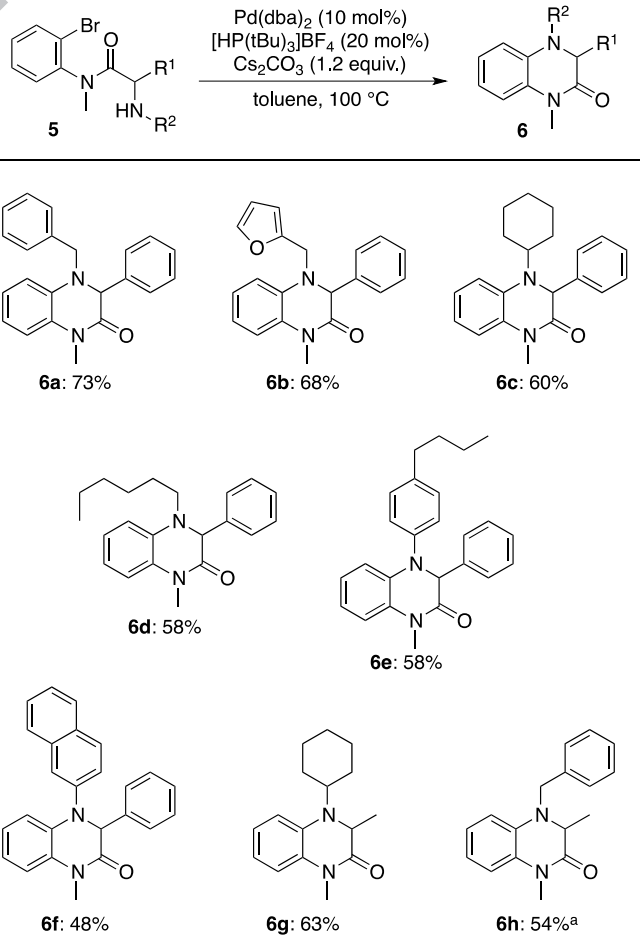
Attempts to incorporate the amine directly from compound **3** through reductive amination were not successful.[17] This is attributed to failure to form the necessary imine intermediate. Attempts to discretely prepare the imine failed under acid-catalyzed Dean-Stark distillation, with no reaction occurring in benzene and only decomposition occurring at reflux in toluene. The presence of the bromine atom may be responsible for this decomposition, given that related reactions have been demonstrated from non-halogenated analogues of **3**.[18]



Scheme 3: The synthesis of key mesyl substrate **4**.

With the requisite amidoamines **5** in hand we turned our attention to palladium-catalyzed cyclization. We first explored cyclization of **5a** under our previously reported conditions for benzoxazinone preparation (1 mol% $Pd(dba)_2$, 2 mol% $[HP(tBu)_3]BF_4$,[19] and 1.2 equiv. Cs_2CO_3 in toluene at 80 °C),[9] with very low conversions being obtained. Increasing the

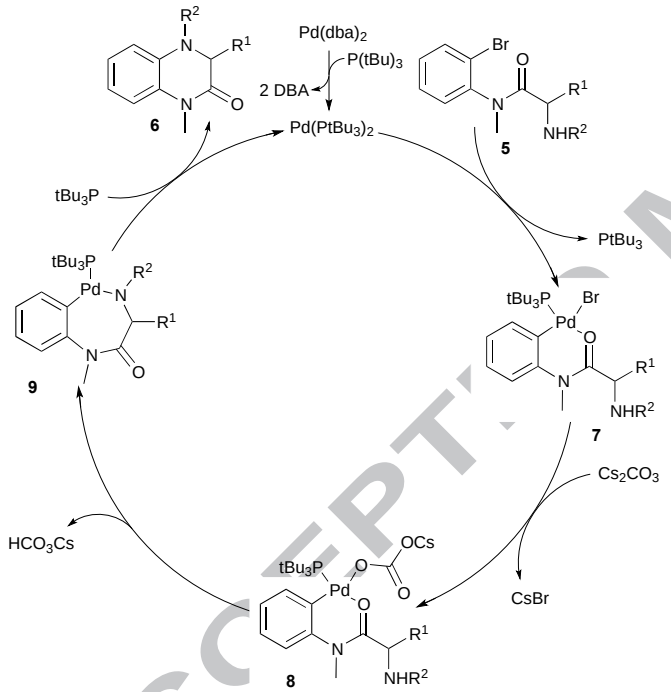
Table 2: Pd-catalyzed cyclization.[11]



[a] 20 mol% $Pd(dba)_2$ and 40 mol% $[HP(tBu)_3]BF_4$

temperature to 100 °C resulted in enhanced conversion, yet still incomplete reaction. To achieve full conversion at 100 °C, it was necessary to increase the catalyst loading to 10 mol%. Varying the base did not result in significant changes to the conversion rate, with Cs_2CO_3 proving the most effective.[20] The yield of dihydroquinoxaline-2(1*H*)-one products was reasonable in most cases, averaging 60% (Table 2).[21] Both aliphatic and aryl amines cyclized in approximately the same amounts, showing no negative impact from the moderately electron-withdrawing aryl substituents.

The observations are consistent with our previous study on the synthesis of benzoxazinone species; therefore, we propose a similar mechanism is at play (Scheme 4). From the active $Pd(P(tBu_3))_2$ catalyst, C-Br bond activation occurs to yield carbonyl-stabilized palladacycle **7**.[22] Anion exchange yields carbonate complex **8**, followed by deprotonation to yield palladium amide complex **9**. Previous reports have proposed that the superior reactivity of carbonate bases in palladium-catalyzed reactions arises from intramolecular deprotonation.[23] The catalytic cycle is closed through reductive elimination of the C-N bond and regeneration of the Pd-catalyst.



Scheme 4: Proposed catalytic cycle.

In summary, we have demonstrated a new NaI-catalyzed S_N2 substitution for synthesis of amidoamine substrates and their subsequent palladium-catalyzed cyclization to yield dihydroquinoxaline-2(1*H*)-ones. The substitution reaction is effective for alkylamines and has lower yield for arylamines. The cyclization reaction does not display significant substitution dependence, proceeding well for both alkyl and aryl substituted substrates. The resulting products are currently being screened for biological activity.

Acknowledgments

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11. See Supplementary Material for complete experimental details.
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15. General procedure for preparation of **5**: To a toluene solution (ca. 50 - 100 mM) of mesylate compound **4** (1 equiv.) and a catalytic amount of NaI, amine (2 equiv.) was added slowly under nitrogen atmosphere. The reaction mixture was heated at 80 ˚C for 24 h. The reaction was then quenched with water and extracted with EtOAc. The organic extract was washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography, eluted with DCM then 1-3% MeOH in DCM. The fractions were concentrated and residual solvent removed under vacuum.
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20. This reduced reactivity is consistent with the work of Kalinski *et al.* where 5 mol% $Pd_2(dba)_3$ and 10 mol% P(o-tol)$_3$ at 100 °C required 72 - 96 hours to achieve average yields of 39%.[6a]
21. General procedure for preparation of **6**: In a Schlenk flask, $Pd(dba)_2$ (20 mol%), $[HPtBu_3]BF_4$ (40 mol%), and Cs_2CO_3 (1.2 equiv.) were dissolved in toluene (50 - 100 mM with respect to **5**) and heated at 100 °C for 15 min under nitrogen. The solution changed from a red/purple colour to yellow. To this, **5** (1 equiv.) was added and stirred for 16 hours. The reaction was diluted with

diethyl ether and was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography with 5-10% EtOAc/hexane.

22. Analogous intermediates have been characterized crystallographically: Katayev, D.; Jia, Y.-X.; Sharma, A. K.; Banerjee, D.; Besnard, C.; Sunoj, R. B.; Kündig, E. P. *Chem. Eur. J.* **2013**, *19*, 11916.
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Highlights

- Pd-catalyzed C-N coupling for heterocycle preparation.

- NaI-catalyzed S_N2 substitution with alkyl and aryl amine nucleophiles.

- Divergent synthesis of aminoalchols.

- Highly-substituted dihydroquinoxaline-2(1*H*)-one synthesis.