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CuI-Catalyzed Tandem Intramolecular Amidation Using *gem*-Dibromovinyl Systems

Josephine Yuen, Yuan-Qing Fang, and Mark Lautens*

Davenport Chemistry Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, M5S 3H6, Canada

mlautens@chem.utoronto.ca

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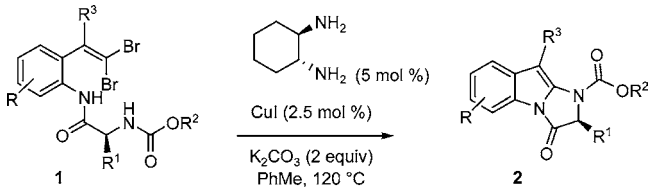
ABSTRACT



Imidazoindolones are present as the key structural motif in the family of antifungals, fumiquinazolines, and the antagonist asperlicin. The first example of a CuI-catalyzed tandem intramolecular amidation forming substituted imidazoindolones from readily accessible *ortho gem*-dibromovinylanilines is described.

The imidazoindolone structural motif appears in the core structures of several biologically active molecules, including the potent cholecystokinin antagonist asperlicin **3**[1] and the antifungal fumiquinazolines[2] **4** (Figure 1). Such 2-amino-substituted indole moieties are difficult to access through traditional synthetic methods such as Fischer indole synthesis. To address this problem, Snider used a Pd-catalyzed intramolecular C−N coupling of a 2-iodoindole with a tethered carbamate[3] as part of his total synthesis of asperlicin **3**.[4] His approach utilized a multistep synthesis of the iodosubstrate involving a challenging mercuration reaction of the preformed indole structure.

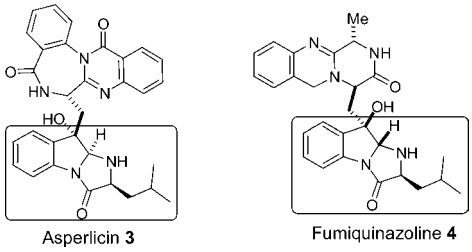
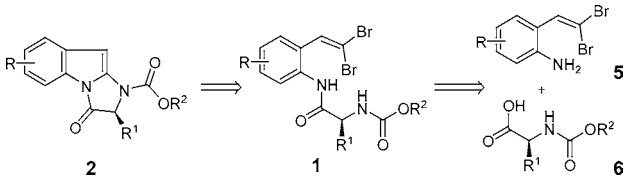


Figure 1.

In the context of developing a selective tandem coupling of readily accessible *gem*-dihalovinyl systems[5] (Scheme 1), we envisaged a double amidation reaction to access substituted imidazoindolones, and we report the results herein.

Scheme 1



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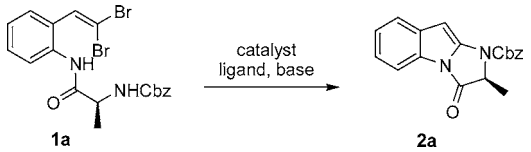
C(aryl)−N bond formation[6] has been extensively researched within the past decade due to the importance of these compounds in diverse fields such as natural products,[7] photography,[8] and materials.[9] The original amination (Ullman)[10] and amidation reactions (Goldberg)[11] suffered from harsh conditions, in particular high temperatures, but due to the pioneering work of Buchwald and co-workers[6b,12] and Hartwig,[13] the mild transition-metal-catalyzed C(aryl)−N coupling reaction is an extremely powerful tool in organic synthesis. Buchwald and co-workers developed a catalytic copper/diamine-ligand-based system[14] enabling coupling of a broad range of aryl and alkyl amides to aryl and heteroaryl halides.[15] They demonstrated the wider tolerance of Cu compared to Pd and also showed that the Goldberg reaction could be performed at room temperature. However, the scope of the Goldberg reaction has not been extensively explored and only recently has this reaction been extended to include an intramolecular vinylation of amides generating lactams.[16]

Our previous studies showed that *gem*-dihalovinylanilines can undergo a Pd-catalyzed tandem C−N/Suzuki−Miyaura coupling.[5] Herein, we describe an extension to this concept whereby the *gem*-dibromovinyl moiety **1** performs an intramolecular amidation, followed by a sequential C−N coupling with the tethered carbamate generating imidazoindolones **2** (Scheme 1). This is the first report of a one-pot synthesis of imidazoindolones from the readily accessible *gem*-dibromovinyl compound **1**.[17]

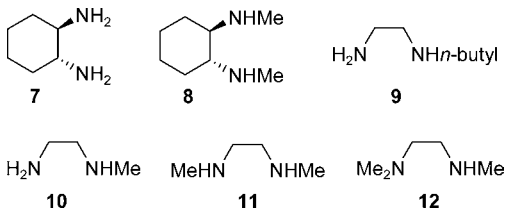
Substrate **1a** was prepared as a single enantiomer by an amide coupling of the *gem*-dibromovinylaniline **5** with Cbz-L-alanine. Our initial attempt at the tandem C−N bond formation (Scheme 2) using Pd/phosphine[18] based systems

Scheme 2



1a **2a**

was unsuccessful in producing the desired product **2a** but gave the corresponding 2-bromoindole in moderate yield. However, Buchwald's combination of CuI and diamine ligand **11** (Figure 2) successfully gave **2a** in moderate yield and 34% ee.



7 **8** **9**

10 **11** **12**

Figure 2.

Initial studies focused on the selection of a diamine ligand for the formation of **2a**. Screening a range of diamine ligands (Figure 2) revealed that all six ligands gave the desired product, although racemic *trans*-1,2-cyclohexyldiamine **7** was found to be superior, followed closely by *N*,*N*-dimethylethylenediamine **11**. Use of chiral *trans*-1,2-cyclohexyldiamine did not significantly change the yield or ee. *N*-(*n*-butyl)-ethylenediamine **9** and *N*,*N*,*N*′-trimethylethylenediamine **12** resulted in the poorest yields.

Toluene was found to be the best solvent for this reaction. Dioxane gave a much lower yield, while DMF failed to give any product, returning mainly starting material and a mixture of very polar compounds. Screening a range of bases (K_2CO_3, K_3PO_4, Cs_2CO_3, and DABCO) revealed that K_2CO_3 gave the highest yield. The weaker organic base, DABCO, failed to promote the reaction.

The greatest effect on yield and ee was observed by simply changing the ratio and quantity of ligand, CuI, and base (Table 1). By reducing the amount of copper/ligand/base to 5 mol %, 10 mol %, and 2 equiv, respectively, the yield increased to 73% (85% ee, Table 1, entry 2). Reducing the amount of copper and ligand further to 2.5 mol % and 5 mol %, respectively, was equally effective (entry 3). Further decreases gave somewhat lower yields but improved ee in the product (entry 5). An excess of the diamine ligand is necessary to prevent multiple ligation of the amide to copper (entry 2 vs entry 4).[14a] Increasing the scale of the reaction to 1 mmol gave 84% of the desired product (entry 6).

The scope of the reaction was initially investigated by coupling a range of amino acids **6** to the *gem*-dibromovin-

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(17) See the Supporting Information for synthesis of the *ortho gem*-dibromovinylaniline from commercially available 2-nitrobenzaldehyde.

(18) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.

Table 1. Effect of Quantity of Ligand, Base, and CuI[a]

entry	CuI (mol %)	K_2CO_3 (equiv)	ligand (mol %)	time (h)	yield[b] (%)	ee[e] (%)
1	20	5	40	12	50[c]	49
2	5	2	10	13	73	85
3	2.5	2	5	13	73 (72[c])	86
4	5	2	5	13	61	96
5	1	2	2	37	62	98
6	2.5	2	5	13	84[d]	86

[a] All reactions performed on a 0.26−0.52 mmol scale in toluene at 120 °C using racemic *trans*-1,2-cyclohexyldiamine as ligand. [b] HPLC yield. [c] Isolated yields. [d] Reaction performed on a 1 mmol scale. [e] ee determined using chiral HPLC.

ylaniline **5** followed by tandem C−N bond formation to provide substituted imidazoindolones **2**.

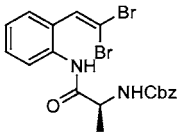
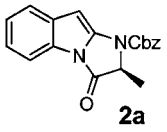
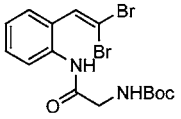
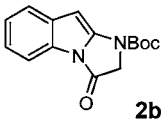
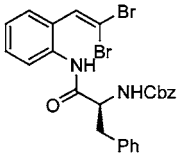
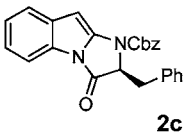
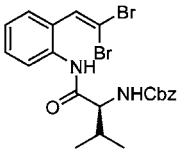
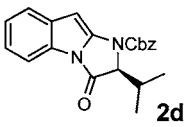
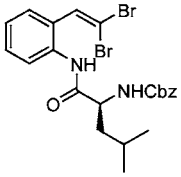
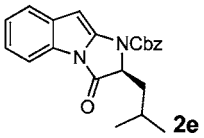
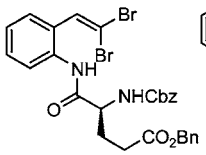
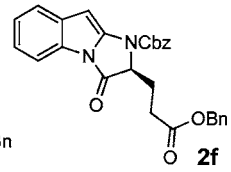
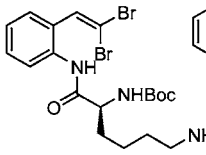
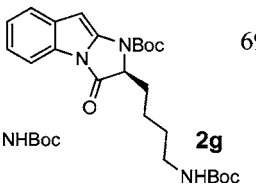
Alkyl groups were well tolerated, even the sterically hindered isopropyl substituent (Table 2, entry 4), although the reaction required a longer time to achieve complete conversion (22 h). The isobutyl analogue **2e** (entry 5) is noteworthy as it forms the core structure of the antifungal fumiquinazolines **4**.[4] The incorporation of heteroatoms in the side chain is particularly useful to allow for further derivatization of the ester or amine functionality (entries 6 and 7). The amide **1g** (entry 7) contains two carbamates that could potentially react to give either the five- or nine-membered ring or intermolecular coupling product. Only the five-membered product **2g** was observed. Both the Cbz and more sterically hindered Boc protecting groups were tolerated.

Exploring a range of electron-donating and electron-withdrawing groups on the aromatic ring indicated that substituents on the aromatic ring do not seem to affect the efficiency of the cyclization reaction, except for the case of the 5-methoxy substituted compound **1m** (Table 3, entry 6), which gave the product in a decreased yield possibly due to the increased steric hindrance. In some cases, a minor byproduct observed was the 2-bromoindole with hydrolysis of the amide bond.

In some cases, the preservation of the chiral center originating from the amino acid remained very high with up to 86% ee for the alanine analogue **2a**, 93% for lysine **2g**, and 89% for leucine **2e**. Similarly, the dibenzyloxy **2i** and fluoro-substituted **2l** aromatic rings both gave the product with 89% ee. For the remaining cases, the ee value was highly variable and the extent of epimerization may be related to a variety of factors. Longer reaction times do not significantly reduce the ee values. A possible rationalization is that the 2-bromoindole intermediate is very susceptible to epimerization because the proton at the stereocenter is much more acidic than that in the starting material due to its ketone character.[19] The extent of epimerization of the 2-bromoindole is related to the lifetime of this intermediate, which is

(19) Treatment of the starting material with either K_2CO_3 or 1,2-cyclohexyldiamine did not result in any racemization. For a reference illustrating the ketone character of an analogous *N*-acyl pyrrole, see: Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365.

Table 2. Scope of Amino Acids

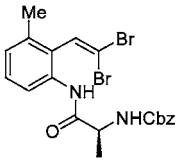
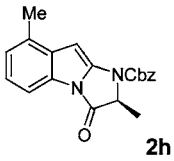
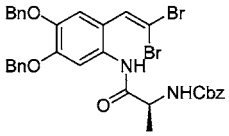
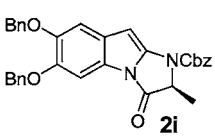
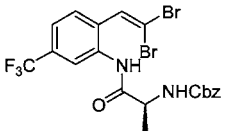
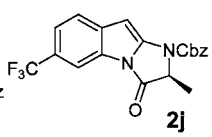
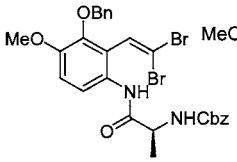
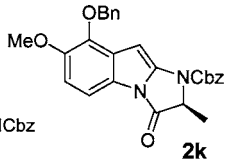
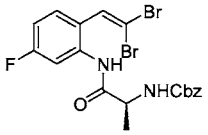
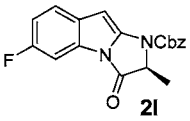
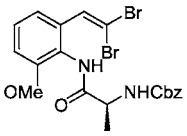
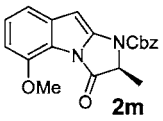
entry	amide	product	yield (%)[a]	ee (%)
1		 **2a**	84	86
2		 **2b**	74	N.A
3		 **2c**	73	76
4		 **2d**	63	4[b]
5		 **2e**	68	89
6		 **2f**	71	6
7		 **2g**	69	93

[a] All isolated yields. Reaction performed using CuI (2.5 mol %), racemic *trans*-1,2-cyclohexyldiamine (5 mol %), and K_2CO_3 (2 equiv) in toluene at 120 °C for 13−24 h. [b] The ee of the starting material was 4%.

dependent on the rate of the second amidation step. Thus, the more electron-rich 2-bromoindoles may experience significant epimerization of the 2-bromoindole intermediate due to the slower oxidative addition of the second step. The analogues that contain electron-withdrawing groups in either the aromatic ring or side-chain substituent possess a more acidic stereocenter, which explains the poor ee values in cases such as **2f**. Further studies to resolve the epimerization problem are ongoing.

The ability to access 3-substituted indoles is very attractive due to the presence of these moieties in many alkaloids. In the event, a higher catalyst loading (10 mol %) was required to obtain the desired product **15** in good yield (52%) since

Table 3. Scope of Aryl Substituents

entry	amide	product	yield[a] (%)	ee (%)
1		 **2h**	78	73
2		 **2i**	69	89
3		 **2j**	67	64
4		 **2k**	67	81
5		 **2l**	65	89
6		 **2m**	56	28

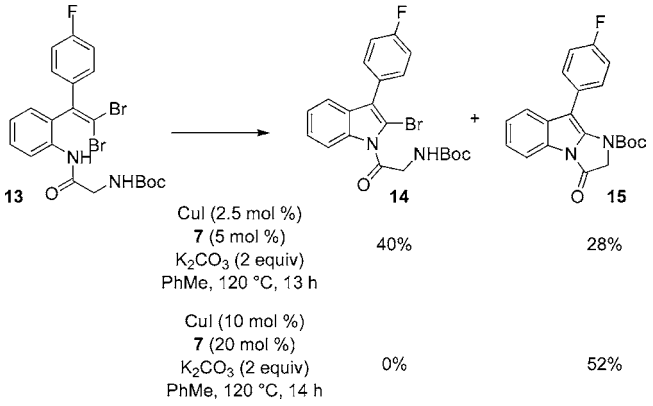
[a] All isolated yields. Reaction performed using CuI (2.5 mol %), racemic *trans*-1,2-cyclohexyldiamine (5 mol %), and K_2CO_3 (2 equiv) in toluene at 120 °C for 12−49 h.

the usual conditions gave mainly monocyclized product (40%) **14** and the desired product (28%) **15** (Scheme 3).

We attempted one "post-ring forming" reaction and found that treatment of **2a** with Adam's catalyst successfully removed the Cbz group with concomitant reduction of the indole to give **16** as a single diastereoisomer (Scheme 4).

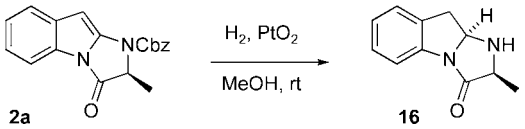
In conclusion, we have developed an efficient one-pot procedure giving rapid access to a wide range of substituted imidazoindolones from readily prepared *gem*-dibromovinyl

Scheme 3. 3-Substituted Imidazoindolones



substrates via a novel tandem intramolecular C−N bond formation. This process is particularly attractive for industrial use since copper iodide is a very cheap, air-stable compound and can be used without purification, in contrast to the high cost of palladium and problematic removal of Pd residues from polar compounds. Additionally, this methodology could provide facile access to the natural products asperlicin **3** and fumiquinazolines **4**.

Scheme 4



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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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