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Authors: Andrew Whyte, Katherine Isabelle Burton, Jingli Zhang, and Mark Lautens

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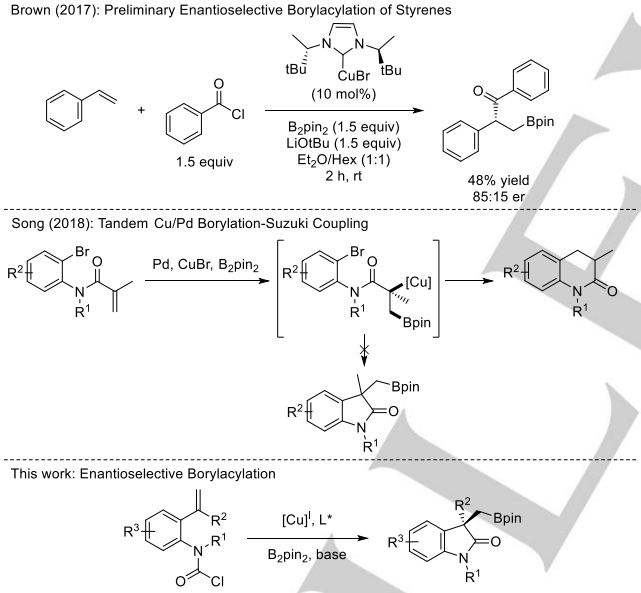
Enantioselective Intramolecular Copper-Catalyzed Borylacylation

Andrew Whyte[a], Katherine I. Burton[a], Jingli Zhang[a,b], and Mark Lautens*[a]

Abstract: *An enantioselective copper-catalyzed intramolecular borylacylation is reported. The reaction proceeds through an initial enantioselective borylcupration of the styrene, followed by a nucleophilic attack on the tethered carbamoyl chloride. The products, chiral borylated 3,3-disubstituted oxindoles, were generated in excellent yields and enantioselectivities. The versatile carbon-boron bond provides a platform for a wide array of diversification.*

Enantioselective addition of a nucleophilic boron species to double bonds represents a powerful strategy in organic chemistry, as the carbon-boron bond readily facilitates further functionalization. In recent years, copper has emerged as a cost-effective catalyst to introduce boron in an asymmetric fashion[1]. These reactions often achieve a difunctionalization of the alkene or alkyne, initiated by a borylcupration and terminated using an electrophilic reagent. Significant recent contributions by Ito[2], Brown[3], Hoveyda[4], Yun[5], and others[6] have established the versatility in this process, typically utilizing an intermolecular electrophilic termination. Although intramolecular termination has been explored[7] there have been few examples in the synthesis of heterocycles[8].



Scheme 1. Selected examples of previous reports of copper-catalyzed borylation and our work on enantioselective borylacylation.

[a] A. Whyte, K. I. Burton, Dr. J. Zhang, Prof. Dr. Mark Lautens
Davenport Research Laboratories, Department of Chemistry
University of Toronto
80 St. George Street, Toronto, Ontario M5S 3H6 (Canada)
E-mail: mlautens@chem.utoronto.ca
[b] Dr. J. Zhang
School of Chemistry, Chemical Engineering and Life Sciences
Wuhan University of Technology
122 Luoshi Road, Wuhan 430074 (China)

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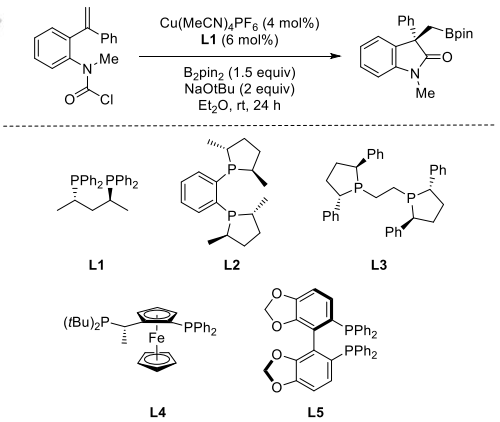
In 2017, Brown reported preliminary results on enantioselective borylacylation (shown in Scheme 1)[9]. Recent efforts to further this methodology have focused on utilizing different acylating reagents[10]. However, little attention has been paid to development of enantioselective variants and amides are yet to be introduced through copper-catalyzed borylacylation. We envisioned tethering a reactive olefin to a carbamoyl chloride for use in enantioselective borylacylation and subsequent transformation into chiral borylated 3,3-disubstituted oxindoles (shown in Scheme 1). The carbamoyl chloride moiety is a readily accessible and easy to handle acylating source, which forges new amide bonds. Previous work in our group applied an approach through a proposed chloropalladation of an alkyne, followed by termination with a tethered carbamoyl chloride to obtain chlorinated methylene oxindoles[11]. Recently, Meng disclosed enantioselective borylacylation using anhydrides[12].

Oxindoles exhibit a wide range of biological activities and have become sought-after targets in medicinal chemistry[13]. Borylated oxindoles have previously been synthesized by van der Eycken in an achiral fashion[14]. Song recently reported an effort to generate the same products using a dual copper/palladium system but the dihydroquinolinones were obtained as a result of protodemetallation[15]. Thus far, enantioenriched 3,3-disubstituted borylated oxindoles have not been reported and represent a valuable intermediate for the synthesis of bioactive products.

Table 1. Optimization of reaction conditions



Entry	Variation of Standard Condition	Yield [%][a]	er[b]
1	none	>99 (94)	98:2
2	**L2** instead of **L1**	59	70.5:29.5
3	**L3** instead of **L1**	98	87:13
4	**L4** instead of **L1**	68	38.5:61.5
5	**L5** instead of **L1**	77	97:3
6	LiO*t*Bu instead of NaO*t*Bu	76	96:4
7	KO*t*Bu instead of NaO*t*Bu	82	98:2

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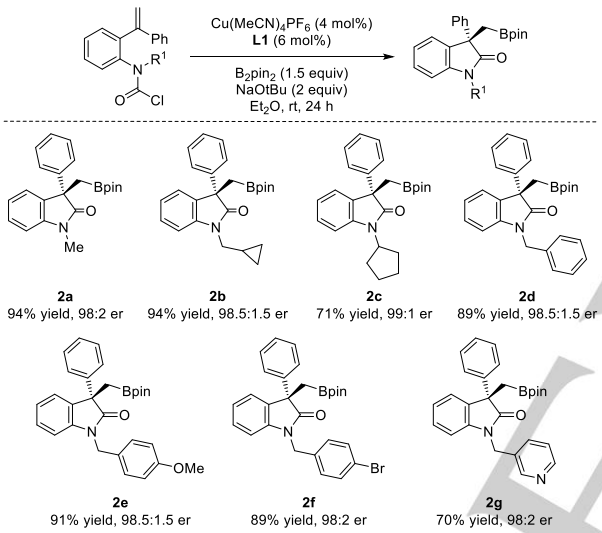
8	THF instead of Et_2O	>99	97.5:2.5
9	MTBE instead of Et_2O	86	97.5:2.5
10	dioxane instead of Et_2O	87	97:3

[a] NMR yield determined by using 1,3,5-trimethoxybenzene as standard, isolated yield in parenthesis [b] determined by chiral HPLC using IA column eluting with 10% IPA in hexanes

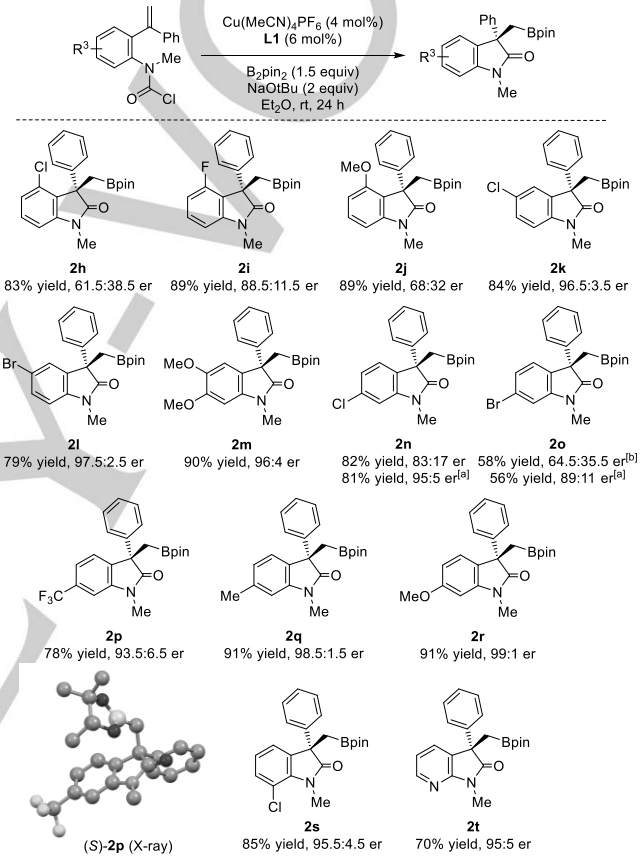
We began our investigations with conditions based on Xiong's hydroboration of 1,1-disubstituted olefins[16], obtaining the product (**2a**) in both excellent yield and enantioselectivity. Further evaluation of other bisphosphine ligands showed no improvement (Table 1, Entries 2-4), however, SEGPHOS delivered the product (**2a**) in 97:3 er (Table 1, Entry 5). Further, sodium tert-butoxide and diethyl ether proved superior to other bases (Table 1, Entries 6-7) and ethereal solvents (Table 1, Entries 8-10) respectively.



Scheme 2. Reaction scope with varied nitrogen substitution (0.2 mmol scale). All reported yields are after isolation, er determined by chiral HPLC.

We explored the scope of the reaction by varying the substituent on the nitrogen (Scheme 2). Both the methylene cyclopropane (**2b**) and cyclopentyl (**2c**) were tolerated providing excellent enantioselectivities. A variety of benzyl substitutions (**2d, 2e**) including halides (**2f**) and heteroaromatics (**2g**) were also produced with excellent enantioselectivities.

We continued to probe the reaction by varying the substitution of the backbone aromatic ring (Scheme 3). Substituents *ortho* to the styrene (**2h**, **2i**, **2j**) on the substrate led to a substantial decrease in the enantioselectivities likely due to steric effects in the substrate. However, a smaller moiety (**2i**), showed moderate enantioselectivity (88.5:11.5 er). *meta*-Substituted chloride (**2k**), bromide (**2l**), and dimethoxy (**2m**) containing products were obtained in good yields and excellent enantioselectivities. Halogens positioned *para* to the styrene (**2n** and **2o**) showed large decreases in enantioselectivity and in the case of bromide substitution, longer reaction times were required. Further optimizations revealed higher ligand loading, and the use of dioxane as a solvent were critical to restoring good enantioselectivities. The electron-withdrawing trifluoromethyl moiety (**2p**) showed slightly lower yield and enantioselectivity compared to the electron rich methyl (**2q**) and methoxy (**2r**). The absolute stereochemistry was determined for **2p** via X-ray crystallography, while the configuration of all other products is assigned by analogy. When a chloride was positioned *ortho* to the nitrogen (**2s**), nearly identical results were observed in comparison to **2k**. Finally, the phenyl backbone could be replaced with a heteroaromatic pyridine backbone (**2t**) while maintaining good yield and enantioselectivity.



Scheme 3. Reaction scope with varied aryl substitution (0.2 mmol scale). All reported yields are after isolation, er determined by chiral HPLC. [a] Run in dioxane with 8 mol% ligand. [b] Reaction run for 48 h

We also examined the effect of varying the pendant aromatic ring (Scheme 4). As observed in **2o**, we found that product **2u** led to a large decrease in enantioselectivity, delivering the product as a near racemate. Switching to dioxane and increasing the ligand concentration did not have the same effect as was found with **2o**. Similarly, product **2v** was obtained with low er which only saw slight improvement using dioxane as a solvent. Other para substitutions such as fluoride (**2w**) and methyl (**2x**) gave excellent yields and enantioselectivities. The dioxolane group (**2y**) and meta substitution (**2z** and **2aa**) were both well tolerated. Interestingly, a 2-substituted thiophene (**2ab**) were successful. Finally, we explored alkyl substitution in place of the aryl rings. While methyl substitution (**2ac**) performed satisfactorily, we were

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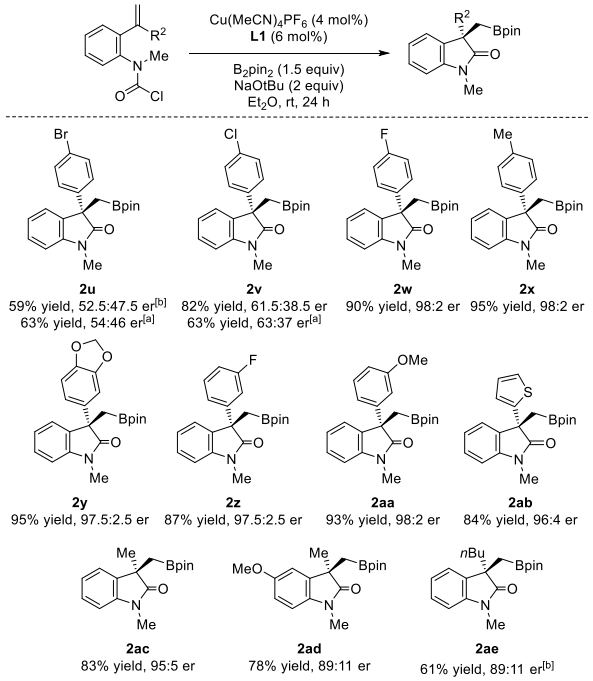
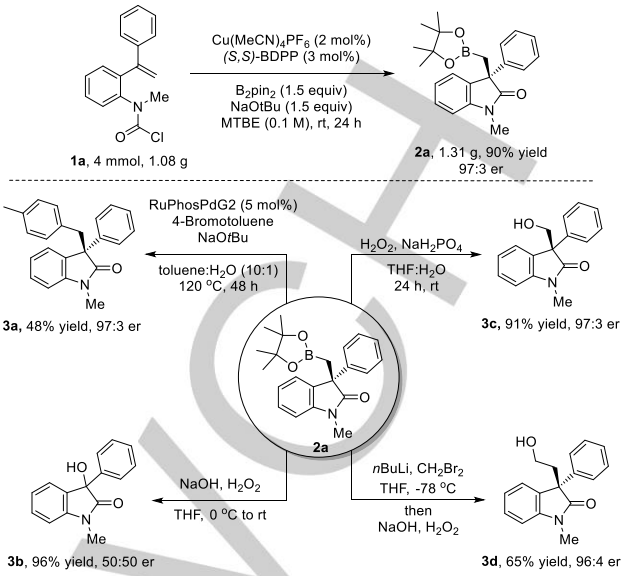
disappointed that introduction of a methoxy group on the aryl ring (**2ad**) showed lower enantioselectivity. A butyl group (**2ae**) on the alkene required longer reaction times and gave decreased enantioselectivity.



Scheme 4. Reaction scope with alkene substitution (0.2 mmol scale). All reported yields are after isolation, er determined by chiral HPLC. [a] Run in dioxane with 8 mol% ligand. [b] Reaction run for 48 h

To demonstrate the versatility of this methodology we performed the reaction on a larger scale, utilizing 4 mmol of substrate **1a** to produce product **2a**. Further, we dropped the catalyst and ligand loading, switched to a safer solvent (MTBE), used less base (1.5 equivalents), and increased the concentration of the reaction to 0.1 M. The desired product, **2a**, was obtained in 90% yield and 97:3 er, showing a slight decrease in yield and enantioselectivity compared to the standard reaction conditions (Scheme 5).

We further aimed to diversify the carbon-boron bond, in order to demonstrate the versatility of the borylated 3,3-disubstituted oxindole scaffold (Scheme 5). Suzuki coupling was successfully performed under conditions established by van der Eycken,[53] delivering the arylated product (**3a**) in 48% yield with no change in er. We then attempted to oxidize the carbon-boron bond using hydrogen peroxide and sodium hydroxide but were surprised to obtain the dealkylated alcohol (**3b**) in racemic form. We hypothesize the basic and oxidizing reaction conditions trigger a retro-aldol of the desired alcohol followed by oxidation of the enolate to generate product **3b**. By using a weaker base, we obtained the oxidized product (**3c**) maintaining chirality in excellent yield. Finally, we performed Matteson homologation followed by oxidation to obtain the extended alcohol (**3d**) in 65% yield with no loss in stereochemistry.



Scheme 5. Scaled up reaction, see SI for details. Product derivatizations were run on 0.2 mmol scale. All reported yields are after isolation, er determined by chiral HPLC.

In conclusion, we have developed an enantioselective copper-catalyzed intramolecular borylacylation process, successful in accessing chiral 3,3-disubstituted oxindoles. We exploited a tethered carbamoyl chloride as an electrophilic trap for the benzylic copper intermediate, generated from borylcupration. A wide variety of substitution patterns afforded the products in generally excellent yields and enantioselectivities. We also demonstrated the versatility afforded by the carbon-boron bond to generate a library of compounds that could serve as building blocks towards medicinally relevant molecules. This method represents the effectiveness of copper-catalyzed borylation in the synthesis of chiral, functionalized heterocycles.

Acknowledgements

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Keywords: copper • borylacylation • oxindoles • cyclization • asymmetric catalysis

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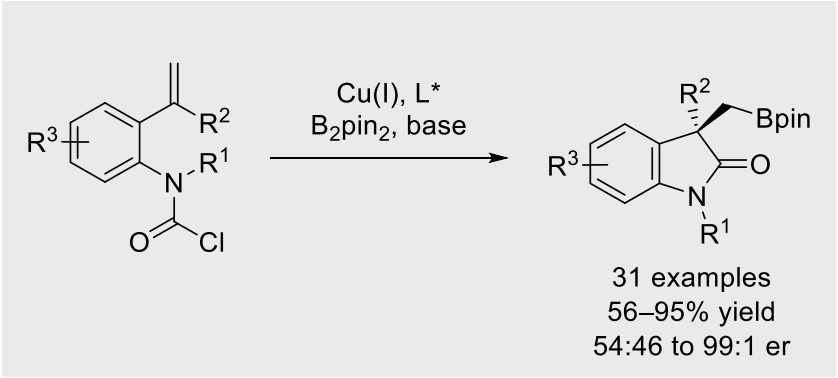

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Enantioselective Intramolecular Copper-Catalyzed Borylacylation

The synthesis of chiral 3,3-disubstituted borylated oxindoles is reported in good yields and enantioselectivities. The reaction employed a chiral copper catalyst to perform an enantioselective borylcupration followed by intramolecular acylation with a tethered carbamoyl chloride. The chiral oxindole products are readily diversifiable to a range of substituted oxindole products.