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Interrupted Fischer-Indole Intermediates via Oxyarylation of Alkenyl Boronic Acids

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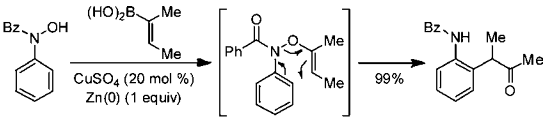
ABSTRACT



The oxyarylation of alkenyl boronic acids with *N*-arylbenzhydroxamic acids has been achieved under both copper-mediated and copper-catalyzed conditions to provide access to interrupted Fischer-indole intermediates. This transformation is believed to proceed through a copper-promoted C−O bond forming event followed by a [3,3] rearrangement. The scope of the method is described and mechanistic experiments are discussed.

The Fischer-indole reaction is a powerful transformation that has been widely used to form new C−C bonds through the [3,3] rearrangement of an aryl hydrazone and new C−N bonds via the intramolecular 1,2-addition of an aniline to an imine.[1,2] Unfortunately, under the conditions of the Fischer-indole reaction, it is impossible to separate these two events. A method designed to halt the process after C−C bond formation would provide a simple route to α-arylated ketones with *o*-amide substituents. These compounds are challenging to synthesize due to the lack of a general preparative method and because they represent a limitation of transition-metal-catalyzed α-arylation procedures.[3−7]

Recently, we investigated the use of *N*-enoxyphthalimides as precursors to α-hydroxy ketones.[8] To further exploit *O*-alkenyl hydroxamates as rearrangement precursors for the construction of challenging bonds, we decided to target an alkenyl ester of *N*-phenylbenzhydroxamic acid **1a** by copper-mediated C−O bond coupling (Scheme 1).[9] We were intrigued by this intermediate because we reasoned that **3aa** could potentially undergo two distinct [3,3]

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(1) For Fischer-indole reaction reviews, see: (a) Downing, R. S.; Kunkeler, P. J. The Fischer Indole Synthesis. In *Fine Chemicals through Heterogeneous Catalysis*; Sheldon, R. A., Van Bekkum, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 178−183. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, *25*, 607. (c) Ambekar, S. Y. *Curr. Sci.* **1983**, *52*, 578. (d) Robinson, B. *The Fischer Indole Synthesis*: John Wiley & Sons: Hoboken, 1983.

(2) For a mechanistic study of the Fischer-indole reaction, see: Hughes, D. L.; Zhao, D. *J. Org. Chem.* **1993**, *58*, 228.

(3) For reviews of transition-metal-catalyzed α-arylation reactions, see: (a) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2009**, *49*, 676. (b) Mazet, C. *Synlett.* **2012**, *23*, 1999. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(4) For selected examples of transition-metal-catalyzed α-arylation of ketones, see: (a) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330. (b) Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264. (c) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (d) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (e) Huang, K.; Li, G.; Huang, W.-P.; Yu, D.-G.; Shi, Z.-J. *Chem. Commun.* **2011**, *47*, 7224. (f) Kale, A. P.; Pawar, G. G.; Kapur, M. *Org. Lett.* **2012**, *14*, 1808. (g) Danoun, G.; Tlili, A.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12815.

(5) For intramolecular examples of α-arylation of *N*-phenylamides to form oxindoles, see: (a) Ju, X.; Liang, Y.; Jia, P.; Li, W.; Yu, W. *Org. Biomol. Chem.* **2012**, *10*, 498. (b) Wu, L.; Falivene, L.; Drinkel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2870. (c) Beyer, A.; Buendia, J.; Bolm, C. *Org. Lett.* **2012**, *14*, 3948.

(6) For examples of Cu-catalyzed α-arylation of malonates, β-keto-esters, and 1,3-diones with *o*-haloanilides, see: (a) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625. (b) Chen, Y.; Xie, X.; Ma, D. *J. Org. Chem.* **2007**, *24*, 9329. (c) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050. (d) Huang, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 1028.

(7) For a mechanistic discussion describing the inability to use Pd-catalyzed α-arylation to convert an *o*-haloaryl amine to an α-(*o*-aminoaryl)ketone and the inability to use a Buchwald-Hartwig reaction to convert an α-(*o*-haloaryl)ketone to an α-(*o*-aminoaryl)ketone, see: Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588.

(8) Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson, L. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 7799.

(9) For reviews and examples of *O*-alkenylation with boronic acids, see: (a) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415. (b) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927. (c) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829. (d) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381. (e) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202. (f) Winternheimer, D. J.; Merlic, C. A. *Org. Lett.* **2010**, *12*, 2508. (g) Chan, D. G.; Winternheimer, D. J.; Merlic, C. A. *Org. Lett.* **2011**, *13*, 2778. (h) Winternheimer, D. J.; Shade, R. E.; Merlic, C. A. *Synthesis* **2010**, 2497.

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rearrangements to give either a new C–C bond **4aa** or a new C–O bond **5aa**.[10] To our delight, we discovered that treatment of **1a** with cyclohexenyl boronic acid **2a** in the presence of CuBr exclusively gave α-arylated ketone **4aa**. This transformation implies that copper-mediated C–O bond formation triggers a spontaneous and chemoselective [3,3] rearrangement to provide direct access to isolable interrupted Fischer-Indole intermediates.[11] Herein we present the optimization and scope of this operationally convenient method for the oxyarylation of alkenyl boronic acids and insight into the mechanism of this process for the preparation of α-(*o*-anilido)ketones.

Scheme 1. Chemoselective [3,3] Rearrangements

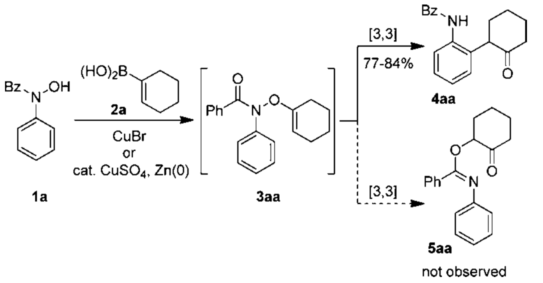
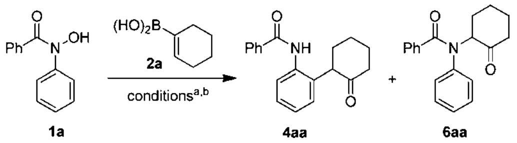


Table 1. Optimization of Coupling and Rearrangement[a,b]



entry	copper salt	[Cu]	additive (1 equiv)	yield (%)	**4aa**/**6aa**
1	$Cu(OAc)_2$	1 equiv	none	76	only **4aa**
2	CuBr	1 equiv	none	84	only **4aa**
3	$CuBr\cdot SMe_2$	1 equiv	none	65	only **4aa**
4	CuI	1 equiv	none	nr	
5	CuOTf·Tol	1 equiv	none	69	only **4aa**
6	CuTC	1 equiv	none	47	only **4aa**
7	CuBr	20 mol %	BQ	nr	
8	CuBr	20 mol %	$PhI(OAc)_2$	dec	
9	CuBr	20 mol %	Zn dust	60	2/1
10	CuBr	20 mol %	Mn dust	nr	
11	$Cu(OAc)_2$	20 mol %	Zn dust	50	5/1
12	CuCl	20 mol %	Zn dust	33	5/2
13	CuI	20 mol %	Zn dust	41	9/1
14	$CuSO_4$[c]	20 mol %	Zn dust	75	7/1

[a] Reaction mixtures were prepared as 1:2:5:1 mixture of **1**/**2**/pyridine/4 Å MS in DCE (0.1 M) and were run in air. [b] % yield determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference. [c] $CuSO_4\cdot 5H_2O$.

The coupling of *N*-phenylbenzhydroxamic acid **1a** with cyclohexenyl boronic acid **2a** was tested with a variety of copper(I) and copper(II) salts to determine optimal conditions for the preparation of α-(*o*-anilido)ketones (Table 1). Several copper reagents were shown to efficiently convert mixtures of **1a** and **2a** to **4aa** in the presence of pyridine, a halogenated solvent, and air. The most efficient reagent was identified as CuBr (entries 1–6). While unassisted, substoichiometric amounts of CuBr did not exhibit any turnover for the desired transformation. Considering that inefficient oxidation state changes may have been responsible for the lack of catalyst turnover, common oxidants and reductants were screened as additives (entries 7–10). While the use of benzoquinone and $PhI(OAc)_2$ failed to promote the conversion of **1a** to **4aa** in the presence of 20 mol % of CuBr, we were delighted to discover that the addition of 1 equiv of Zn dust provided the desired product in good yield. Surprisingly, under these copper-catalyzed conditions, the preparation of **4aa** was accompanied by α-aminated ketone **6aa** (entry 9).[12] This competing side product could be generated via a formal [1,3] rearrangement of the proposed intermediate **3aa**.[13] Compound **6aa** was removed from the crude oxyarylation product mixtures by column chromatography and was not converted to **4aa** under the reaction conditions. Other common reductants such as Mn(0), Al(0), and $SnCl_2$ were tested for comparison to Zn(0) but none promoted the desired catalysis.[14] Further screening of the choice of copper catalyst led to increased conversion and varying ratios of **4aa** and **6aa** (entries 11–14). The best combination of yield and selectivity for C–C bond formation was provided by 20 mol % of $CuSO_4\cdot 5H_2O$ when used with a single of equivalent of Zn(0). The optimal conditions described in entries 2 and 14 of Table 1, were chosen to further explore the scope of the oxyarylation of alkenyl boronic acids with *N*-arylhydroxamic acids.

Several alkenyl boronic acids were screened under both copper-catalyzed and copper-mediated conditions (Table 1, entries 2 and 14, respectively) to determine the tolerance of the oxyarylation for the alkenyl coupling partner.[15] As shown in Scheme 2, a variety of cyclic and

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(10) For examples of similar [3,3] rearrangements of *N*-arylhydroxamate-substituted ketene acetals, see: (a) Endo, Y.; Uchida, T.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 2113. (b) Endo, Y.; Uchida, T.; Hizatate, S.; Shudo, K. *Synthesis* **1994**, 1096. (c) Almeida, P. S.; Prabhakar, S.; Lobo, A. M.; Marcelo-Curto, M. J. *Tetrahedron Lett.* **1991**, *32*, 2671. (d) Miller, S. J.; Bayne, C. D. *J. Org. Chem.* **1997**, *62*, 5680. (e) Santos, P. F.; Srinivasan, N.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron* **2005**, *61*, 9147. (f) Mao, Z.; Baldwin, S. W. *Org. Lett.* **2004**, *6*, 2425. (g) Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 3858.

(11) For examples of the use of other types of interrupted Fischer-indole intermediates in synthesis, see: (a) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458. (b) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687. (c) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877. (d) Bunders, C.; Cavanagh, J.; Melander, C. *Org. Biomol. Chem.* **2011**, *9*, 5476. (e) Schammel, A. W.; Chiou, G.; Garg, N. K. *J. Org. Chem.* **2012**, *77*, 725. (f) Schammel, A. W.; Chiou, G.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4556.

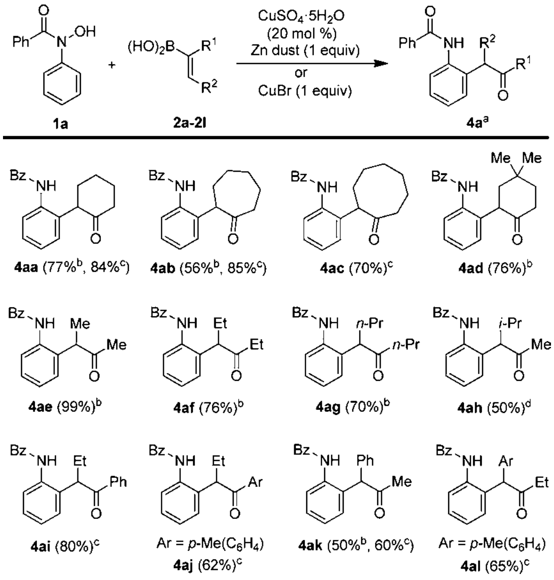
(12) Compound **6aa** was identified by comparison of spectroscopy data to α-(*N*-phenylamino)cyclohexanone: Liu, S.; Xie, J.-H.; Li, W.; Kong, W.-L.; Wang, L.-X; Zhou, Q.-L. *Org. Lett.* **2009**, *11*, 4994.

(13) For examples of formal [1,3] rearrangements of *O*-vinyl oximes that we have observed previously, see: (a) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Kapadia, R.; Londino, H. N.; Anderson, L. L. *J. Org. Chem.* **2011**, *76*, 3203. (b) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290.

(14) Zn(0) and Zn(II) salts did not promote the oxyarylation in the absence of CuBr or $CuSO_4\cdot 5H_2O$.

(15) Literature procedures were used to prepare alkenyl boronic acids **2**. See the Supporting Information for details.

Scheme 2. Scope of Alkenylboronic Acid Reagents for Oxyarylation

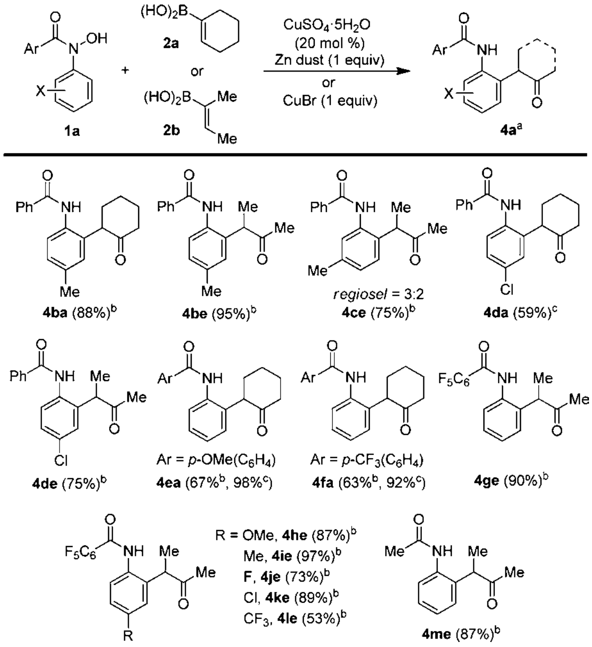


[a] Percent isolated yield. [b] 20 mol % of $CuSO_4 \cdot 5H_2O$ and 1 equiv of Zn. [c] 1 equiv of CuBr. [d] 20 mol % of $Cu(OAc)_2$ and 1 equiv of Zn.

linear, *Z*-disubstituted alkenyl boronic acids were successfully transformed into the corresponding α-(*o*-anilido)-ketones. Cyclic alkenyl boronic acids provided good to excellent yields of **4aa**, **4ab**, and **4ad** under copper-catalyzed conditions and larger ring sizes were well-tolerated under copper-mediated conditions. *Z*-2-Butenyl boronic acid **2e** was identified as the most efficient coupling partner with **1a** and longer alkyl chain analogues and branched substituents were similarly well-tolerated (see **4af**–**ah**). Strylboronic acids **2i**–**l** were efficiently converted to α-arylated ketones **4ai**–**al** under copper-mediated conditions, while copper-catalyzed conditions were also shown to be effective for **4ak**. To the best of our knowledge, none of the products illustrated in Scheme 2 have previously been reported in the literature. For comparison, we attempted to synthesize **4ai** using literature procedures for palladium-catalyzed α-arylation but no reaction was observed and starting materials were recovered.[16] These control experiments emphasize the practical importance of the new method in addressing current limitations of α-arylation reactions.

The scope of the oxyarylation reaction was further evaluated by testing a variety of *N*-arylhydroxamic acids for the coupling and rearrangement process (Scheme 3).[17] Benzhydroxamic acids with *N*-*p*-tolyl substituents provided excellent yields of α-arylated cyclohexanone **4ba** and acetone **4be**. While *N*-(*m*-tolyl)benzhydroxamic acid **1c** was similarly effective, it gave a 3:2 regioisomeric mixture of **4ce**.[18] *N*-*p*-Chlorophenyl hydroxamic acid **1d** was converted to analogous α-arylated ketones **4da** and **4de**, in somewhat attenuated yields compared to the tolyl analogues. The oxyarylation method was also shown to tolerate both electron-rich and electron-poor *N*-benzoyl protecting groups under both copper-catalyzed and copper-mediated conditions (**4ea** and **4fa**). *N*-Perfluorobenzoyl hydroxamic acids, in particular, proved to be excellent substrates when treated with boronic acid **2e**. Alkyl-, halogen-, and OMe-substituted *N*-aryl groups gave α-arylated ketones **4he**–**ke** in excellent yields while the efficiency of the conversion of *N*-(*p*-CF_3)phenyl hydroxamic acid **1l** to **4le** was moderate. *N*-Aryl acetohydroxamic acids were also shown to be amenable to the oxyarylation process but were less efficient than *N*-benzoyl substrates (**4me**). Carbamate derivatives were tested but these compounds provided mixtures of the desired products and the corresponding indole. These results demonstrate that the mild conditions of the oxyarylation reaction enable broad functional group tolerance to access a range of α-(*o*-anilido)ketones.

Scheme 3. Scope of *N*-Arylhydroxamic Acid Reagents for Oxyarylation



[a] Percent isolated yield. [b] 20 mol % of $CuSO_4 \cdot 5H_2O$ and 1 equiv of Zn. [c] 1 equiv of CuBr.

To better understand the copper-catalyzed oxyarylation process, several experiments were designed to compare the individual steps of the proposed mechanism illustrated in Scheme 1.[19] An intramolecular competition experiment was used to assess the C–H functionalization event.

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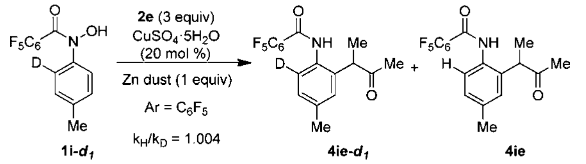
(16) No reaction was observed when a mixture of *N*-(2-bromophenyl)-benzamide and butyrophenone was subjected to the α-arylation conditions provided in the following references: (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(17) Literature procedures were used to prepare *N*-arylhydroxamic acids **1**. See the Supporting Information for details.

(18) For a discussion on the limits of regioselectivity in the Fischer-indole reaction, see: Phillips, R. R. *Org. React.* **1959**, *10*, 1143 (ref 1d) and references cited therein.

(19) In changing from copper-mediated to copper-catalyzed conditions, the only step of the proposed mechanism that is thought to be affected in our current working model is catalyst regeneration.

Scheme 4. Intramolecular Competition Experiment



As shown in Scheme 4, when hydroxamic acid **1i-**d_1 was treated with **2e** under the reaction conditions, a primary kinetic isotope effect was *not* observed. This suggests that C–H functionalization is not involved in the rate-determining step of the oxyarylation. To distinguish between the C–O and C–C bond forming events, the dependence of the rate of product formation on the electronic nature of the *N*-aryl group was evaluated. *Para*-substituted *N*-aryl groups were used to examine both the C–O and the C–C bond-forming steps of the transformation by comparison of relative rates to σ_p and σ_m values, respectively. Competition experiments between *para*-substituted *N*-hydroxyanilides **1h**–**l** and *N*-hydroxyanilide **1g** were used to determine relative initial rates of oxyarylation. As shown in Figure 1, the relative rate dependence on the type of *N*-aryl substituent had a linear correlation with σ_p values with a ρ-value of -1.01 and a nonlinear correlation with σ_m values.[20] These data suggest that C–O bond formation is the slow-step of the oxyarylation process and are consistent with the fact that intermediate **3** was not observed. The negative ρ-value may be indicative of electron-donating groups facilitating the transmetalation of the boronic acid which has been suggested to be the slow step of a Chan-Lam-Evans coupling.[21] Previous studies have shown that mechanistic data supports cyclization of the imino anilide as the rate-determining step of the Fischer-indole reaction if the substrate has an *N*-acetyl substituent.[22] This implies that the key to our ability to isolate the interrupted Fischer-Indole intermediates described above is that our coupling conditions are mild enough to suppress cyclization to the corresponding indole.

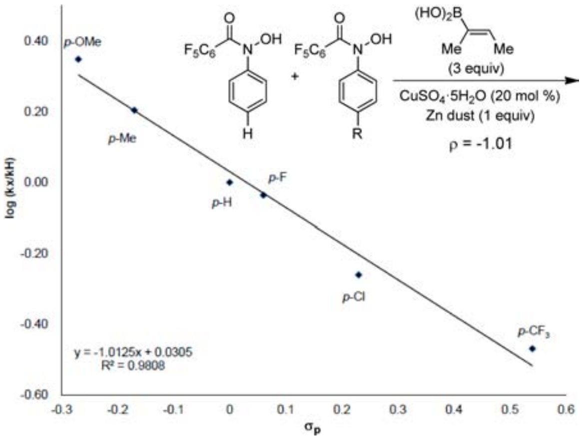


Figure 1. Correlation of relative initial rates to Hammett σ_p values.

In summary, we have shown that interrupted Fischer-indole intermediates can be prepared by copper-mediated or copper-catalyzed oxyarylation of alkenyl boronic acids with *N*-arylbenzhydroxamic acids. These transformations provide access to α-(*o*-anilido)ketones which are challenging to prepare because of their propensity to cyclize to the corresponding indole and the inability of α-arylation procedures to access these types of structures. Mechanistic data suggests that C–O bond formation is the slow-step of the oxyarylation process and that the mild conditions used to affect this transformation allow for the isolation of an interrupted Fischer-indole intermediate after the [3,3] rearrangement and before a cyclization to the corresponding indole can occur.

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Supporting Information Available. Experimental procedures and compound characterization data. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

[20] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

[21] (a) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829. (b) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

[22] (a) Douglas, A. W. *J. Am. Chem. Soc.* **1978**, *100*, 6463. (b) Douglas, A. W. *J. Am. Chem. Soc.* **1979**, *101*, 5676.