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# A Tandem Heck-Carbocyclization/ Suzuki-Coupling Approach to the Stereoselective Syntheses of Asymmetric 3,3-(Diarylmethylene)indolinones

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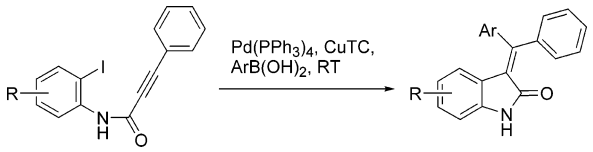


An efficient and versatile method for stereoselective synthesis of (*E*)-3,3-(diarylmethylene)indolinones by a palladium-catalyzed tandem Heck-carbocyclization/Suzuki-coupling sequence is presented. Factors influencing yield and selectivity, namely catalyst, coordinating ligand, and solvent, are detailed.

The 2-indolinone system has been incorporated in a significant number of pharmaceutically relevant compounds. Potential utilities for such compounds have been identified in virtually all of the major therapeutic areas including oncology, inflammation, CNS, immunology, and endocrinology. Indolinones bearing a substituted exocyclic methylene at the 3-position have gained particular prominence in the fields of oncology and inflammation, as this pharmacophore has demonstrated a unique ability to inhibit kinase activities through a competitive interaction at the ATP binding sites of these enzymes. While many 3-(arylidenyl)indolinone analogues have been extensively evaluated for kinase inhibitory activities, these have by and large been monoaryl-substituted methylidenyl analogues, e.g., SU6668[1] and SU11248 (Figure 1).[2] 3-(Arylaminomethylenyl)indolinones have also been identified as potent kinase inhibitors. As exemplified by GW-491619, these have also largely been trisubstituted olefinic derivatives.[3] One notable exception is the recently identified Aurora B inhibitor, hesperadin (**1**), in which the exocyclic olefin is tetrasubstituted.[4]

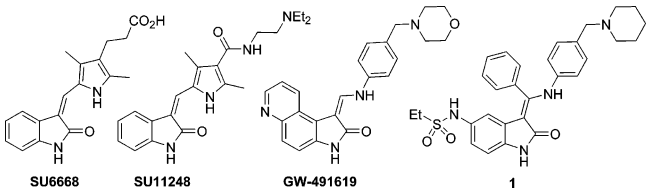


**FIGURE 1.** Indolinone-based kinase inhibitors.

Only a limited number of medicinally relevant 3-(diarylmethylenyl)indolinones have been disclosed. These tend to be symmetrically substituted derivatives such as 3-[bis(4-methoxyphenyl)methylene]-1,3-dihydroindol-2-one, which are readily accessible by condensation reactions between an oxindole and a symmetrical diaryl ketone, bis-(4-methoxyphenyl)methanone.[5]

Performing this intermolecular condensation with an unsymmetrical diaryl ketone would be expected to give rise to a mixture of both geometrical isomer products, absent overriding directing group effects. The lack of a general method for the synthesis of unsymmetrically substituted 3-(diarylmethylenyl)indolinone isomers may partially explain why these systems have not been more extensively investigated. Herein, we report the development of a versatile stereoselective synthesis of asymmetric 3-(diarylidenyl)indolinones, **2**. Our method involves a two-step tandem Heck-carbocyclization/Suzuki-coupling process starting from 2-iodoanilines and arylpropionic acids.[6]

To introduce asymmetry at the exocyclic methylene carbon, we sought a method by which two aryl groups could be incorporated at this site independent of one another. Retrosynthetically (Scheme 1) we envisioned a process wherein an intramolecular Heck-carbocyclization of an arylpropynamide **5** might favor a single (*E*)-vinylpalladium intermediate, **4**. Subsequent coupling with an aryl boronic acid **3** would serve to incorporate the second aryl substituent in a stereoselective fashion, provided that this kinetic vinylpalladium species would resist isomerization to the thermodynamic (*Z*)-configuration under conditions of the reaction. Arylpropynamides **5** in turn, would be readily accessible from arylpropynoic acids (**6**) and 2-iodoanilines (**7**) (Table 1).

Unsubstituted phenylboronic acid was initially chosen in order to test the feasibility of this sequence and for carrying out a cursory probe of coupling conditions. Thus, phenylpropiolic acid (**6**) was converted to its acid chloride

(1) (a) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J. Y.; Nematalla, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. *J. Med. Chem*. **2003**, *46*, 1116−9. (b) Sun, L.; Tran, N.; Liang, C.; Hubbard, S.; Tang, F.; Lipson, K.; Schreck, R.; Zhou, Y.; McMahon, G.; Tang, C. *J. Med. Chem.* **2000**, *43*, 2655−63.

(2) Mendel, D. B.; Laird, A. D.; Xin, X.; Louie, S. G.; Christensen, J. G.; Li, G.; Schreck, R. E.; Abrams, T. J.; Ngai, T. J.; Lee, L. B.; Murray, L. J.; Carver, J.; Chan, E.; Moss, K. G.; Haznedar, J. O.; Sukbuntherng, J.; Blake, R. A.; Sun, L.; Tang, C.; Miller, T.; Shirazian, S.; McMahon, G.; Cherrington, J. M. *Clin. Cancer Res.* **2003**, *9*, 327−37.

(3) (a) Eberwein, D. J.; Harrington, L.; Griffin, R.; Tadepalli, S.; Knick, V.; Phillips, K.; Dickerson, S.; Davis, S. *Proc. Am. Assoc. Cancer Res.* **2002**, *43*: Abst 1611. (b) Davis, S. T.; Dickerson, S. H.; Harris, P. A.; Hunter, R. N.; Kuyper, L. F.; Luzzio, M. J.; Veal, J. M.; Walker, D. H. US Pat. 6,387,919, 2002.

(4) Hauf, S.; Cole, R. W.; LaTerra, S.; Zimmer, C.; Schnapp, G.; Walter, R.; Heckel, A.; van Meel, J.; Rieder, C. L.; Peters, J. M. *J. Cell Biol.* **2003**, *161*, 281−94.

(5) Sato, A.; Asao, T.; Hagiwara, Y.; Kitade, M.; Yamazaki, Y. US Pat. 5,965,600, 1999.

(6) While this paper was in preparation, Yanada et al. published a complementary method for the syntheses of 3-diarylmethylidenyloxindoles involving tandem indium carbometalation and palladium-catalyzed coupling reactions. The applicability of their method with N-containing heterocycles was not presented. Yanada, R.; Obika, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825−2828.

10.1021/jo050016d CCC: $30.25 
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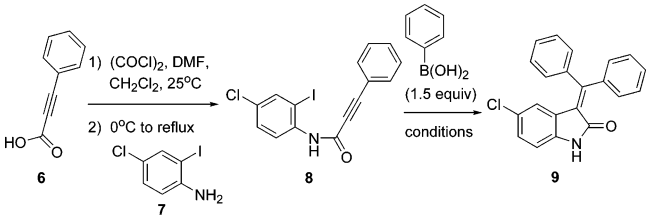
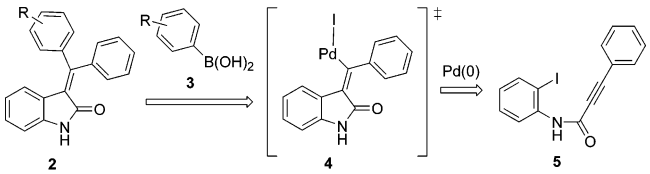
**TABLE 1. Tandem Heck-Carbocyclization/ Suzuki-Coupling: Catalyst Evaluation**




| Entry | Reaction condition | % yield* | Entry | Reaction condition | % yield* |
|---|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ (0.1 equiv), $K_3PO_4$ (2.5 equiv), THF, 100°C microwave, 30 min. | 78% | 4 | $Pd(OAc)_2$ (0.1 equiv), $K_3PO_4$ (2.5 equiv), THF, 100°C microwave, 30 min. | 6% |
| 2 | CombiPhos-Pd6 (0.1 equiv), $K_3PO_4$ (2.5 equiv), THF, $H_2O$, 100°C microwave, 30 min. | 65% | | $Cy_2P$ **11** (0.2 equiv) | |
| 3 | $Pd(OAc)_2$ (0.1 equiv), $K_3PO_4$ (2.5 equiv), THF, 100°C microwave, 30 min. | 72% | 5 | $Pd(OAc)_2$ (0.2 equiv), $K_3PO_4$ (2.5 equiv), THF, **10** (0.2 equiv), 25°C, 25 h. | 75% |
| | **10** (0.1 equiv) | | 6 | $Pd(OAc)_2$ (0.2 equiv), $K_3PO_4$ (2.5 equiv), THF, **11** (0.4 equiv), 25°C, 14 h. | 48% |
| | | | 7 | $Pd(PPh_3)_4$ (0.1 equiv), THF, phenylboronic acid (1.2 equiv), CuTC (1.2 equiv), 25°C, 25 h. | 69% |

*Yields are isolated following chromatographic purification.

**SCHEME 1**

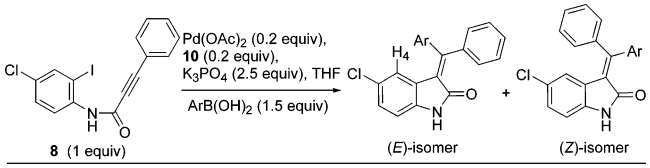


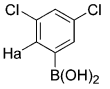
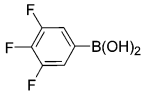
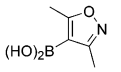
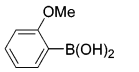

Diarylidenyl indolinone

and reacted with 4-chloro-2-iodoaniline (**7**) to afford the 2-iodoanilide **8** in 94% yield (Table 1). A standard Suzuki coupling reaction condition was first investigated, utilizing tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] as catalyst source and potassium phosphate as base in THF (entry 1).[7] While no reaction took place after 14 h at room temperature, brief microwave irradiation[8] provided the desired diarylidenyl indolinone product **9** in 78% isolated yield (Table 1).[9]

As follow up, a small screening set of different palladium catalysts was evaluated in order to determine if the reaction could be effected at ambient temperature. An air-stable mixture of palladium catalysts, CombiPhos-Pd6[10] (entry 2), was ineffective at promoting this cascade reaction at 25 °C. Under the microwave conditions used previously, the reaction proceeded to completion, though not as cleanly as was the case with $Pd(PPh_3)_4$. Similarly,

**TABLE 2. Tandem Reaction: Initial Investigation with Various Arylboronic Acids**




| Entry | $ArB(OH)_2$ | isomeric ratio (*E*:*Z*) | Entry | $ArB(OH)_2$ | isomeric ratio (*E*:*Z*) |
|---|---|---|---|---|---|
| 1 |  | (*E*)-**12** : (*Z*)-**12** = 4 :1 | 3 |  | (*E*)-**14** : (*Z*)-**14** = 3 :1 |
| 2 |  | (*E*)-**13** : (*Z*)-**13** = 2 :1 | 4 |  | (*E*)-**15** : (*Z*)-**15** = 2 :1 |

a mixture of palladium acetate and the highly active carbene ligand **10**[11] also failed to trigger a room-temperature transformation. Microwave irradiation was still required to force the reaction to completion, affording the desired indolinone in 72% yield (entry 3). Interestingly, Buchwald's ligand, 2-(dicyclohexylphosphino)biphenyl **11**,[12] which is usually regarded as a more activating ligand (entry 4), did not promote the reaction, even under the microwave conditions.

We next examined the reaction under conditions of increased palladium catalyst and ligand loading. We were gratified to find that with 0.2 equiv of $Pd(OAc)_2$ and carbene ligand **10**, a complete reaction could be effected at room temperature within 24 h (entry 5). A similar increase in load of catalyst **11** (entry 6) did not result in a complete reaction in 14 h. Finally, under the base-free Suzuki coupling reaction conditions of copper(I) thiophene-2-carboxylate (CuTC) with $Pd(PPh_3)_4$,[13] the cascade reaction proceeded almost to completion, with only a minor amount (~10%) of **8** remaining after 25 h at room temperature (entry 7).

Proceeding with the reaction conditions identified in entry 5 (Table 1), we turned our attention to the regioselectivity of this transformation. The 5-chloro substituent of the indolinone product (***E*)-12** (Table 2, entry 1) was incorporated to assist in the regiochemical assignment of the newly formed exo-alkene. Adjacent phenyl proton $H_4$, readily identifiable in the $^1H$ NMR spectra (~6.4−6.8 ppm; doublet), was appropriately positioned to interact with protons on the aryl ring positioned *anti* to the carbonyl, but not with those of the *syn*-aryl group. Thus, the presence of NOE cross-peak(s) between phenyl proton $H_4$ and an aromatic proton(s) of the newly coupled aryl ring served to unambiguously assign the olefin regiochemistry of our asymmetric diarylmethylidenyl-indolinones.

Four aryl boronic acids were chosen for our initial investigation of regiochemical selectivity (Table 2). In the case of 3,5-dichlorophenylboronic acid (entry 1), the reaction proceeded very slowly at 25 °C for 15 h. Heating (60 °C, 6 h) was required to force the reaction to completion. Both regioisomers formed under these conditions in a ratio of 4:1; these were separated by silica gel

(7) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(8) **Synthesis of 9.** To a solution of **8** (0.060 g, 0.157 mmol) in 2 mL of anhydrous THF were added $Pd(PPh_3)_4$ (0.018, 0.0157 mmol), $K_3PO_4$ (0.083 g, 0.393 mmol), and phenylboronic acid (0.029 g, 0.236 mmol). The sealed reaction mixture was irradiated in a microwave synthesizer (Smith Synthesizer, Personal Chemistry) at 100 °C for 30 min. The reaction mixture was concentrated under reduced pressure, and the resulting crude product was purified by silica gel chromatography [hexanes/EtOAc (4:1)] to afford **9** (78%) as yellow oil.

(9) The structure of this product was confirmed by comparison with the authentic diphenylmethylidene indolinone, prepared from the condensation of 5-chlorooxindole and benzophenone with sodium hydroxide in refluxing toluene.

(10) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643.

(11) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761.

(12) Wolf, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(13) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *1*, 2149.

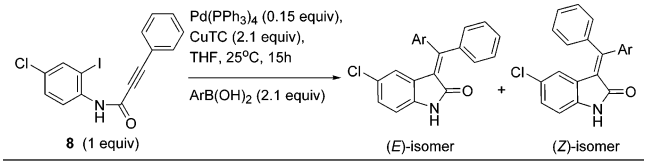
chromatography and each was analyzed by NOE experiments. A cross-peak was found between indolinone proton $H_4$ and $H_a$ of the dichlorophenyl ring, thus establishing an (*E*)-olefinic geometry of the major product (***E*)-12**. No such cross-peak signal was observed with minor product (***Z*)-12**, supporting its (*Z*)-configurational assignment. Subjecting 3,5-dimethylisoxazole-4-boronic acid (entry 2) to the same reaction conditions produced an inseparable mixture of regioisomeric products, (***E*)-13** and (***Z*)-13,** in an approximate ratio of 2:1 ($^1$H NMR determination). Again, NOE experiments clearly identified the dominant isomer (***E*)-13** as having the (*E*)-configuration based on the presence of cross-peak between $H_4$ and the isoxazole methyl groups and an absence of any cross-peak between $H_4$ and the pendant phenyl protons. Consistent with this assignment, $H_4$ of minor isomer (***Z*)-13** exhibited no such NOE cross-peak with these methyl protons. With 3,4,5-trifluorobenzeneboronic acid as the coupling partner (entry 3), heating was again required to force the cascade reaction to completion (70 °C, 4 h). As with the former reactions, the higher temperature led to the production of a pair of regioisomers, (***E*)-14** and (***Z*)-14** in a ratio of ~3:1. Similarly, employing 2-methoxyphenylboronic acid afforded (after heating) (***E*)-15** and (***Z*)-15** in a ratio of ~2:1 (entry 4).

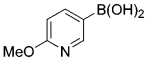
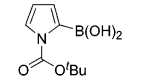
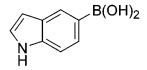
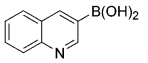
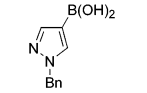
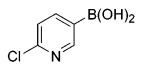
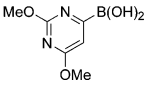
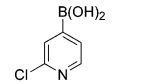
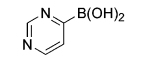
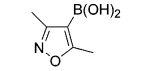
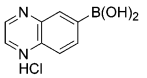
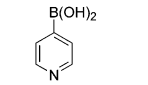
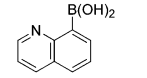
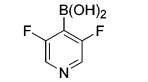
Thus, under these reaction conditions ($Pd(OAc)_2$, carbene ligand **10**, and $K_3PO_4$ in THF), a complete room-temperature transformation occurred only with the unsubstituted phenylboronic acid. Electron-deficient, electron-rich, and heterocyclic aromatic boronic acids each reacted sluggishly at room temperature; elevating the temperature resulted in complete conversion to indolinone products, but with modest and variable regioselectivities.

Returning to the conditions investigated in Table 1, we focused on entry 7 and optimized the catalyst load. Utilizing 0.2 equiv of $Pd(PPh_3)_4$ along with CuTC (2 equiv) and 3,5-dichlorophenylboronic acid (2 equiv) at room temperature, a complete conversion of **8** to indolinone was obtained after 4 h. Furthermore, isomer (***E*)-12** was generated (93% isolated yield) as the sole product of this reaction. With the success of this reaction, we next examined the applicability of the protocol with a variety of heteroaryl boronic acids.

A variety of nitrogen-containing heteroaryl boronic acids were selected as coupling components because of the prevalence of such heterocyles in biologically important compounds. As indicated in Table 3, pyridyl, indole, and pyrimidinyl boronic acids (entries 1−5) were successfully incorporated, providing the corresponding diarylidene indolinone in good yields (80−96%). In each of these cases, only the (*E*)-isomer was produced. Phthalazine (entry 6), quinoline (entry 7), and pyrrole (entry 8) boronic acids provided the desired indolinones in good yields (85−91%) and regioselectivities (*E*/*Z* = 13−25:1). Reactions with quinoline (entry 9), 2-chloropyridine (entries 10, 11), and isoxazole (entry 12) boronic acids provided the corresponding diarylidene indolinone in yields ranging from 62 to 93%, though in these cases, regioselectivities were lower (*E*/*Z* = 4−7:1). Contrary to the results obtained with other pyridyl boronic acids, pyridine-4-boronic acid (entry 13) failed to undergo the cascade reaction at room temperature. Mild heating (40 °C) was required to completely consume propynamide **8**.

**TABLE 3. Tandem Reaction with Boronic Acids of Nitrogen Heterocycles**




| Entry | $ArB(OH)_2$ | % yield, isomeric ratio (*E*:*Z*) | Entry | $ArB(OH)_2$ | % yield, isomeric ratio (*E*:*Z*) |
|---|---|---|---|---|---|
| 1 |  | 96%, (*E*)- isomer | 8 |  | 87%, 25:1 |
| 2 |  | 91%, (*E*)- isomer | 9 |  | 62%, 4:1 |
| 3 |  | 93%, (*E*)- isomer | 10 |  | 85%, 5:1 |
| 4 |  | 82%, (*E*)- isomer | 11 |  | 93%, 6.3:1 |
| 5 |  | 80%, (*E*)- isomer | 12 |  | 86%, 6.5:1 |
| 6 |  | 83%, 13:1 | 13 |  | 42%, 23:1* |
| 7 |  | 85%, 15:1 | 14 |  | 0%* |

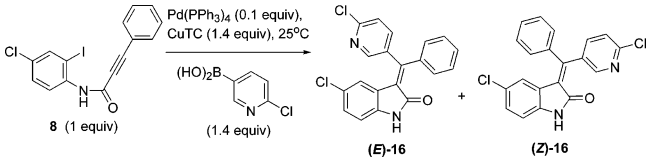
*Reaction carried out at 40 °C.

In this case, a moderate yield (40%) of diarylidene indolinone regioisomers (*E*/*Z* = 23:1) was obtained. With 3,5-difluoropyridine-4-boronic acid (entry 14), the cascade reaction failed to afford the desired product, even at an elevated temperature. Presumably, the two strongly electronegative ortho fluorine substituents deactivate the boronic acid, thereby precluding it from participating in the cross-coupling reaction to any significant extent. To our knowledge, no Suzuki-type couplings with this boronic acid have yet been reported in the literature.

To probe the effects of the coordinating ligand on regioselectivity, we examined six structurally diverse phosphines[14] in the reaction of 2-chloropyridine-5-boronic acid with $Pd_2(dba)_3$.[15] All trials with these ligands resulted in incomplete reactions and reduced regioselectivities. Similarly, an expanded set of palladium sources[16] failed to provide an improvement for this process.[17]

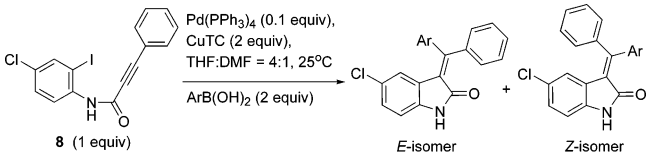
Finally, we investigated the role of solvent effects upon the reaction rate and regioselectivity (Table 4). Polar solvents are clearly preferable, providing good selectivities (MeCN) and/or good rates of conversion (methanol or DMF). Nonpolar or fluorinated solvents (entries 1, 2, 7, and 8) are unsuitable for this process. Combinations of polar solvents afforded a practical compromise in achieving high regioselectivities within short reaction times. Thus, in MeCN/MeOH (4:1, entry 11) and MeCN/DMF (4:1, entry 12), the reactions were complete in 1 h (*E*/*Z* = 17:1) and in 2 h (*E*/*Z* = 14:1), respectively.[18] Though the process was not complete after 2 h when THF/DMF (4:1) was utilized (entry 13), the *E*-isomer was generated as the sole product of the reaction. However, by increasing the number of equivalents of boronic acid and CuTC from 1.4 to 2.0, a complete transformation

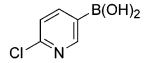
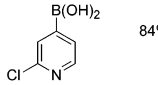
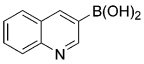
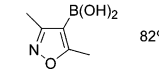
**TABLE 4. Tandem Reaction: Solvent Effects**




| entry | solvent | % conv of **8**, isomeric ratio (*E*/*Z*) | entry | solvent | % conv of **8**, isomeric ratio (*E*/*Z*) |
|---|---|---|---|---|---|
| 1 | toluene | 0 | 8 | $CF_3CH_2OH$ | 0 |
| 2 | $CH_2Cl_2$ | 10 | 9 | DMF | 100, 12:1 |
| 3 | DME | 70, 11:1 | 10 | MeCN | 75, 28:1 |
| 4 | dioxane | 70, 11:1 | 11 | MeCN/MeOH 4:1 | 100, 17:1 |
| 5 | $Et_2O$ | 5 | 12 | MeCN/DMF 4:1 | 100, 14:1 |
| 6 | MeOH | 100, 11:1 | 13 | THF/DMF 4:1 | 82, *E*-isomer |
| 7 | $CF_3C(OH)$-$HCF_3$ | 0 | 14 | | |

**TABLE 5. Tandem Reaction: Optimized Selectivity**

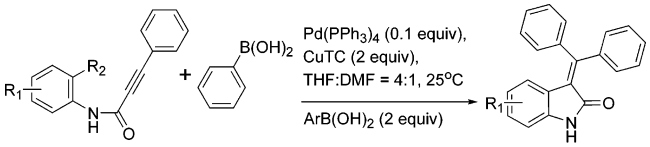



| Entry | $ArB(OH)_2$ | % yield, isomeric ratio (*E*:*Z*) | Entry | $ArB(OH)_2$ | % yield, isomeric ratio (*E*:*Z*) |
|---|---|---|---|---|---|
| 1 |  | 93%, *E*:*Z* = 27:1 | 3 |  | 84%, *E*-isomer |
| 2 |  | 57%, *E*-isomer | 4 |  | 82%, *E*:*Z* = 12:1 |

occurred within 2 h, providing a highly isomerically enriched product mixture (*E*/*Z* ≈ 27:1; Table 5, entry 1).

Encouraged by these results, we applied these optimized conditions to some of the more problematic boronic acids identified earlier. As indicated in Table 5, these conditions provided a significant improvement in both yield and selectivity in each case. Single isomers were generated with 3-quinoline-3-boronic acid and 2-chloropyridine-4-boronic acid (entries 2 and 3, respectively); in the case of dimethylisoxazolyl boronic acid (entry 4), a 2-fold improvement in regioselectivity was obtained compared with the reaction in THF alone.

**TABLE 6. Tandem Reaction: Anilide Substituent Effects**




| anilide | $R_1$ | $R_2$ | product (yield, %) | anilide | $R_1$ | $R_2$ | product (yield, %) |
|---|---|---|---|---|---|---|---|
| **8** | 4-Cl | I | **9** (95) | **8b** | 5-MeO | I | **9b** (92) |
| **8a** | H | I | **9a** (94) | **8c** | 4-Cl | Br | **9** (56) |

With an optimized process in hand, we investigated whether substituent effects on the anilide ring would play a significant role in the success of this sequence (Table 6). The 4-chloro substituent, which had been included to facilitate stereochemical assignments, might have propitiously activated the system by functioning as a stabilizer of the intermediate Heck cyclization product. However, omission of this substituent had no detrimental effect on the reaction outcome as evidenced by the generation of oxindole **9a** in high yield. Furthermore, incorporating a 5-methoxyl group on the anilide, (**8b**), which might have deactivated the 2-position toward palladium insertion, similarly had no adverse effect on this sequence. Finally, we questioned whether the methodology would extend to 2-bromoanilides. In this case (**8c**), the reaction was less efficient but nevertheless afforded oxindole product **9** in a moderate yield (56%). Thus, while the reaction optimally proceeds from the 2-iodoanilide, it can also be successfully carried out from 2-bromoanilides in cases where the former is not readily available.

In summary, we have developed and optimized a tandem Heck−Suzuki coupling reaction for the syntheses of asymmetric diarylmethylidenyl indolinones. At ambient temperatures, the process is high yielding, highly regioselective, and can be accelerated by judicious choice of solvent mixtures. This method could readily be extended to a diverse range of coupling partners and, as such, should allow for the rapid generation of novel compound libraries for biological evaluations.

**Acknowledgment.** We thank Mr. George Elgar and Mr. Michael Kolpak for NMR assistance and Mr. William Jones for carrying out HRMS analyses.

**Supporting Information Available:** Experimental procedures and $^1H$, COSY (Table 3, entry 3), and NOE spectra for ***E*-12**, ***Z*-12**, ***E*/*Z*-13**, and selected examples from Tables 3 (entries 1−5) and 5 (entries 1−3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Phosphine ligands investigated included the monodentate ligands: (2-dicycohexyphosphino)biphenyl, (2-di-*tert*-butylphosphino)-biphenyl, and 2,8,9-triobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]-undecane, as well as bidentate ligands: 2-di-*tert*-butylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (XANTPHOS), and 1,1′-bis(diphenylphosphino)-ferrocene (dppf).

(15) The general protocol involved stirring **8** (1 equiv), $Pd_2(dba)_3$ (0.05 equiv), phosphine ligand (0.1−0.2 equiv), copper 2-thiophenecarboxylate CuTC (1.4 equiv), and of 2-chloropyridine-5-boronic acid (1.4 equiv) in THF at ambient temperature for 15 h.

(16) Catalysts examined included palladium(0) catalysts: bis(tri-*tert*-butylphosphine)palladium(0), bis(tricyclohexylphosphine)palladium-(0), and bis[1,2-bis(diphenylphosphino)ethane]palladium (0) and palladium(II) catalysts: *trans*-dichlorobis(tri-*o*-tolylphosphine)palladium (II), *trans*-dichlorobis(triphenylphosphine)palladium(II), [1,1′-bis-(diphenylphosphine)palladium(II) complexed with $CH_2Cl_2$, dichlorobis-(benzonitrile)palladium(II), and dichloro(acetonitrile)palladium(II).

(17) The general procedure involved stirring palladium catalyst (0.1 equiv), CuTC (1.4 equiv), 2-choropyridine-5-boronic acid (1.4 equiv), and **8** (1 equiv) in anhydrous THF at room temperature for 10 h.

(18) Lesser concentrations of MeOH or DMF resulted in incomplete reactions. In contrast, excess MeOH or DMF was detrimental to the regioselectivity of this process.