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Palladium-Catalyzed Oxidative Cross-Coupling Reaction of Arylboronic Acids with Diazoesters for Stereoselective Synthesis of (*E*)-α,*β*-Diarylacrylates

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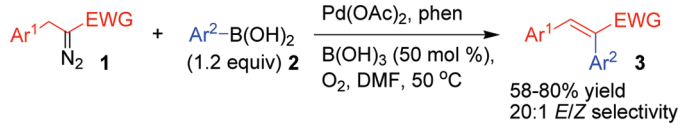
ABSTRACT



A Pd-catalyzed oxidative cross-coupling reaction of arylboronic acids with α-diazoesters was achieved using molecular oxygen as the sole reoxidant, and *E*-α,*β*-diarylacrylates were obtained in good yields and >20:1 *E*-to-*Z* selectivity.

Palladium-catalyzed cross-coupling reactions are powerful tools for C−C and C−heteroatom single bond formation. Notable examples include the Suzuki−Miyaura coupling, Buchwald−Hartwig amination, and Mizoroki−Heck reactions,[1] wherein organoboron, amines, and alkenes are the common nucleophilic partners. Apart from these conventional nucleophiles, Van Vranken and co-workers[2c,f,h,j] were pioneers in exploring α-diazoesters as coupling partners for organopalladium complexes. It is believed that a palladium−carbene species would be formed by reacting diazoesters with the organopalladium complexes. By analogy to the migratory CO insertion, similar migratory carbene insertion to organopalladium would furnish a new C−C bond. Significant advances have been made by the research groups of Wang[2a,b,d,e] and Barluenga,[2g,i] and highly efficient coupling reactions with aryl halides and carbenoid reagents have been achieved. Encouraged by our earlier studies on Pd-catalyzed direct C−H ethoxycarbonylation,[3c] arylation,[3a] and amidation reactions[3d] based on carboradical and nitrene coupling, we developed a Pd-catalyzed coupling of benzyl bromides with α-aryldiazoacetates to afford (*E*)-α,*β*-diarylacrylates with >20:1 stereoselectivity.[3b] α,*β*-Diarylacrylates are useful scaffolds for pharmaceutically active compounds, and Perkin aldol condensation

(1) For reviews, see: (a) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004. (b) Tsuji, J. *Palladium Reagents and Catalysis: Innovation in Organic Synthesis*; John Wiley & Sons: Chichester, U. K., 1995.

(2) Examples of Pd-catalyzed carbenoid-mediated cross-coupling reactions for C=C bond formation, see: (a) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139. (b) Zhao, X.; Jing, J.; Ku, K.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, 1724. (c) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (d) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (e) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566. (f) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. (g) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2008**, *14*, 4792. (h) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047. (i) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587. (j) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438.

(3) (a) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 3174. (b) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (c) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 33048. (d) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 904.

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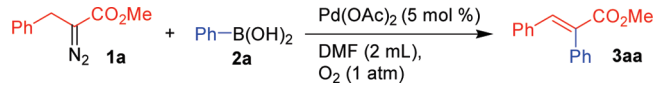
Table 1. Reaction Optimization[a]



entry	**1a**:**2a**	ligand (5.5 mol %)	additive	temperature (°C)	yield[b] (%)	*E*/*Z* ratio
1[c]	1:2	phen[d]	–	70	18	18:1
2	1:2	phen	–	70	65	21:1
3[e]	1:3	–	–	70	0	–
4	1:2	bpy[f]	–	70	64	21:1
5	1:2	dmbpy[g]	–	70	18	1.8:1
6	1:2	tmeda[h]	–	70	16	3.2:1
7	1:2	dppe[i]	–	70	7	3.5:1
8	1:2	pyridine[j]	–	70	5	2.5:1
9[k]	1:3	phen	–	70	81[l]	21:1
10[k]	1:1.5	phen	$B(OH)_3$ (25 mol%)	70	69[l]	21:1
11[k,m]	**1:1.2**	**phen**	**$B(OH)_3$(50mol%)**	**50**	**80**[l]	**21:1**

[a] The reactions were carried out in a 0.2 mmol scale of **1a** with 10 h syringe pump addition of **1a**, and the reaction was run for 11 h. [b] Yields were determined by GC/FID using dodecane as the internal standard. [c] Single batch addition of **1a** was employed. [d] 1,10-Phenanthroline. [e] Absence of $Pd(OAc)_2$ and phen. [f] 2,2′-Bipyridine. [g] 6,6′-Dimethyl-2,2′-bipyridine. [h] *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine. [i] 1,2-Bis(diphenylphosphino)ethane. [j] 11 mol % of pyridine. [k] O_2 purging for 15 min before substrate addition. [l] Isolated yield. [m] Reaction run for 31 h.

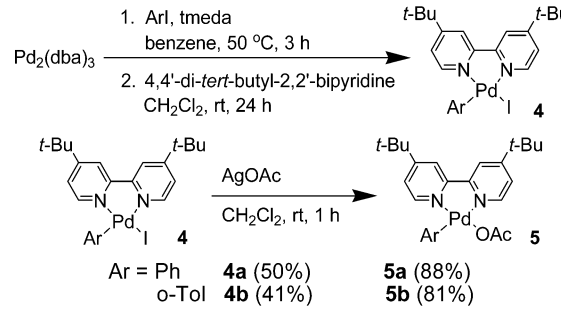
is a common method for their synthesis.[4] However, the Perkin aldol reactions suffer from rather poor substrate scope and product yield. While our "benzyl bromide + diazoester" coupling reaction required the use of excess PPh_3 and reactive benzyl bromides for operation,[3b] this reaction is far from ideal for environmentally sound organic synthesis.

Since C=C bond formation is of fundamental interest for organic synthesis, we considered that the coupling of organoborons with diazoacetate under oxidative Pd catalysis would be a versatile platform for stereoselective alkene formation. In this regard, Wang and co-workers described the coupling of arylboronic acids with diazoesters to form substituted acrylates by employing $Pd(PPh_3)_4$ as the catalyst and benzoquinone as the stoichiometric oxidant, but the reaction exhibited low alkene stereoselectivity (*E*:*Z* ratio <2:1).[2d] During our investigation, Wang and co-workers reported an analogous coupling reaction with *N*-tosylhydrazones[2a] by employing CuCl (10 mol %) and dioxygen as the reoxidant. Prompted by these developments, we report herein a stereoselective diarylacrylate synthesis (*E*:*Z* ratio >20:1) by catalytic coupling of arylboronic acids and α-diazoesters/ketones using $Pd(OAc)_2$ as catalyst and 1,10-phenanthroline (phen) as ligand with molecular dioxygen *alone* as reoxidant. Our results showed that the nitrogen ligand is critical for attaining high stereoselectivity.

We began by treating α-diazo-*β*-phenylpropionate (**1a**, 0.2 mmol) with phenylboronic acid (**2a**, 0.4 mmol), $Pd(OAc)_2$ (5 mol %), and phen (5.5 mol %) in DMF at 70 °C for 3 h under an O_2 atmosphere, and **3aa** was formed in 18% yield with an *E*:*Z* ratio = 18:1 (Table 1, entry 1). By syringe pump addition of **1a** over 10 h, **3aa** was obtained in 65% yield with an *E*:*Z* ratio = 21:1 (entry 2). Notably, benzoquinones and Cu salts are not required for reoxidation of the Pd catalyst. By GC-MS monitoring, the stereoselectivity (i.e., *E*:*Z* = 21:1) of the diazo coupling reaction remained the same throughout the reaction. No **3aa** was obtained in the absence of the Pd catalyst (entry 3).[5] We found that phen and bpy produced comparable results (entries 2 and 4); results for other ligands such as 6,6′-dimethyl-2,2′-bipyridine (dmbpy), tmeda, and dppe were less satisfactory (entries 5−8). Up to 81% yield and *E*:*Z* = 21:1 were attained for **3aa** when 3 equiv of **2a** was employed (entry 9).

To devise a more efficient protocol, we turned to examine the stoichiometric diazo coupling reactions with well-defined arylpalladium(II) complexes. As depicted in Scheme 1, treatment of $Pd_2(dba)_3$ with iodobenzene and tmeda, followed by ligand substitution with 4,4′-di-*tert*-butyl-2,2′-bipyridine, afforded **4**.[6b,c] After AgOAc metathesis, **5** was obtained. Complex **5a** has been structurally characterized by X-ray crystallography (Figure 1); the Pd atom adopted a distorted square planar configuration that contains the coordinated phenyl and η^1-acetate ligands and the bidentate 4,4′-di-*tert*-butyl-2,2′-bipyridine. The measured Pd−C(19) distance is 1.977(3) Å, which is comparable to the related distances of

Scheme 1. Synthesis of the Arylpalladium(II) Complexes **4** and **5**



(4) For examples, see: (a) Moreau, A.; Chen, Q.-H.; Praveen Rao, P. N.; Knaus, E. E. *Bioorg. Med. Chem.* **2006**, *14*, 7716. (b) Jonnalagadda, S. S.; Haar, E. T.; Hamel, E.; Lin, C. M.; Magarian, R. A.; Day, B. W. *Bioorg. Med. Chem.* **1997**, *5*, 715. (c) Nodiff, E. A.; Tanabe, K.; Seyfried, C.; Matsuura, S.; Kondo, Y.; Chen, E. H.; Tyagi, M. P. *J. Med. Chem.* **1971**, *14*, 921.

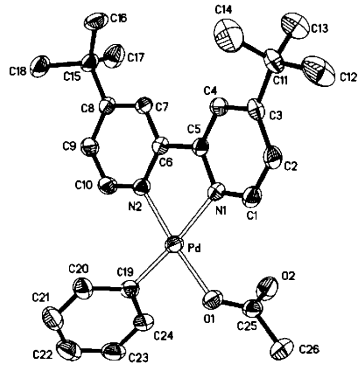
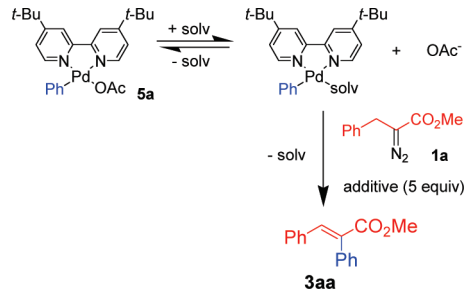


Figure 1. ORTEP representation of complex **5a**. Selected bond distances [Å] and angles [°]: Pd−C(19) 1.977 (3), Pd−O(1) 2.015 (2), Pd−N(1) 2.100 (3), Pd−N(2) 2.026 (2), C(19)−Pd−O(1) 88.62 (12), C(19)−Pd−N(2) 97.05 (12), O(1)−Pd−N(2) 174.32 (10), N(2)−Pd−N(1) 79.72 (10).

Pd(BrettPhos)(2-methyl-4-trifluoromethylphenyl)F [2.001(2) Å][7] and Pd(bpy)(I)Ph [1.996(10) Å].[6c]

When **5a** was reacted with **1a** (1 equiv) in DMF at 70 °C under an O_2 atmosphere, **3aa** was obtained exclusively (i.e., no *Z*-acrylate detected) in only 11% yield (Table 2, entry 1). Consistent with

Table 2. Stoichiometric Reactions of **5a** with **1a**[a]



entry	additive (5 equiv)	temperature (°C)	yield[b] (%)
1	–	70	11
2	$PhB(OH)_2$	70	95
3	$B(OH)_3$	70	51
4	H_3PO_4	70	48
5	CF_3CO_2H	70	30
6	$C_6H_5CO_2H$	70	18
7	$CH_3CH_2CO_2H$	70	28
8	*o*-$CH_3C_6H_4SO_3H$	70	trace
9[c]	**$B(OH)_3$**	**rt**	**72**

[a] The reactions were carried out in a 0.05 mmol scale of **4b**, DMF (2.5 mL), O_2 (1 atm), 70 °C for 1 h. [b] Yields were determined by NMR using dibromomethane as the internal standard. [c] The reaction was carried out for 3 h, and cinnamate (21%) was detected.

our earlier results, employing excess $PhB(OH)_2$ (5 equiv) would promote the "**5a** + **1a** (1 equiv)" coupling reaction to give **3aa** in 95% yield (entry 2). We conjectured that the OAc^- may be a stronger nucleophile than **1a** in competing for the vacant site on the Pd(II). After several experiments, employing $B(OH)_3$ (5 equiv) as additive[8] led to improved **3aa** formation (51%; entry 3) versus the 11% yield for the additive-free reaction. Other acids such as H_3PO_4, CF_3COOH, and benzoic acids are less effective additives (entries 4−8). If the coupling reaction was performed at room temperature with 5 equiv of $B(OH)_3$, **3aa** was furnished in 72% yield (entry 9).

With the stoichiometric results at hand, we studied the effect of the $B(OH)_3$ additive on the catalytic reactions. When **2a** (1.5 equiv) was treated with **1a** (1 equiv) via syringe pump addition over 10 h in the presence of $Pd(OAc)_2$ (5 mol %), phen (5.5 mol %), and $B(OH)_3$ (50 mol %) in DMF at 70 °C under an O_2 atmosphere, **3aa** was furnished in 69% yield with *E*:*Z* selectivity = 21:1 (Table 1, entry 10). After further optimization, **3aa** was obtained in up to 80% yield (*E*:*Z* = 21:1) when the reaction was undertaken with **2a** (1.2 equiv) at 50 °C over 31 h (Table 1, entry 11).

Scheme 2 depicts the scope of the Pd-catalyzed diazo coupling reaction. Both electron-donating and -withdrawing groups (including halogen, nitro) were tolerated, and good product yields and *E*-stereoselectivities were obtained (**3aa**−**3ai**). *o*-Tolylboronic acid was a less effective substrate for the diazo coupling reaction, with **3aj** being formed in ∼20% yield. Yet, effective coupling of the mesityl-substituted diazoester afforded **3da** and **3dk** in 75% and 68% yield, respectively. Recently, indole-containing diarylacrylates were shown to exhibit potent glycine-site *N*-methyl-D-aspartate receptor antagonist activity, indicating that they are potential neuroprotective agents.[9] In this work, treatment of some indole-substituted diazoesters with arylboronic acids by the Pd-catalyzed protocol gave the *E*-acrylates **3ea**, **3el**, **3em**, and **3en** exclusively in 58−72% yields. Likewise, diaryl vinyl ketones[10a] such as **3fa** (79%) and **3ga** (71%) and isoflavone[10b] **3ha** (60%) were also obtained by the catalytic diazo coupling reactions; diaryl vinyl ketones and isoflavones are useful scaffolds for some bioactive molecules.

The reaction is probably initiated by transmetalation with arylboronic acids to [Pd(phen)$(OAc)_2$] to form arylpalladium complex **I** (Scheme 3). The active arylpalladium complex **II** could be formed

(5) Metal-free reactions of diazo carbonyl compounds with arylboronic acids, see :(a) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494. (b) Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667.

(6) For examples of synthesis of arylpalladium(II) complexes, see: (a) Forniés, J.; Martínez, F.; Navarro, R.; Urriolabeitia, E. P. *J. Organomet. Chem.* **1995**, *495*, 185. (b) De Felice, V.; Cucciolito, M. E.; De Renzi, A.; Ruffo, F.; Tesauro, D. *J. Organomet. Chem.* **1995**, *493*, 1. (c) Markies, B. A.; Canty, A. J.; de Graaf, W.; Boersma, J.; Janssen, M. D.; Hogerheide, M. P.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1994**, *482*, 191.

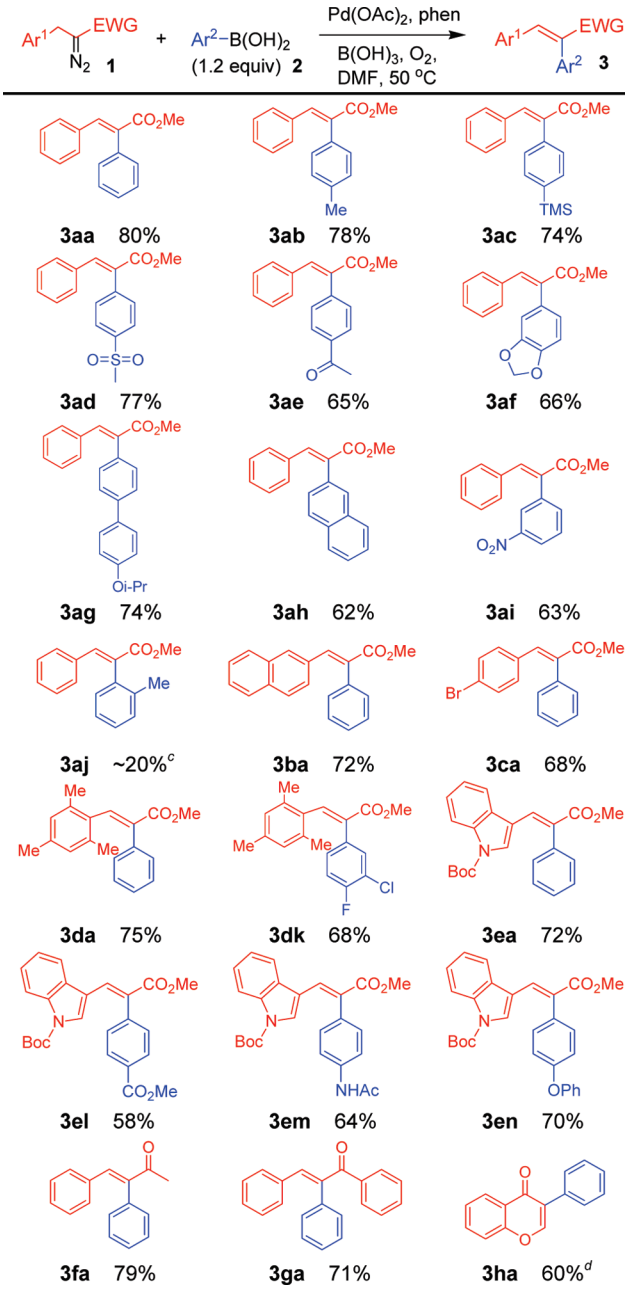
(7) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

(8) Addition of boric acid was found to favor the acetate ion dissociation from **5a**. On the basis of the pK_a values of boric acid [9.236 (water, 298 K)] and acetic acid [4.756 (water, 298 K) [Gokel, G.W. *Dean's Handbook of Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, U.S., 2004], spontaneous protonation of the acetate by boric acid seems unlikely. To account for the finding, we conjectured that the boric acid would stabilize the dissociated acetate by hydrogen bonding, thereby lowering its nucleophilicity for recoordination to the unsaturated Pd(II) complex.

(9) (a) Bourderioux, A.; Routier, S.; Bénéteau, V.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 9465. (b) Baron, B. M.; Cregge, R. J.; Farr, R. A.; Friedrich, D.; Gross, R. S.; Harrison, B. L.; Janowick, D. A.; Matthews, D.; McCloskey, T. C.; Meikrantz, S.; Nyce, P. L.; Vaz, R.; Metz, W. A. *J. Med. Chem.* **2005**, *48*, 995.

(10) Examples of diaryl vinyl ketone and flavone as scaffolds of bioactive compounds: (a) Zhu, J.; Zhong, C.; Lu, H.-F.; Lee, G.-Y.; Sun, X. *Synlett* **2008**, *3*, 458. (b) Stachulski, A. V.; Berry, N. G.; Lilian Low, A. C.; Moores, S. L.; Row, E.; Warhurst, D. C.; Adagu, I. S.; Rossignol, J.-F. *J. Med. Chem.* **2006**, *49*, 1450.

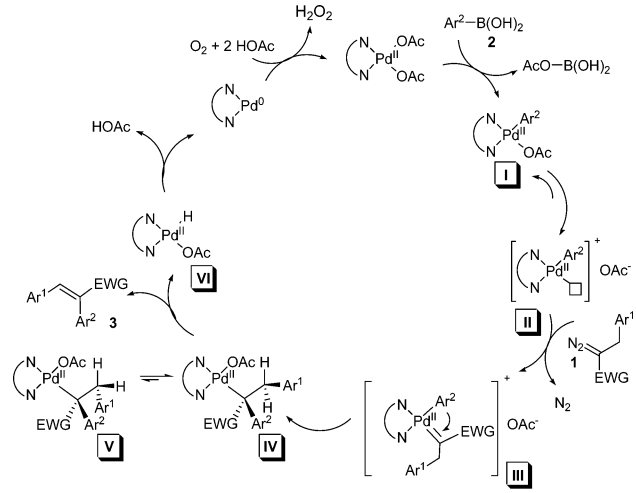
Scheme 2. Pd-Catalyzed Oxidative Cross-Coupling of Arylboronic Acids with Diazoesters[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (5 mol %), phen (5.5 mol %), boric acid (50 mol %), O_2 (1 atm), DMF (2 mL), 50 °C for 31 h. [b] Isolated yield. [c] NMR yield. [d] $Pd(OAc)_2$ (10 mol %), phen (11 mol %), $PhB(OH)_2$ (3 equiv), no $B(OH)_3$ added, 70 °C, reaction run for 21 h.

by boric acid-assisted acetate dissociation. The subsequent reaction of **II** with the diazoester **1** would form putatively a reactive palladium−carbene complex **III**, and migratory insertion of the aryl group would afford the alkylpalladium complex **IV**.[11] Migratory insertion reactions for palladium carbenes are well precedented in amino- and methoxycarbene palladium complexes. β-Elimination should yield the acrylate **3** and Pd^{II}−hydride complex **VI**. To complete the catalytic cycle, **VI** was transformed to the Pd complex **I** with molecular oxygen.[12]

Scheme 3. Proposed Catalytic Cycle



The high *E*-stereoselectivity is intriguing since the transition state in the β-elimination for formation of trisubstituted alkenes should favor the two bulky aryl groups in a *trans*-arrangement (i.e., **V**), and a *Z*-alkene product is anticipated.[2i] The observed *E*-trisubstituted acrylate formation is incompatible with this notion. Nevertheless, the *E*-trisubstituted acrylate formation was also observed for the Perkin aldol condensation,[13] and the preference for the seemingly "less favored" transition state is not clear and is under investigation.

In conclusion, a stereoselective synthesis of (*E*)-α,β-diarylacrylates was developed based on ligand-modulated oxidative Pd-catalyzed coupling of arylboronic acids and diazoesters, and molecular oxygen was used as the reoxidant. Apart from their ease of handling and lack of toxicity, arylboronic acids are available in great structural diversity. This Pd-catalyzed protocol would form the foundation for future development of regio- and stereocontrolled oxidative catalysis for C=C bond formation.

Acknowledgment. We thank the Hong Kong Research Grants Council (PolyU5019/06P; SEG_1 PolyU) and University Grants Committee Areas of Excellence Scheme (AoE/P-10-01) for financial support.

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

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(11) Examples of migratory insertion of metal−carbenes, see: (a) Albéniz, A. C.; Espinet, P.; Pérez-Mateo, A.; Nova, A.; Ujaque, G. *Organometallics* **2006**, *25*, 1293. (b) Albéniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Chem.−Eur. J.* **2005**, *11*, 1565. (c) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *Organometallics* **2004**, *23*, 1438.

(12) For reviews, see: (a) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854. (b) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612.

(13) (a) Zimmermann, H.; Ahramjian, L. *J. Am. Chem. Soc.* **1959**, *81*, 2086. (b) Pálinkó, I.; Török, B.; Tasi, G.; Körtvélyesi, T. Experimental and Computational Tools for Mechanistic Study: A Modified Perkin Condensation leading to Alpha-Phenylcinnamic Acid Isomers; *Electronic Conference on Trends in Organic Chemistry-1*, June 12−July 7, 1995.