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Rhodium-Catalyzed Cross-Coupling Reaction of Arylboronates and Diazoesters and Tandem Alkylation Reaction for the Synthesis of Quaternary α,α-Heterodiaryl Carboxylic Esters

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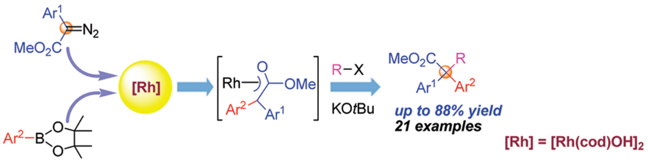
ABSTRACT



A rhodium-catalyzed one-pot three-component coupling reaction was developed for the synthesis of quaternary α,α-heterodiaryl carboxylic esters. This reaction involves cross-coupling of the arylrhodium(I) complexes with α-aryldiazoacetates to form oxa-π-allylrhodium complexes. With KO*t*Bu and alkyl halides, tandem alkylation of the allyl complex occurs to form a quaternary stereocenter at the carbenic carbon.

Advances in transition metal catalyzed cross-coupling reactions have led to the development of highly efficient transformations such as Suzuki–Miyaura reactions,[1a] Buchwald–Hartwig aminations,[1b] and Heck–Mizoroki reactions.[1c] Underlying these transformations is the effective coupling of organotransition metal complexes with nucleophilic organoborons, amines, and alkenes/alkynes. The use of diazo compounds as coupling partners for catalytic cross-coupling reactions is attracting current interest.[2] Pioneered by Van Vranken and co-workers, the research groups of Wang and Barluenga have developed a highly efficient Pd-catalyzed coupling of aryl halides with carbenoid reagents to afford highly substituted alkenes.[3] Recently, our group also achieved a highly stereoselective oxidative cross-coupling of arylboronic acids with diazoacetates to produce (*E*)-1,2-diarylacrylates with dioxygen as the sole oxidant.[4a] Mechanistically, migratory carbene insertion into the Pd–C bond is involved in these carbenoid coupling reactions.[5] Despite the apparent successes,

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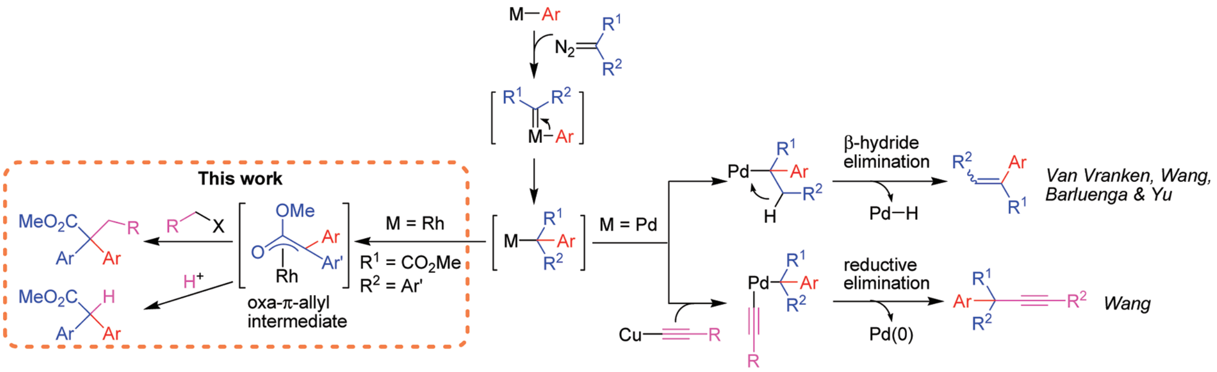
(1) (a) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 41–124. (b) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 699–760. (c) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 217–316.

(2) For reviews, see: (a) Franssen, N. M. G.; Walters, A. J. C.; Reek, J. N. H.; de Bruin, B. *Catal. Soc. Technol.* **2011**, *1*, 153. (b) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (c) Jellema, E.; Jongerius, A. L.; Reek, J. N. H.; de Bruin, B. *Chem. Soc. Rev.* **2010**, *39*, 1706.

(3) For examples of Pd-catalyzed carbenoid-mediated cross-coupling reactions for C=C bond formation, see: (a) Zhou, L.; Ye, F.; Ma, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3510. (b) Zhou, L.; Liu, Y.; Zhang, Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 3622. (c) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510. (d) Peng, C.; Yan, G.; Wang, Y.; Jiang, Y.; Zhang, Y.; Wang, J. *Synthesis* **2010**, *24*, 4154. (e) Zhao, X.; Wu, G.; Yan, C.; Lu, K.; Li, H.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 5580. (f) Zhao, X.; Jing, J.; Lu, K.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, *46*, 1724. (g) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**, *352*, 3235. (h) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2010**, *16*, 12801. (i) Barluenga, J.; Escribano, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6856. (j) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (k) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909.

10.1021/ol2022577

Scheme 1. Mechanistic Hypothesis



these coupling reactions are limited to C=C bond formation due to spontaneous β-hydride elimination of organopalladium species that precludes its further functionalization (Scheme 1). Notably, Wang and co-workers developed a protocol that successfully intercepted the organopalladium by transmetalation with copper-acetylides to furnish two separate C–C σ-bonds at the carbenic carbon.[6]

To examine the synthetic application of the diazo coupling reactions, we pursued an alternative reaction manifold based on Rh catalysis. Being a d^8 metal center, Rh(I) is isoelectronic with Pd(II). Thus, we hypothesized that organorhodium(I) would couple with α-diazoacetates. Migratory carbene insertion should afford an oxa-π-allylrhodium(I) complex, which would be tenable for further functionalization (Scheme 1). Here we present the successful development of a Rh-catalyzed one-pot three-component coupling reaction with two C–C σ-bonds being formed at the carbenic carbon to afford quaternary α,α-heterodiaryl carboxylic acid esters using arylboronates, α-diazoacetates, and alkyl halides as reagents. Quaternary α,α-diaryl carbonyl compounds are common scaffolds in medicinal products such as disopyramide (Norpace),[7a] methadone (Dolophine),[7b] loperamide (Imodium),[7c] and proadifen (SKF525-A).[7d]

Initially, we set out to test the coupling reaction of α-diazoacetate with arylrhodium(I) complexes derived *in situ* from arylboronic acids and [Rh(cod)OH]$_2$. When 4-chlorophenyldiazoacetate (**1a**, 0.2 mmol) was treated with phenylboronic acid (0.6 mmol) and [Rh(cod)OH]$_2$ (3 mol % Rh) in a 1,4-dioxane–water (10:1 v/v) mixture, 2-(4-chlorophenyl)-2-phenylacetate (**5a**) was obtained in 95% yield. The **5a** formation can be rationalized by the coupling of the phenylrhodium(I) complex with α-phenyldiazoacetate to produce an oxa-π-allylrhodium(I) species *via* migratory carbene insertion. The subsequent protonation of the oxa-π-allylrhodium complex should afford **5a** as product. Indeed, oxa-π-allylrhodium(I) complexes are known to undergo aldol reactions with aldehydes.[8] Thus, it appeared to us that a one-pot three-component cross-coupling reaction would be possible through further functionalization of the putative oxa-π-allylrhodium complex with some electrophiles. After some screening, we were gratified that treating **1a** (0.2 mmol) with phenylboronic acid pinacol ester (**2a**, 0.6 mmol), benzyl bromide (**3a**, 0.6 mmol), KO*t*Bu (0.4 mmol), and [Rh(cod)Cl]$_2$ (3 mol % Rh) in diethyl ether at 40 °C for 5 h furnished the coupled product **4a** in 59% yield (Table 1, entry 2). However, when phenylboronic acid was utilized as the aryl source, **5a** was produced exclusively without any **4a** formation (entry 3). Notably, no **4a** and **5a** formation was observed in the absence of the Rh catalyst (entry 14). Employing other boronic acid esters or solvents (e.g., toluene, acetone, DMF, THF, and dioxane) failed to give better results (entries 4–10). After several attempts, **4a** was eventually obtained in up to 86% yield with [Rh(cod)OH]$_2$ as catalyst and methyl *tert*-butyl ether (MTBE) as solvent (entry 1). In this work, we found that Rh(PPh$_3$)$_3$Cl and

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(4) (a) Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 4506. (b) Yu, W.-Y.; Tsoi, Y.-T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (c) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 604. For related studies on carboradicals and nitrenes as coupling partners, see:Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 3926. (d) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (e) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 3174. (f) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. (g) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048.

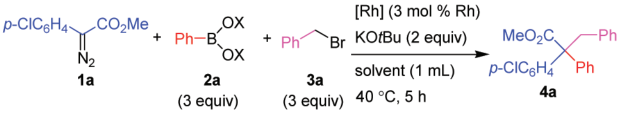
(5) For examples of migratory insertion of palladium-carbenes, see: (a) Albéniz, A. C.; Espinet, P.; Pérez-Mateo, A.; Nova, A.; Ujaque, G. *Organometallics* **2006**, *25*, 1293. (b) Albéniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Chem.—Eur. J.* **2005**, *11*, 1565. (c) Solé, D.; Vallverdú,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

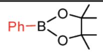
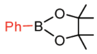
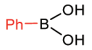
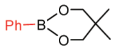
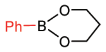
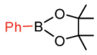
(6) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590.

(7) (a) Skokie, J. W. C.; Deerfield, H. W. S. U.S. Patent 3,225,054, 1965. (b) Schultz, E. M.; Robb, C. M.; Sprague, J. M. *J. Am. Chem. Soc.* **1947**, *69*, 2454. (c) Stokbroekx, R. A.; Vandenberk, J.; Van Heertum, A. H. M. T.; van Laar, G. M. L. W.; Van der Aa, M. J. M. C.; Van Bever, W. F. M.; Janssen, P. A. J. *J. Med. Chem.* **1973**, *16*, 782. (d) Lu, M. C.; Wung, W. E.; Shih, L. B.; Gearien, J. E.; Thompson, E. B. *J. Med. Chem.* **1987**, *30*, 273.

(8) Example of stoichiometric reaction of oxa-π-allylrhodium(I) complexes with aldehydes: (a) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938. For catalytic examples of oxa-π-allylrhodium(I) complexes with aldehydes, see:(b) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110. (c) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528.

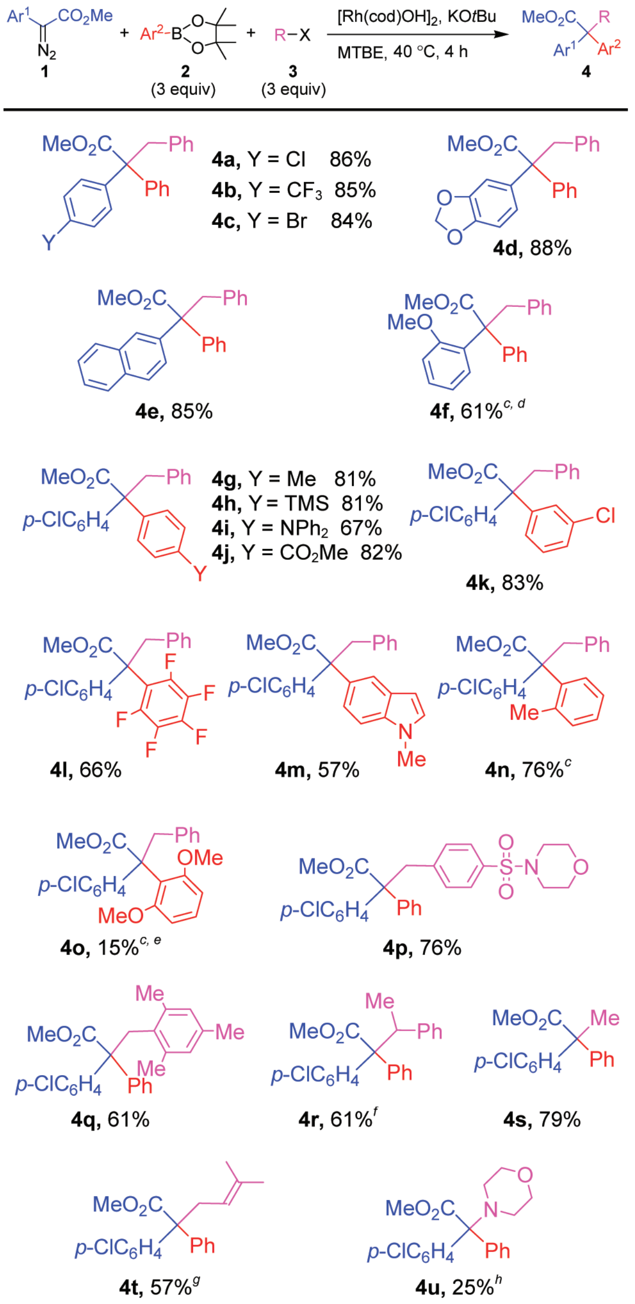
Table 1. Reaction Optimization[a]



entry	boron source	[Rh]	solvent	yield[b] **4a** (%)
1[c, d]		[Rh(cod)OH]$_2$ (2 mol % Rh)	MTBE[e]	86
2		[Rh(cod)Cl]$_2$	Et$_2$O	59
3		[Rh(cod)Cl]$_2$	Et$_2$O	0
4		[Rh(cod)Cl]$_2$	Et$_2$O	18
5		[Rh(cod)Cl]$_2$	Et$_2$O	2
6		[Rh(cod)Cl]$_2$	dioxane	58
7	〃	[Rh(cod)Cl]$_2$	THF	50
8	〃	[Rh(cod)Cl]$_2$	toluene	4
9	〃	[Rh(cod)Cl]$_2$	acetone	2
10	〃	[Rh(cod)Cl]$_2$	DMF	2
11	〃	[Rh(cod)Cl]$_2$	MTBE	68
12[d]	〃	[Rh(dppe)Cl]$_2$	MTBE	<1
13[d]	〃	Rh(PPh$_3$)$_3$Cl	MTBE	0
14[d]	〃	-	MTBE	0

[a] The reactions were carried out at a 0.2 mmol scale of limiting reagent. [b] Yields were determined by GC/FID using dodecane (0.1 mmol) as internal standard. [c] The reaction was run for 4 h. [d] 3 equiv of base were used. [e] Methyl *tert*-butyl ether.

Scheme 2. Rh-Catalyzed One-Pot Three-Component Coupling Reactions[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), **3** (0.6 mmol), KO*t*Bu (0.6 mmol), [Rh(cod)OH]$_2$ (2 mol % Rh), MTBE (1 mL), 40 °C for 4 h. See Supporting Information for experimental details. [b] Isolated yield. [c] NMR yield. [d] Methyl 2-(2-methoxyphenyl)-2-phenylacetate was obtained in 30%. [e] **1a** was recovered in 55%. [f] A 1:1 mixture of diastereomeric products was obtained based on NMR analysis. [g] **5a** was obtained in 8% yield. [h] **5a** was obtained in 58% yield.

[Rh(dppe)Cl]$_2$ are ineffective catalysts for the three-component coupling reaction (entries 12 and 13).

Scheme 2 depicts the scope of the Rh-catalyzed three-component coupling reaction. Evaluation of some substituted aryldiazoacetates established that diazoesters bearing electron-donating and -withdrawing substituents are effective coupling partners for the Rh-catalyzed reaction. Due to intrinsic reactivity, bromo substituents are not compatible with the Pd(0)-catalysis. For example, the Pd(0)-catalyzed coupling of benzyl bromides with 4-bromophenyldiazoacetates afforded the product acrylate in 48% yield.[4b] In this work, however, the Rh-catalyzed three-component coupling reaction with 4-bromophenyldiazoacetates produced **4c** in 84% yield. Moreover, polycyclic aryldiazoacetates would couple effectively to give **4d** and **4e** in good yields. Previously, we found that 2-methoxyphenyldiazoacetate was a poor reagent for carbenoid C–H functionalization of NH-free indoles with [(cymene)RuCl$_2$]$_2$ as catalyst, presumably due to coordination of the ortho-methoxy group.[4c] In this work, the analogous Rh-catalyzed reaction afforded **4f** in 61% yield.

The substrate scope is further extended to a broad variety of arylboronates; electron-rich and -poor arylboronates (including pentafluorophenylboronates) are effective aryl donors, and trimethylsilyl, diphenylamino, carboxylate, and indole groups are tolerated. While 2-tolylboronate would undergo facile coupling with **1a** and **3a** to furnish **4n** in 76% yield, the analogous reaction with 2,6-dimethoxylphenylboronate was sluggish due to steric hindrance to the transmetalation step, and **4o** was obtained in 15% yield. 3-Thiopheneboronate is known to be an effective substrate for the Rh-catalyzed conjugate addition

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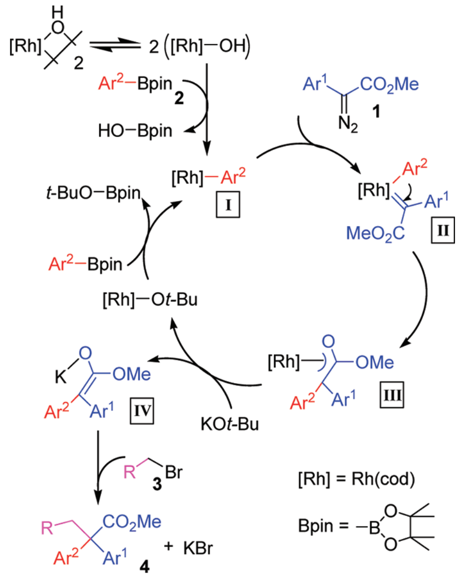
(9) Yoshida, K.; Hayashi, T. *Heterocycles* **2003**, *59*, 605.

reaction to enones.[9] In this work, however, we failed to obtain the desired coupled product with 3-thiopheneboronate. Yet, when **1a** reacted with 3-thiopheneboronate in a 1,4-dioxane−water (10:1 v/v) mixture, 2-phenyl-2-(thiophen-3-yl)acetate was formed in 65% yield.

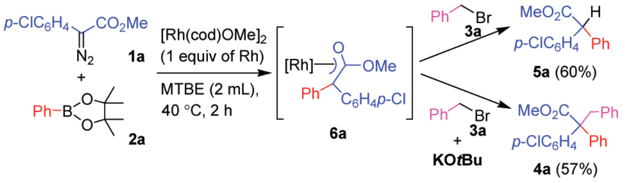
Scheme 3. A Plausible Mechanism



Likewise, a range of functionalized alkyl halides would couple effectively under the Rh-catalyzed conditions. For example, coupling of the benzyl bromides bearing sulfonylmorpholino and mesityl groups gave **4p** (molecular structure established by X-ray crystallography) and **4q** in 76 and 61% yield, respectively. The analogous reaction of other organohalides including (1-bromoethyl)benzene (**4r**: 61%), methyl iodide (**4s**: 79%), and 3,3-dimethylallyl bromide (**4t**: 57%) afforded their respective coupling products in good to moderate yields. Besides alkyl halides, *N*-chloromorpholine was found to couple effectively to afford α-morpholinoacetate **4u**, albeit in 25% yield.

The mechanism of the three-component coupling reaction may involve an initial formation of arylrhodium(I) complex **I** through transmetalation with the arylboronic acid ester (Scheme 3). The research groups of Hayashi and Hartwig already characterized the arylrhodium(I) complexes from the reaction of arylboronic acids with Rh(I) complexes.[10,11] Analogous to the isoelectronic arylpalladium(II) complexes, **I** should react with diazoesters to form reactive rhodium-carbene complexes **II**,[12] which could undergo migratory carbene insertion to give oxa-π-allylrhodium complexes **III**. As mentioned earlier, protonolysis of **III** in aqueous dioxane would produce α,α-diarylacetates.

Scheme 4. Reactivity of Oxa-π-allylrhodium Complex toward Benzyl Bromide



To probe the role of the oxa-π-allylrhodium in the second C−C bond formation, we prepared the oxa-π-allylrhodium complex **6a** *in situ* by reacting $[Rh(cod)OMe]_2$ with **1a** and **2a** in MTBE. The choice of $[Rh(cod)OMe]_2$ is to avoid possible protonation of the allylrhodium **6a**. We found that treating **6a** with benzyl bromide **3a** *alone* for 2 h afforded **5a** exclusively after workup (i.e., **4a** was not obtained). However, **6a** would react with **3a** in the presence of KO*t*Bu (6 equiv) to give **4a** in 57% yield (Scheme 4). Based on these findings, **III** should apparently exchange with KO*t*Bu to form a potassium enolate **IV**,[13] which then reacts with the alkyl halides to establish the quaternary carbon center. Consistent with this proposal, treating **5a** with KO*t*Bu (3 equiv) and **3a** (3 equiv) in MTBE at 40 °C for 1 h produced **4a** in 40% yield.

In summary, $[Rh(cod)OH]_2$ catalyzes the one-pot three-component coupling of α-aryldiazoesters, arylboronates, and alkyl halides to form quaternary α,α-heterodiaryl carboxylic acid esters probably involving migratory carbene insertion as one of the principal steps. This reaction tolerates many commonly encountered functional groups such as bromo, trifluoromethyl, indole, and esters. This study demonstrates the versatility of metal-carbene in the development of highly efficient cascade C−C bond formation reactions, which would be useful for creating molecular structures of higher complexity.

Acknowledgment. We are thankful for the financial support from the Hong Kong Research Grants Council (PolyU5038-11P; SEG_01PolyU) and The Area of Excellence Scheme (AoE/P-10-01) administered by the Hong Kong University Grants Committee. Special thanks is given to Mr. Chun-Yin Yip (PolyU) for some initial studies.

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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(10) (a) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876. (b) Krug, C.; Hartwig, J. F. *Organometallic* **2004**, *23*, 4594. (c) Hayashi, T.; Takahashi, M.; Tanaka, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(11) In this work, the putative arylrhodium species **I** can be trapped by methyl acrylate to yield 3-phenylpropanoate (58%) and 3,3-diphenylpropanoate (22%).

(12) For an example of an isolable rhodium-carbene complex, see: Werner, H.; Schwab, P.; Bleuel, E.; Mahr, N.; Steinert, P.; Wolf, J. *Chem.—Eur. J.* **1997**, *3*, 1375.

(13) It is possible that the allyl exchange with KO*t*Bu would occur via oxygen-bound rhodium(I) enolate complexes. For an example of oxygen-bound rhodium(I) enolate complexes, see: Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938.