Homogeneous Catalysis Hot Paper

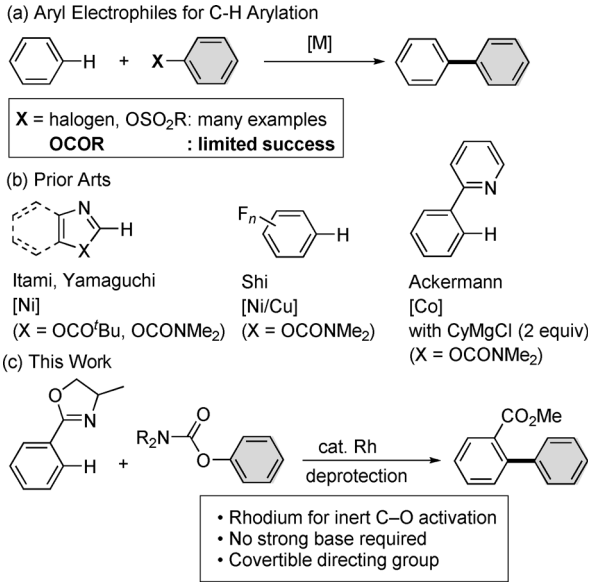
International Edition: DOI: 10.1002/anie.201610409
German Edition: DOI: 10.1002/ange.201610409

# C–O Activation by a Rhodium Bis(N-Heterocyclic Carbene) Catalyst: Aryl Carbamates as Arylating Reagents in Directed C–H Arylation

*Mamoru Tobisu,* Kosuke Yasui, Yoshinori Aihara, and Naoto Chatani**

***Abstract:*** *Despite recent progress in the catalytic transformation of inert phenol derivatives as alternatives to aryl halides and triflates, attempts at the cross-coupling of inert phenol derivatives with the C–H bonds of arenes have met with limited success. Herein, we report the rhodium-catalyzed cross-coupling of aryl carbamates with arenes bearing a convertible directing group. The key to success is the use of an in situ generated rhodium bis(N-heterocyclic carbene) species as the catalyst, which can promote activation of the inert C($sp^2$)–O bond in aryl carbamates.*

Metal-catalyzed cross-coupling of organometallic nucleophiles with aryl halides has been established as the predominant method for the functionalization of aromatic compounds.[1] Recently, phenol and its unactivated derivatives, such as ethers and esters, have emerged as less expensive and more environmentally benign alternatives to aryl halides and triflates.[2] An even more important advantage of using these phenol derivatives is that their metal-coordinating ability and robustness allows new synthetic strategies, including late-stage functionalization and directing-group manipulation. Nickel is the best catalyst to activate C(aryl)–O bonds, and it mediates a range of cross-coupling reactions with inert phenol derivatives.[2] Considering that C–H cross-coupling reactions have become increasingly popular methods,[3] it is natural to expect that C–H arylation with inert phenol derivatives should enable a dramatic increase in the scope and application of C–O cross-coupling reactions of inert phenol derivatives (Scheme 1 a). However, attempts at C–H cross-coupling with inert phenol derivatives have found limited success. Itami, Yamaguchi and co-workers first reported this type of reaction in the nickel-catalyzed cross-coupling of aryl pivalates with azoles.[4] Shi and co-workers recently reported that a C–H bond in perfluorinated arenes can be arylated by nickel/copper dual catalysis with aryl carbamates.[5] Although these two reactions provide valuable products related to pharmaceuticals and organic materials, the substrates are limited to those bearing a relatively acidic C–H bond.[6]




***Scheme 1.*** C–H/C–O cross-coupling.

Ackermann and Song achieved cross-coupling of non-acidic unactivated C–H bonds with aryl carbamates using a cobalt catalyst.[7] Although this reaction represents an important advance, the requirement for the use of excess Grignard reagent leaves several issues to be addressed: 1) electrophilic functional groups, such as ketones and nitriles, are not compatible, and 2) the applicable directing group is limited to a robust but synthetically less attractive pyridine ring. With these considerations in mind, we herein report a rhodium-catalyzed cross-coupling of arenes bearing a convertible directing group with aryl carbamates in the absence of a strong base.

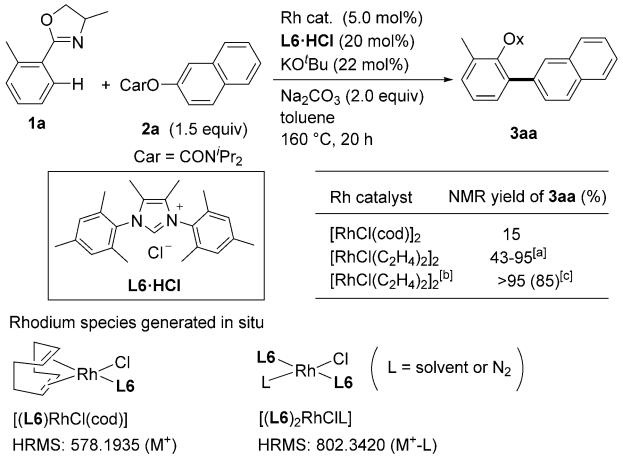
To realize the cross-coupling of unactivated C–H bonds with inert phenol derivatives, the catalyst needs to efficiently mediate the activation of both C–H and C–O bonds. Based on its remarkable activity in C–H activation,[8] we decided to use a rhodium catalyst, even though rhodium complexes are rarely used for C–O bond activation processes.[9] Reported rhodium complexes that can activate the C(aryl)–O bond require the use of a pincer-type ligand[9a,b] or boron-based reagents,[9c–e] both of which cannot be directly applied to our target C–H/C–O cross-coupling reactions. We chose *ortho* arylation of **1a**[10] with aryl carbamate **2a** as our model reaction for catalyst development. It should be noted that the oxazoline substrates are readily accessible from the corresponding carboxylic acids through condensation with 2-aminopropan-1-ol. Initial ligand screening led us to identify the NHC-based ligand **L6** as a potential lead for further

[*] K. Yasui, Y. Aihara, N. Chatani
Department of Applied Chemistry, Faculty of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
E-mail: chatani@chem.eng.osaka-u.ac.jp
M. Tobisu
Center for Atomic and Molecular Technologies
Graduate School of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
E-mail: tobisu@chem.eng.osaka-u.ac.jp

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201610409.

optimization.[11,12] Interestingly, the use of $[RhCl(C_2H_4)_2]_2$ instead of $[RhCl(cod)]_2$ as the catalyst precursor along with **L6** considerably improved the yield of **3aa**, although the yields were variable between experiments (Scheme 2). It was

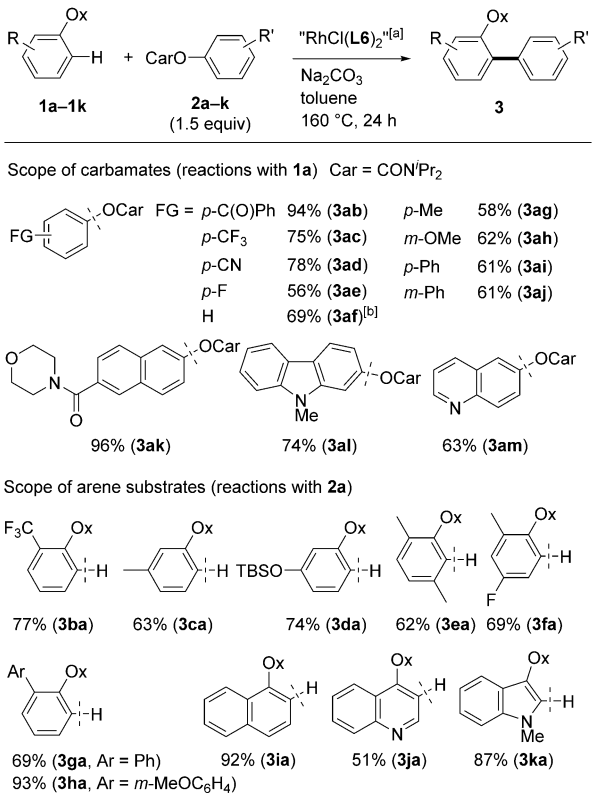



***Scheme 2.*** Optimization of rhodium-catalyzed cross-coupling of arene **1a** with aryl carbamate **2a**. [a] Results of six independent experiments. [b] $RhCl(C_2H_4)]_2$, **L6**·HCl, KO$^t$Bu, and $Na_2CO_3$ were stirred at 60 °C for 1 h prior to being used for the catalytic reaction. [c] Yield of isolated product. OCar = *N*,*N*-diisopropylcarbamate, Ox = 4-methyl-4,5-dihydroxooxazol-2-yl.

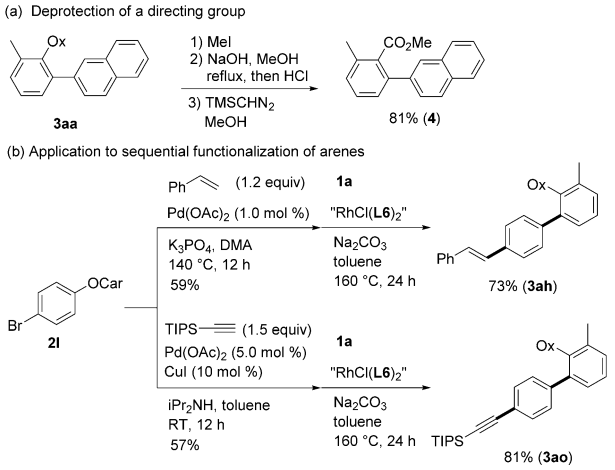
found that a consistently high yield of **3aa** can be obtained using a catalyst generated by preheating (60 °C, 1 h) a mixture of $[RhCl(C_2H_4)_2]_2$ and **L6**. FAB-MS and $^{13}C$ NMR analysis of the preheated solution of $[RhCl(C_2H_4)_2]_2$ and **L6** suggested exclusive generation of the bis-NHC species[13] $[(\mathbf{L6})_2RhCl^+$: 802.3420; $^{13}C$ NMR of C2: $\delta = 190.2$ ppm (d, $J_{Rh\text{-}C} = 40$ Hz)], whereas only the mono-NHC species $[(\mathbf{L6})RhCl(cod)^+$: 578.1935; $^{13}C$ NMR of C2: $\delta = 185.1$ ppm (d, $J_{Rh\text{-}C} = 52$ Hz)] was generated from a preheated solution of $[RhCl(cod)]_2$ and **L6**.

With the method to generate an active catalyst in hand, we next examined the scope of the C–H/C–O cross-coupling with respect to the aryl carbamate component. As shown in Scheme 3, this transformation is applicable to aryl carbamates bearing a range of functional groups, including ketones (**3ab**), nitriles (**3ad**), fluorides (**3ac** and **3ae**), and amides (**3ak**). Moreover, heteroaromatic carbamates (**3al** and **3am**) can also be successfully coupled with **1a**. The scope with respect to the arene substrate was next evaluated. When *meta*-substituted arenes were reacted with **2a**, arylation exclusively occurred at the less hindered C–H bond, as in **3ca** and **3da**. However, a sterically congested C–H bond can be arylated when it is the only reactive site, as evidenced by the formation of **3ea**. This arylation is also applicable to fused arenes (**3ia**) and heteroarenes (**3ja** and **3ka**).

The 4-methyl-4,5-dihydrooxazol-2-yl group used as the directing group in the present study can be readily converted into the corresponding carboxylic acid derivative, which allows further synthetic elaboration of the C–H/C–O coupling products (Scheme 4a). Because the carbamate group is




***Scheme 3.*** Reaction scope. [a] $RhCl(\mathbf{L6})_2$ was prepared by stirring a mixture of $[RhCl(C_2H_4)]_2$ (0.015 mmol), **L6**·HCl (0.060 mmol), KO$^t$Bu (0.066 mmol), and $Na_2CO_3$ (0.060 mmol) at 60 °C for 1 h. Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol) and catalyst in toluene (1.0 mL) for 24 h. The yield refers to the isolated yield. [b] $[RhCl(C_2H_4)]_2$ (0.023 mmol), **L6**·HCl (0.090 mmol) and KO$^t$Bu (0.099 mmol) were used.



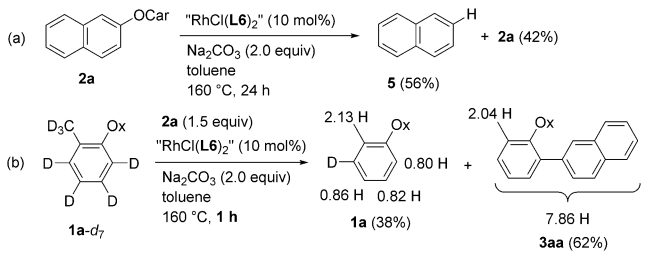

***Scheme 4.*** Synthetic applications.

completely stable under the conditions used for standard palladium-catalyzed cross-coupling of aryl halides, such as the Mizoroki–Heck and Sonogashira reactions, sequential functionalization of C–X and C–O bonds is possible (Scheme 4b).

To obtain insight into the mechanism, several experiments were performed. When aryl carbamate **2a** was subjected to

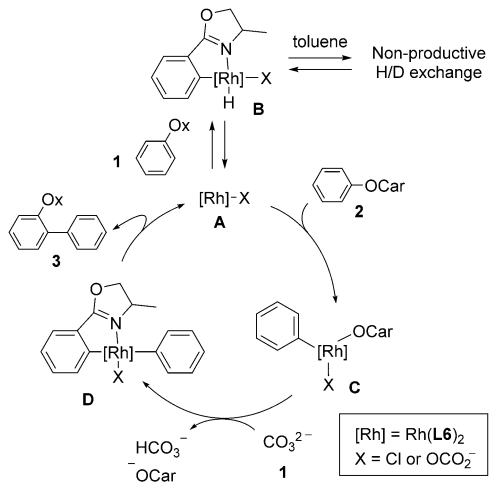
the rhodium-catalyzed conditions in the absence of an arene substrate, naphthalene (**5**) was formed in 56% yield (Scheme 5a). This observation indicates that $Rh^I(\mathbf{L6})_2$ can activate




***Scheme 5.*** Mechanistic studies.

the C–O bond of **2a**, presumably through oxidative addition,[9] and the resulting arylrhodium(III) species undergoes protonation to form **5**. Labeling studies revealed that $Rh^I(\mathbf{L6})_2$ can also activate a C–H bond (Scheme 5b). When deuterated arene **1a-$d_7$** was reacted with **2a** in the presence of a $Rh^I(\mathbf{L6})_2$ catalyst for 1 h (62% conversion), the deuterium content of the recovered **1a** was significantly reduced. Interestingly, H/D exchange took place not only at the *ortho* position of **1a** but also at the *meta*, *para*, and even benzylic positions. Therefore, non-selective C–H activation by $Rh^I(\mathbf{L6})_2$ can occur under these conditions.[9e,14] The decrease in the deuterium content of **1a** was less when the rhodium-catalyzed reaction of **1a**-$d_7$ with **2a** was performed in deuterated solvent, thus indicating that the solvent toluene is the main source of hydrogen incorporated into the recovered **1a** (see the Supporting Information).

A possible mechanism is shown in Scheme 6. Although $Rh^I(\mathbf{L6})_2$ species **A** can activate both C–H and C–O bonds, the initial C–H activation only leads to non-productive H/D exchange via intermediate **B**. The catalytic cycle that gives arylated product **3** begins with oxidative addition of the C–O bond in carbamate **2** to form arylrhodium(III) intermediate **C**. The subsequent *ortho* C–H activation by rhodium(III) species **C**, presumably through a concerted metalation/deprotonation pathway,[15] gives diarylrhodium **D**, which finally gives arylated product **3** with concurrent regeneration of **A**.




***Scheme 6.*** Proposed mechanism.

In summary, we have developed a rhodium-catalyzed arylation of non-acidic $C(sp^2)$–H bonds using aryl carbamates as the arylating reagent. The key to success is the use of a bis(NHC) complex of rhodium(I) as the catalyst, which facilitates activation of inert $C(sp^2)$–O bonds in aryl carbamates. This readily generated rhodium species enables the activation of inert $C(sp^2)$–O bonds in the absence of a strong base, thereby allowing the use of a synthetically useful directing group in C–H/C–O coupling. Further studies aiming at the catalytic transformation of inert bonds using rhodium bis(NHC) complexes are underway.

## Acknowledgements

This work was supported by ACT-C (J1210B2576) from JST, Japan and Scientific Research on Innovative Area "Precisely Designed Catalysts with Customized Scaffolding" (16H01022)from MEXT, Japan. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for their assistance with HRMS.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** arylation · C–H activation · C–O activation · N-heterocyclic carbenes · rhodium

[1] Reviews on cross-coupling: a) *Cross-Coupling Reactions: A Practical Guide* (Ed.: N. Miyaura), Springer: Berlin, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; A recent themed issue on cross-coupling: c) *Chem. Lett.* **2011**, *40*, 894.

[2] Reviews on cross-coupling with inert phenol derivatives: a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346; b) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 1728; c) J. Yamaguchi, K. Muto, K. Itami, *Eur. J. Org. Chem.* **2013**, 19; d) J. Cornella, C. Zarate, R. Martin, *Chem. Soc. Rev.* **2014**, *43*, 8081; e) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717.

[3] Selected reviews on catalytic C–H functionalization: a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; c) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; d) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; e) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; f) M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; g) F. Kakiuchi, T. Kochi, S. Murai, *Synlett* **2014**, *25*, 2390; h) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*,

1461; i) B. Su, Z.-C. Cao, Z.-J. Shi, *Acc. Chem. Res.* **2015**, *48*, 886; j) L. C. M. Castro, N. Chatani, *Chem. Lett.* **2015**, *44*, 410.

[4] a) K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 169; b) K. Muto, J. Yamaguchi, A. Lei, K. Itami, *J. Am. Chem. Soc.* **2013**, *135*, 16384; c) H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami, D. G. Musaev, *J. Am. Chem. Soc.* **2014**, *136*, 14834; d) K. Muto, T. Hatakeyama, J. Yamaguchi, K. Itami, *Chem. Sci.* **2015**, *6*, 6792.

[5] Y. Wang, S.-B. Wu, W.-J. Shi, Z.-J. Shi, *Org. Lett.* **2016**, *18*, 2548.

[6] Intramolecular C–H/C–O coupling was reported: J. Wang, D. M. Ferguson, D. Kalyani, *Tetrahedron* **2013**, *69*, 5780.

[7] W. Song, L. Ackermann, *Angew. Chem. Int. Ed.* **2012**, *51*, 8251; *Angew. Chem.* **2012**, *124*, 8376.

[8] Reviews on rhodium-catalyzed C–H functionalization: a) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; b) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; c) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212.

[9] a) Y. Zhu, D. A. Smith, D. E. Herbert, S. Gatard, O. V. Ozerov, *Chem. Commun.* **2012**, *48*, 218; b) G. A. Edouard, P. Kelley, D. E. Herbert, T. Agapie, *Organometallics* **2015**, *34*, 5254; c) H. Kinuta, J. Hasegawa, M. Tobisu, N. Chatani, *Chem. Lett.* **2015**, *44*, 366; d) K. Nakamura, K. Yasui, M. Tobisu, N. Chatani, *Tetrahedron* **2015**, *71*, 4484; e) H. Kinuta, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2015**, *137*, 1593.

[10] 4,5-Dihydrooxazol-2-yl and 4,4-dimethyl-4,5-dihydrooxazol-2-yl groups as well as an imine and an pyrazole ring were found to be less effective directing groups. See the Supporting Information for details.

[11] See the Supporting Information for the results using other NHC ligands.

[12] Our works on inert C–O bond activation using NHC ligands: a) M. Tobisu, T. Shimasaki, N. Chatani, *Chem. Lett.* **2009**, *38*, 710; b) T. Shimasaki, M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2010**, *49*, 2929; *Angew. Chem.* **2010**, *122*, 2991; c) M. Tobisu, A. Yasutome, K. Yamakawa, T. Shimasaki, N. Chatani, *Tetrahedron* **2012**, *68*, 5157; d) M. Tobisu, A. Yasutome, H. Kinuta, K. Nakamura, N. Chatani, *Org. Lett.* **2014**, *16*, 5572; e) M. Tobisu, T. Takahira, A. Ohtsuki, N. Chatani, *Org. Lett.* **2015**, *17*, 680; f) M. Tobisu, T. Takahira, N. Chatani, *Org. Lett.* **2015**, *17*, 4352; g) M. Tobisu, T. Morioka, A. Ohtsuki, N. Chatani, *Chem. Sci.* **2015**, *6*, 3410; h) T. Morioka, A. Nishizawa, K. Nakamura, M. Tobisu, N. Chatani, *Chem. Lett.* **2015**, *44*, 1729; i) K. Nakamura, M. Tobisu, N. Chatani, *Org. Lett.* **2015**, *17*, 6142.

[13] A related $RhCl(SIPr)_2(N_2)$ complex: O. V. Zenkina, E. C. Keske, R. Wang, C. M. Crudden, *Angew. Chem. Int. Ed.* **2011**, *50*, 8100; *Angew. Chem.* **2011**, *123*, 8250.

[14] Nonselective C–H activation of arenes by a rhodium complex: a) C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1999**, *121*, 6616; b) C.-H. Jun, C. W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung, Y.-H. Kim, *Chem. Eur. J.* **2002**, *8*, 485.

[15] Rhodium(III)-mediated C–H bond activation through concerted metalation/deprotonation: a) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449; b) A. P. Walsh, W. D. Jones, *Organometallics* **2015**, *34*, 3400.

Manuscript received: October 24, 2016
Final Article published: ■■ ■■, ■■■■

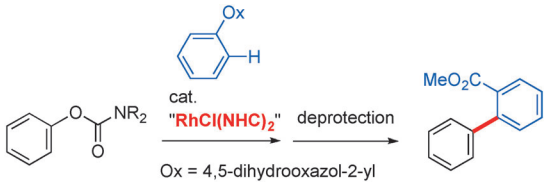
  

# Communications

**Homogeneous Catalysis**

M. Tobisu,* K. Yasui, Y. Aihara,
N. Chatani* ——— ■■■–■■■

C–O Activation by a Rhodium Bis(N-Heterocyclic Carbene) Catalyst: Aryl Carbamates as Arylating Reagents in Directed C–H Arylation




**One for the rhodium**: The rhodium-catalyzed cross-coupling of aryl carbamates with arenes bearing a convertible directing group is described. The key to success is the use of an in situ generated rhodium bis(N-heterocyclic carbene) species as the catalyst, which can promote activation of the inert C($sp^2$)–O bond in aryl carbamates.