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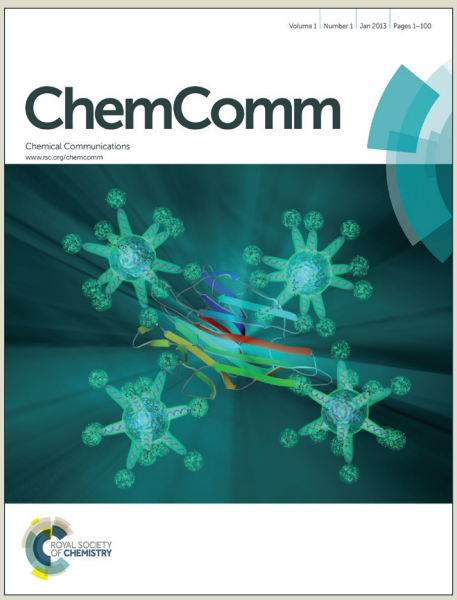

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Coupling of carboxylic acids with internal alkynes by supported ruthenium catalysts: Direct and selective syntheses of multi-substituted phthalide derivatives

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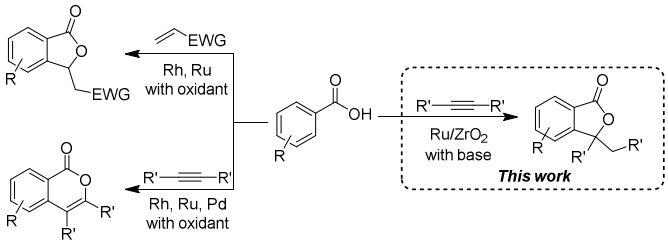
Supported ruthenium catalysts promotes coupling of various kinds of aromatic carboxylic acids with internal alkynes, giving the corresponding multi-substituted phthalide derivatives in high yields. The supported Ru catalyst can be recycled at least five times with no loss of activity.

Isobenzofuranone, commonly termed as phthalide, often can be found in natural products that show a broad range of important bioactivities, such as antibacterial, anti-HIV, antifungal, antibiotic, antitumor and immunosuppressive activity.[1] Various methodologies to obtain phthalides utilizing organic syntheses have been reported,[2] many of them were, however, achieved through multistep reactions. Novel synthetic route that realizes facile and direct construction of phthalide moieties remains to be explored.

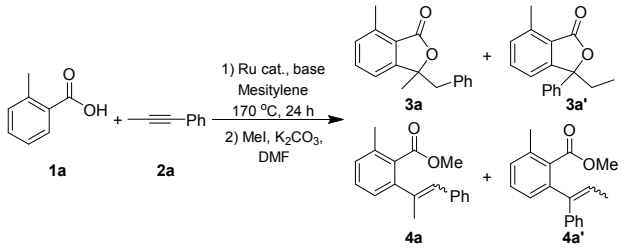
Carbon-carbon bond forming reactions involving cleavage of less-reactive carbon-hydrogen bonds has attracted much interest from the consideration of atom-economical synthesis.[3] Thanks to recent remarkable progress in C-H bond functionalization by transition-metal catalysts, rapid and selective construction of carbon skeletons has become made available. So far, oxidative coupling of benzoic acids with electron-deficient alkenes pioneered by Miura and Satoh should be regarded as one of the most straightforward route to the syntheses of phthalides.[4] The oxidative coupling of benzoic acids with internal alkynes is also reported to produce six membered lactones, namely, isocoumarins.[5] Such dehydrogenative C-C coupling strategies, however, have an inevitable problem with the fact that they require the addition of stoichiometric oxidant, such as copper or silver salt. The development of novel method that can avoid the formation of unwanted byproduct is, therefore, highly desired.

Also, efficient organic transformation with recyclable supported catalysts is important from the perspective of green and sustainable



Scheme 1.Transition-metal catalysed functionalization of benzoic acids.

Table 1. Ru-catalysed reaction of *o*-toluic acid (**1a**) with 1-phenyl-1-propyne (**2a**)[a]



entry	catalyst	additive	yield (%)[b]			
			3a	**3a'**	**4a**	**4a'**
1	Ru/ZrO_2	KOAc	93	0	0	3
2	Ru/CeO_2	KOAc	70	0	3	7
3	Ru/Y_2O_3	KOAc	59	0	1	3
4	Ru/SiO_2	KOAc	0	0	0	3
5	Ru/Al_2O_3	KOAc	3	0	1	5
6	Ru/TiO_2	KOAc	1	0	0	1
7	$[RuCl_2(p\text{-cymene})]_2$	KOAc	82	0	0	3
8	Ru/ZrO_2	KOH	86	0	4	1
9	Ru/ZrO_2	K_2CO_3	68	0	4	3
10	Ru/ZrO_2	HCO_2Na	74	0	3	7
11	Ru/CeO_2	HCO_2Na	80	0	2	12
12	Ru/ZrO_2	—	0	0	0	0

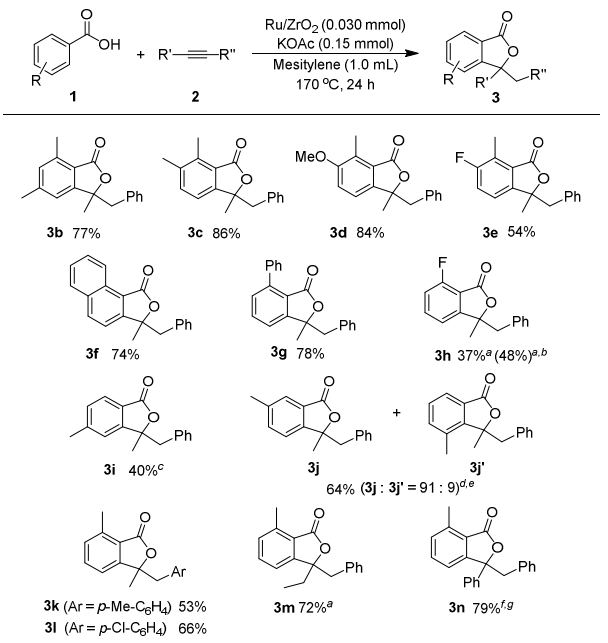
[a] Reaction conditions: (1) **1a** (1.0 mmol), **2a** (1.3 mmol), Ru catalyst (0.03 mmol as Ru), base (0.15 mmol), mesitylene (1.0 mL), at 170 °C, 24 h, under Ar. (2) MeI, K_2CO_3, DMF at rt. [b] Yields were determined by GLC based on **1a**.

chemistry.[6,7] We have already found and reported that CeO_2 and ZrO_2 supported Ru catalysts efficiently promoted various kinds of organic transformations such as arylation and alkylation of aromatic C-H bonds,[8] and the regio- and stereo-selective addition of carboxylic acids to terminal alkynes to yield vinyl esters.[9] These results encouraged us to develop further synthetic protocols for selective and efficient construction of carbon skeletons. In this communication, therefore, we demonstrate novel synthetic route to multi-substituted phthalides through the coupling of benzoic acids with internal alkynes by the use of supported Ru catalyst with a catalytic amount of base. The supported Ru catalyst shows high activity and selectivity as well as excellent recyclability.

Supported Ru catalysts were prepared as follows: An oxide support was added to a methanol solution of $[RuCl_2(p\text{-cymene})]_2$ at room temperature. After impregnation, the resulting powder was calcined at 400 °C in air to afford supported Ru catalyst. The loading of ruthenium was 2.0 wt%.

The reaction of *o*-toluic acid (**1a**) with 1-phenyl-1-propyne (**2a**) by the use of Ru/ZrO_2 with a catalytic amount of potassium acetate in mesitylene at 170 °C for 24 h produced phthalide **3a** in the yield of 93%. A trace amount of *o*-alkenylated esters **4a** and **4a'** were formed as byproducts (Table 1, entry 1).[10] The reaction was catalysed by CeO_2 and Y_2O_3-supported Ru catalysts, generating **3a** in a moderate or a good yield (entries 2 and 3). However, Ru catalysts supported on SiO_2, Al_2O_3 or TiO_2 did not show sufficient activities.[11] The reaction with $[RuCl_2(p\text{-cymene})]_2$ as a homogeneous catalyst could also produce **3a**, but its yield was lower than one with Ru/ZrO_2 (entry 7). What is noteworthy is that regioisomer **3a'** was not obtained at all in all cases. In the absence of base (entry 8), no product was obtained, which indicated that a catalytic amount of base was necessary for this reaction. Among the bases examined, potassium or sodium salts resulted in good yields of the products. Although Rh- or Ru-catalysed coupling of benzoic acids with internal alkynes in the presence of $Cu(OAc)_2$ as an external oxidant has been known to produce isocoumarin derivatives exclusively[5], no isocoumarins was observed under any conditions, in our supported Ru catalyst system.

Table 2. Scope of substrates



[a] Reaction time 40 h. [b] Ru/CeO_2 and HCO_2Na were used. [c] Reaction time 48 h. [d] Reaction time 60 h. [e] The ratio of the regioisomers was determined by ^1H NMR. [f] Reaction time 72 h. [g] Yield was determined by GLC.

Under the optimized reaction conditions, the coupling of various kinds of aromatic acids with internal alkynes was investigated by using Ru/ZrO_2 or Ru/CeO_2 catalysts (Table 2). The reactions of benzoic acids having methyl substituent at *ortho*-position proceeded efficiently to produce the corresponding phthalides **3b**-**3e** in a good or a high yield. 1-Naphtoic acid and 2-biphenylcarboxylic acid could participate in the present catalytic system to produce **3f** and **3g** in high yields. The reaction of benzoic acid having fluoro substituent at *ortho*-position resulted in a moderate yield of **3h**. The reactions of *meta*- or *para* methyl substituted benzoic acids were also carried out and the corresponding products (**3i** and **3j**) were obtained in moderate to good yields. Furthermore, unsymmetrical internal alkynes other than **2a** were employed in this reaction to produce the corresponding phthalide (**3k–3m**) in moderate to good yields. Note that the reactions of unsymmetrical internal alkynes proceeded with high regioselectivities and only a trace amount of byproducts (**4** or **4'**, < ca. 5% yield) were formed in each reaction. Even if longer period of reaction was required, desired product **3n** was obtained from bisarylacetylene in a high yield.

Figure 1 shows the time course of the coupling reaction of **1a** with **2a** by the use of Ru/ZrO_2 under the condition shown in the table 1, entry 1. At the initial stage of the reaction, **4a** was rapidly formed. After 3 h, the formation of final product **3a** and the decreasing yield of **4a** were observed. These results clearly indicate that the formation of phthalide **3a** was achieved through regioselective addition of aromatic C-H bond to internal alkynes[12] followed by nucleophilic intramolecular cyclization.[4,13] Although a small amount of **4a'** was formed, subsequent cyclization leading to **3a'** did not occur.

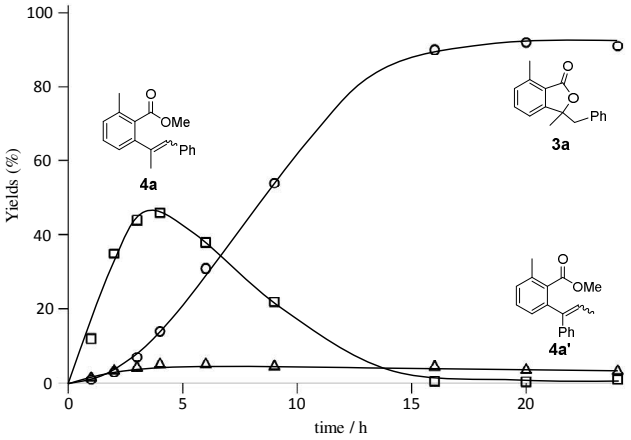
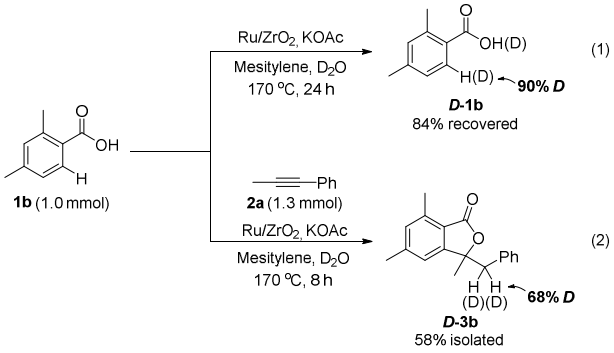
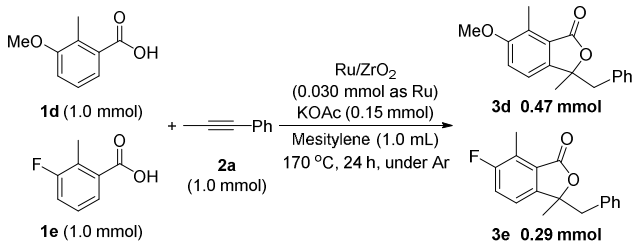


Figure 1. Time-course of the reaction of **1a** with **2a**; yield of **3a**(○), **4a**(□) and **4a'**(△)

To get information about the reaction mechanism, deuterium labeling experiment was carried out. When aromatic acid **1d** was treated with D_2O in mesitylene at 170 °C for 24 h, significant deuterium incorporation at *ortho*-position of **1d** was observed

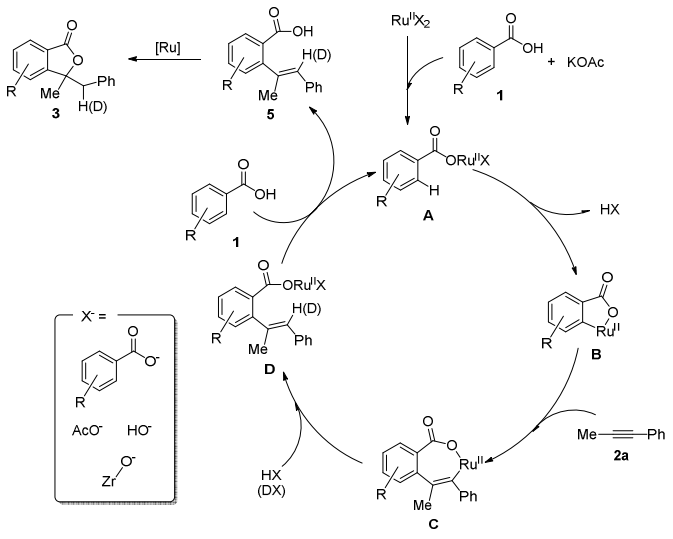


Scheme 2. Deuterim labeling experiment



Scheme 3. Intermolecular competition experiment with alkyne **2a**.

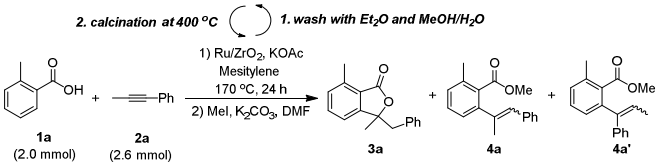
(Scheme 2, eq 1). This suggests that the reaction includes reversible *ortho*-ruthenation step.[3i,5c,5d,14] When the reaction of **1b** with **2a** was performed by the use of D_2O, desired product **3b** was obtained in 58% isolated yield, and 68% of methylene group hydrogen of the formed phthalide **3b** was deuterated (Scheme 2, eq 2). Intermolecular competition experiment was also conducted. As is shown in Scheme 3, benzoic acid with electron-donating substituent was preferentially converted to corresponding phthalide, suggesting that electrophilic C-H bond cleavage was the rate-determining step.[15] From these results, a possible reaction mechanism shown in Scheme 4 is proposed. Our previous study revealed the formation of a Ru^{IV}–oxo species on the surface of CeO_2 or ZrO_2, and the Ru^{IV}–oxo species were readily reduced to Ru^{II} species by refluxing in organic solvents.[8] The catalytic reaction is initiated by the ligand exchange of *in-situ* generated Ru^{II} species with **1** to form ruthenium benzoate **A** and the addition of potassium acetate is supposed to accelerate this step. Subsequently, *ortho*-ruthenation of **A** produces ruthenacycle intermediate **B**. And then regioselective insertion of alkyne to Ru-C bond, and protonation at the Ru-C bond of **C** take place to provide **D**. The reaction at a high temperature of 170 °C may promote the protonation step of the alkenyl Ru species **C** by acids to produce **D**. Ligand exchange of **D** with **1** produces *ortho*-alkenylated benzoic acid **5** accompanying regeneration of catalytically active ruthenium benzoate **A**. Finally, nucleophilic intramolecular cyclization occurs to produce final product phthalide **3**.[4,13]



Scheme 4. Possible reaction mechanism

The most advantageous feature of supported catalysts is their high recyclability and low contamination of the products by metallic species after the reactions. After the reaction of **1a** with **2a**, the supported ruthenium catalyst was separated from the reaction mixture by centrifugation and washed with diethyl ether and water/methanol. The resulting powder was calcined in air at 400 °C for 30 min to recover Ru/ZrO_2 for subsequent catalytic runs. As is shown in Table 3, the Ru/ZrO_2 catalyst was successfully applied to the present reactions to produce **3a** without any decreases in yields and selectivities for at least five times. After the reaction of **1a** with **2a** for 24 h by the fresh Ru/ZrO_2 catalyst, the amount of ruthenium species leaching into the solution was only 1.17 μmol as Ru (3.9% of the ruthenium species in the fresh catalyst).[16]

Table 3. Recyclability of Ru/ZrO_2[a]



cycle	amount of Ru/ZrO_2 (mg)	yield (%)[b]		
		3a	**4a**	**4a'**
1	300	88	1	4
2	291	89	0	4
3	285	91	1	3
4	279	92	1	5
5	271	94	0	3

[a] Reaction conditions; (1) **1a** (2.0 mmol), **2a** (2.6 mmol), Ru/ZrO_2 (0.060 mmol as Ru), KOAc (0.30 mmol), mesitylene (2.0 mL), at 170 °C, 24 h, under Ar. (2) MeI, K_2CO_3, DMF at rt. [b] Determined by GC, based on **1a**.

Conclusions

We have developed direct and regioselective synthesis of multi-substituted phthalide derivatives through Ru/ZrO_2-catalysed addition of aromatic carboxylic acid to internal alkynes and subsequent intramolecular cyclization. The reaction requires no addition of metallic oxidant. The supported Ru catalyst shows excellent activities and environmental compatibility resulting from their high recyclability and low contamination of products by metallic species. Further investigation of mechanistic insight and development of novel catalytic reaction are underway in our laboratory.

Notes and references

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1. (a) R. Karmakar, P. Pahari and D. Mal, *Chem. Rev.*, 2014, **114**, 6213; (b) G. Strobel. E. Ford, J. Worapong, J. K. Harper, A. M. Arif, D. M. Grant, P. C. W. Fung and R. M. W. Chau, *Phytochemistry*, 2002, **60**, 179; (c) A. Arnone, G. Assante, G. Nasini, S. Strada and A. Vercesi, *J. Nat. Prod.* 2002, **65**, 48; (d) T. H. Chou, I. S. Chen, T. L. Hwang, T. C. Wang, T. H. Lee, L. Y. Cheng, Y. C. Chang, J. Y. Cho and J. J. Chen, *J. Nat. Prod.,* 2008, **71**, 1692; (e) L. P. L. Logrado, C.

O. Santos, L. A.S. Romeiro, A. M. Costa, J. R. O. Ferreira, B. C. Cavalcanti, O. M. de Moraes, L. V. Costa-Lotufo, C. Pessoa and M. L. dos Santos, *Eur. J. Med. Chem.*, 2010, **45**, 3480;

2. (a) M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya and T. Sakamoto, *Org. Lett.*, 2006, **8**, 5517; (b) C. Kanazawa and M. Terada, *Tetrahedron Lett.*, 2007, **48**, 933; (c) D. Mal, P. Pahari and S. R. De, *Tetrahedron*, 2007, **63**, 11781; (d) D. Parmar, M. S. Maji and M. Rueping, *Chem. Eur. J.*, 2014, **20**, 83; (e) M. Toffano, B. Dudot, A. Zaparucha, J. Royer, M. Sevrin, P. Georgeb and A. Chiaronic, *Tetrahedron: Asymmetry,* 2003, **14**, 3365.
3. (a) G. Dyker, *Angew. Chem. Int. Ed.,* 1999, **38**, 1698; (b) C. G. Jia, T. Kiatamura and Y. Fujiwara, *Acc. Chem. Res.*, 2002, **34**, 633; (c) F. Kakiuchi and S. Murai *Acc. Chem. Res.*, 2002, **35**, 826; (d) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.,* 2002, **102**, 1731; (e) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.,* 2007, **107**, 174; (f) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.,* 2010, **110**, 624; (g) T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147; (h) L. Ackermann, *Chem. Rev.,* 2011, **111**, 1315; (i) W. Shi, C. Liu and A. Lei, *Chem. Soc. Rev.,* 2011, **40**, 2761; (j) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.,* 2011, **111**, 1780; (k) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281.
4. (a) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211; (b) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407; (c) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362; (d) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 6295; (e) F. Wang, G. Song, and X. Li, *Org. Lett.*, 2010, **12**, 5430; (f) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 3024; (g) L. Ackermann and J. Pospech, *Org. Lett.*, 2011, **13**, 4153. (h) L. Chen, H. Li, F. Yu and L. Wang, *Chem. Commun.*, 2014, DOI: 10.1039/C4CC06331G.
5. (a) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407; (b) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362; (c) L. Ackermann, J. Pospech, K. Graczyk and K. Rauch, *Org. Lett.*, 2012, **14**, 930; (d) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 2030.
6. (a) P. T. Anastas and J. Warner, In Green Chemistry: Theory and Practice; Oxford University Press: New York 1998; (b) R. A. Sheldon and R. S. Downing, *Appl. Catal. A: General,* 1999, **189**, 163; (c) B. M. Trost, *Acc. Chem. Res.,* 2002, **35**, 695.
7. (a) P. Laszlo, *Acc. Chem. Res.,* 1986, **19**, 121; (b) Y. Izumi and M. Onaka, *Adv. Catal.,* 1992, **38**, 245; (c) J. H. Clark and D. J. Macquarrie, *Chem. Soc. Rev.,* 1996, **25**, 303; (d) B. F. Sels, D. E. De Vos and P. A. Jacobs, *Catal. Rev. Sci. Eng.,* 2001, **43**, 443; (e) T. Nishimura and S. Uemura, *Synlett,* 2004, 201; (f) S. Kannan, *Catal. Surv. Asia,* 2006, **10**, 117. (g) K. Kaneda, *Synlett,* 2007, 999; (h) M. Tada and Y. Iwasawa, *Coord. Chem. Rev.,* 2007, **251**, 2702; (i) L. Yin and J. Liebscher, *Chem. Rev.,* 2007, **107**, 133.
8. (a) K. Wada, H. Miura, S. Hosokawa and M. Inoue, *J. Jpn. Petro. Inst.,* 2013, **56**, 69; (b) H. Miura, K. Wada, S. Hosokawa, M. Sai, T. Kondo and M. Inoue, *Chem. Commun.,* 2009, 4112; (c) H. Miura, K. Wada, S. Hosokawa and M. Inoue, *Chem. Eur. J.,* 2010, **16**, 4186; (d) H. Miura, K. Wada, S. Hosokawa and M. Inoue, *ChemCatChem,* 2010, **2**, 1223; (e) H. Miura, S. Shimura, S. Hosokawa, S. Yamazoe, K. Wada and M. Inoue, *Adv. Synth. Catal.,* 2011, **353**, 2837; (f) S. Shimura, H. Miura, K. Wada, S. Hosokawa, S. Yamazoe and M. Inoue, *Catal. Sci. Technol.,* 2011, **1**, 1340; (g) S. Shimura, H. Miura, S. Tsukada, K. Wada, S. Hosokawa and M. Inoue, *ChemCatChem,* 2012, **4**, 2062. (h) H. Miura, K. Wada, S. Hosokawa and M. Inoue, *Chem. Eur. J.,* 2013, **19**, 861.
9. (a) M. Nishiumi, H. Miura, K. Wada, S. Hosokawa and M. Inoue, *Adv. Synth. Catal.,* 2010, **352**, 3045; (b) M. Nishiumi, H. Miura, K. Wada, S. Hosokawa and M. Inoue, *ACS Catal.,* 2012, **2**, 1753.
10. After catalytic runs, products were esterized using methyl iodide and potassium carbonate to quantitate the resulting acids by flame ionization detector (FID) gas chromatography.
11. Similar trends were observed in our previous studies on organic transformations with supported Ru catalysts.[8] Detailed analyses of supported Ru catalysts are shown in Supplementary information.
12. Ruthenium–catalyzed regioselective addition of aromatic C-H bonds to internal alkynes, (a) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi, and M. Miura, *Org. Lett.*, 2012, **14**, 2058; (b) P. Zhao, R. Niu, F. Wang, K. Han and X Li, *Org. Lett.*, 2012, **14**, 4166; (b) M. Itoh, Y. Hashimoto, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2013, **78**, 8098; (c) R. Manikandan and M. Jeganmohan, *Org. Lett.*, 2014, **16**, 912; (d) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2014, DOI: 10.1039/C4CC06426G.
13. (a) C. F. Nising and F. Bräze, *Chem. Soc. Rev.,* 2008, **37**, 1218; (b) C. F. Nising and F. Bräze, *Chem. Soc. Rev.,* 2012, **41**, 988. (c) S. Nicolai, S. Erard, D. F. González, and J. Waser, *Org. Lett.*, 2010, **12**, 384.
14. (a) T. K. Hyster and T. Rovis, *J. Am. Soc. Chem.*, 2010, **132**, 10565; (b) L. Yan, B. Qian and H. Huang, *Chem. Eur. J.,* 2012, **18**, 9511; (c) H. Li, X. Xie and L. Wang, *Chem. Commun.*, 2014, **50**, 4218.
15. D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, *J. Am. Soc. Chem.*, 2010, **132**, 18326.
16. Removal of the supported ruthenium catalyst by the hot filtration through a polytetrafluoroethylene (PTFE) filter (pore size 0.45 μm) after the reaction for 3 h partly retarded further progress of reaction of **1a** and **2a** (Figure S1 in the Supplementary information), which indicates that a small contribution of soluble ruthenium species to the catalysis.

