

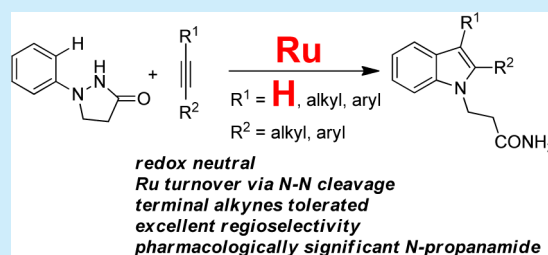
# Ruthenium-Catalyzed Redox-Neutral C–H Activation via N–N Cleavage: Synthesis of N-Substituted Indoles

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**S** Supporting Information

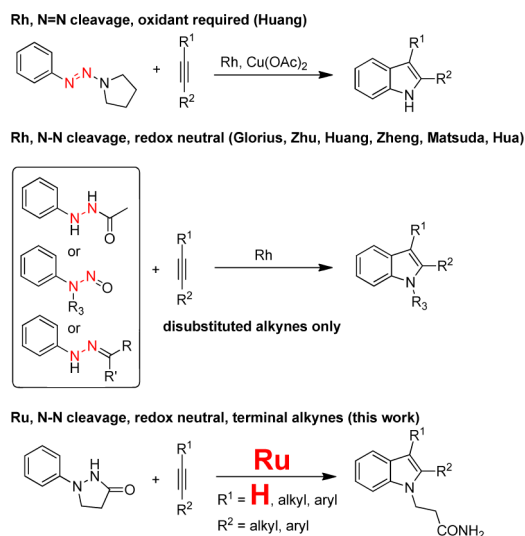
**ABSTRACT:** The first Ru-catalyzed redox-neutral C–H activation reaction via N–N bond cleavage is reported. Pyrazolidin-3-one is demonstrated as an internally oxidative directing group that enables C–H annulation reactions with a broad scope of alkynes, including previously incompetent terminal alkynes. Pharmacologically privileged 3-(1H-indol-1-yl)propanamides were synthesized in high yields.



In the past decade, transition-metal-catalyzed functionalization of inert C–H bonds emerged as the new center stage for synthetic innovations.<sup>1</sup> Its unparalleled advantages over existing methods of chemical bond formation have spurred intensive studies in an effort to make it a general strategy for late-stage functionalization of complex scaffolds. Because of the oxidative nature of these dehydrogenative C–H bond coupling reactions, stoichiometric amounts of sacrificing oxidants are often required in order to turn over the precious transition-metal catalysts. An overwhelming majority of external oxidants reported in the literature are toxic metal salts that are unsuitable for large-scale production. More recently, development of redox-neutral C–H activation reactions has received much attention in which an oxidative functional group serves as both a directing group (DG) and an internal oxidant.<sup>2</sup> This strategy eliminates the need for an external oxidant.

Among reported oxidative DGs, the N–O bond is the most frequently used, which has been demonstrated to successfully turn over Rh, Pd, Ru, etc.<sup>3</sup> On the other hand, redox-neutral C–H activation reactions using N–N cleavage have been limited to Rh catalysis owing to the relatively low oxidative potential of N–N vs N–O (Scheme 1). Recently, Glorius reported the use of hydrazide as the first oxidative N–N DG for the synthesis of indoles.<sup>4</sup> Zhu and we reported that nitrous amide was also a competent group to turn over Rh(III).<sup>5</sup> Subsequently, hydrazones were also reported, independently by Zheng, Matsuda, and Hua, as an internally oxidative N–N DG for Rh(III).<sup>6</sup> However, a major limitation for the Rh-catalyzed alkyne annulation reaction is the requisite use of disubstituted acetylenes. Terminal alkynes are known to be notorious substrates for Rh catalysis due to serious homocoupling and other side reactions.<sup>3d,o</sup> In contrast, the N–N bond has not been demonstrated in C–H activation reactions using Ru, a significantly cheaper metal, despite its catalytic versatility in C–H activation reactions demonstrated extensively by Ackermann and others.<sup>7</sup> Herein, we report our progress on the

## Scheme 1. Indole Synthesis via C–H Activation and N–N Cleavage



development of Ru-catalyzed redox-neutral alkyne annulation reactions via N–N cleavage with substrate scope beyond previous methods using Rh.

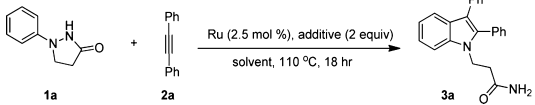
In the past few years, our group has been interested in the synthesis of polysubstituted indole scaffolds using redox-neutral C–H annulation reactions with alkynes.<sup>5a,8</sup> Despite the aforementioned progress on Rh-catalyzed indole synthesis, only internal alkynes were tolerated in the literature. Our own experience showed that terminal alkynes were incompatible with Rh(III) due to homocoupling of alkynes. It would be intuitively wiser to employ an alternative metal, preferably cheaper, for the

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synthesis of indoles with terminal alkynes.<sup>9</sup> Ru has been shown to undergo directed olefination and subsequent cyclization using alkynes. However, two questions need to be answered: (1) can we identify an oxidative DG to make the reaction redox neutral; (2) can terminal alkyne be tolerated? We initially examined arenes bearing various functional groups with diphenylacetylene using Ru catalysts. Unfortunately, most reactions resulted very low yields of the desired 2,3-diphenylindole. For example, *N'*-phenylacetohydrazide, previously used by Glorius in Rh catalysis,<sup>4</sup> only resulted in a small amount of the indole product. Increasing the amount of Ru increased the yield of the indole product. Nevertheless, the reaction was rather messy, and the corresponding N–Nac indole was isolated as the major product. This result suggested that the N–N bond of N–Ac hydrazine was not oxidative enough to turn over the Ru(II) catalyst. In order to further increase the oxidative potential of the N–N bond, we decided to examine cyclic hydrazides in which the N–N might be further activated by ring strain. Gratifyingly, we quickly identified that pyrazolidin-3-one, which possesses a slightly longer N–N bond than their acyclic counterpart,<sup>10</sup> was able to accomplish redox neutral synthesis of indoles using Ru (Table 1)!

**Table 1. Condition Investigation Using Pyrazolidin-3-one as an Oxidative DG<sup>a</sup>**



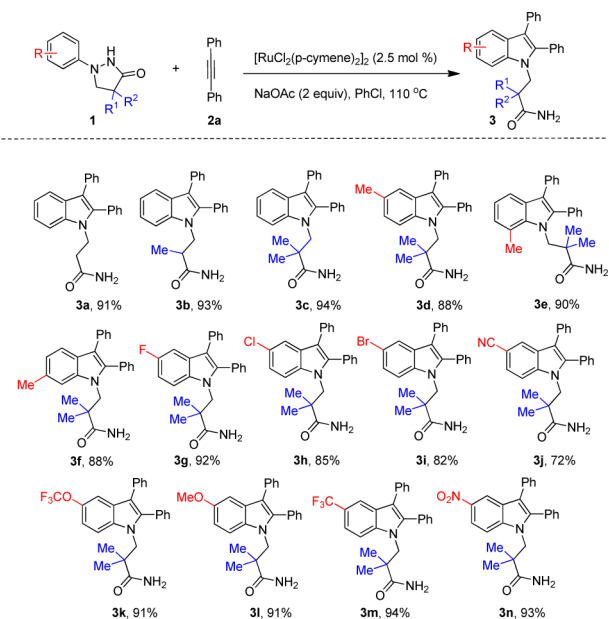
entry	catalyst	additive	solvent	yield <sup>b</sup> (%)
1	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>		<i>t</i> -AmOH	
2	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	Cu(OAc) <sub>2</sub>	<i>t</i> -AmOH	70 (67)
3	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	NaOAc	<i>t</i> -AmOH	83 (87)
4	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	NaOAc	Ph-Cl	89 (91)
5	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	Ph-Cl	90 (90)

<sup>a</sup>Unless specified, the reactions were carried out using 1.5 equiv of diphenylacetylene and 2 equiv of additive at 110 °C under argon for 18 h. <sup>b</sup>Yields were determined by NMR integration. Numbers in the parentheses are isolated yield.

Further, a condition survey was carried out by treating substrate **1a** and diphenylacetylene **2a** with 2.5 mol % of Ru catalyst and an additive in various solvents under an argon atmosphere at 110 °C. Although RuCl<sub>3</sub> was ineffective even in the presence of a stoichiometric amount of copper, the commercially available [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> was a competent catalyst for the C–H indole formation. The desired product **3a** was isolated in 67% yield when 2 equiv of Cu(OAc)<sub>2</sub> was used (Table 1, entry 1). Although the reaction did not proceed in the absence of Cu(OAc)<sub>2</sub>, we quickly found out that the key missing component was the OAc anion, not Cu, that would assist the C–H insertion by Ru. Common carboxylate salts, i.e., NaOAc, KOAc, and Na<sub>2</sub>CO<sub>3</sub>, were equally effective as their copper counterparts (Table 1, entries 3–5). This reaction worked in various solvents, with chlorobenzene affording the highest yields. Although cheaper Na<sub>2</sub>CO<sub>3</sub> promoted this redox neutral C–H annulation smoothly, NaOAc was eventually chosen for substrate scope survey considering its mild basicity that tolerates a broader range of functional groups (*vide infra*).

The scope of the phenylpyrazolidin-3-one was examined using diphenylacetylene (Scheme 2). The pyrazolidin-3-one tolerated substitutions  $\alpha$ - to the cyclic hydrazide carbonyl. This protocol

**Scheme 2. Substrate Scope of Phenylpyrazolidin-3-ones<sup>a</sup>**

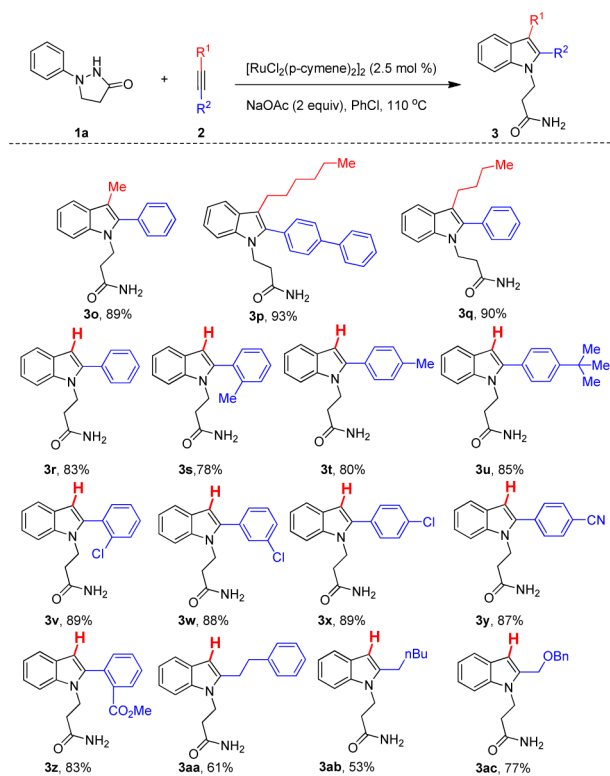


<sup>a</sup>Reactions were carried out on 0.2 mmol scales. Isolated yield.

was particularly effective for a broad range of substituents on the arene. Ortho-, meta- and para-substituents were well tolerated. Halogenated substrates afforded the indole products in good yields. High yields were uniformly obtained regardless of the electronic nature of the substituents. A substrate bearing a strong electron-withdrawing nitro group resulted in 93% yield of the desired product.

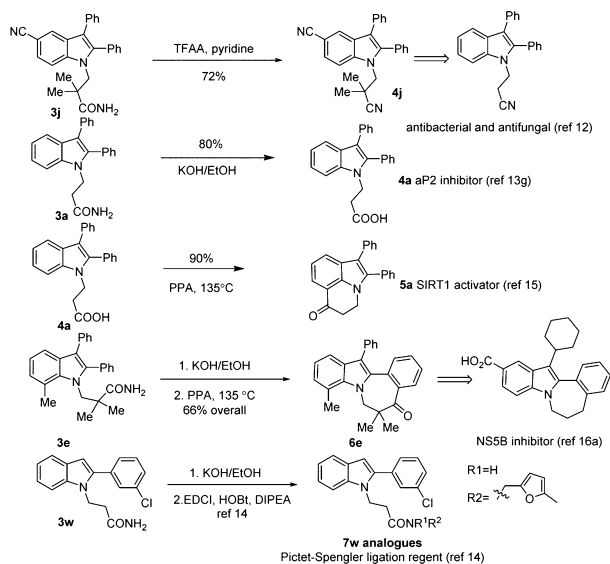
We next studied the scope of alkynes, especially asymmetrical ones (Scheme 3). The standard reaction conditions accommodated both aryl,aryl-, alkyl,aryl-, and alkyl,alkyl-disubstituted alkynes without affecting yield. For asymmetrical alkyl,aryl substrates, single regioisomers (2-aryl-3-alkylindoles) were obtained exclusively (Scheme 3, **3o–q**). Since one major goal of this work was to expand the scope of the triple bond to the uncharted terminal alkynes, various 1-substituted acetylenes were tested using the standard conditions. We were very pleased to find that terminal alkynes not only reacted smoothly, but also generated single regioisomers of the indole products (2-substituted). Due to the redox-neutral nature of this chemistry, very little dimerization of the alkynes were observed. It should be noted that halogen substituted phenylacetylenes were efficiently converted, despite the strong tendency of these substrates to undergo self Sonogashira coupling reactions (Scheme 3, **3v–x**).<sup>11</sup> In addition, cyano (Scheme 3, **3y**), ester (Scheme 3, **3z**), and ether (Scheme 3, **3ac**) groups were also suitable substituents. 1-Alkyl-substituted acetylenes were also effective with slightly lower yields. The broad scope of alkynes represents a major advance for the indole synthesis via C–H annulation reactions.

The product 3-(1*H*-indol-1-yl)propanamides were demonstrated for their pharmacological relevance (Scheme 4). As a matter of a fact, a number of products from Schemes 1 and 2, along with their nitrile and acid derivatives, were studied for antibacterial and antifungal activities.<sup>12</sup> Very recently, they were disclosed as potent inhibitors for aP2 (adipocyte protein 2), a carrier protein for fatty acids that is a potential target for heart disease, diabetes, asthma, obesity, and fatty liver disease.<sup>13</sup> The primary amides were hydrolyzed using KOH/EtOH to give the corresponding acids that were further transformed to several

Scheme 3. Scope of Alkynes<sup>a</sup>

<sup>a</sup>Reactions were carried out on 0.2 mmol scales. Isolated yield.

Scheme 4. Derivatization of the Primary Indole Products

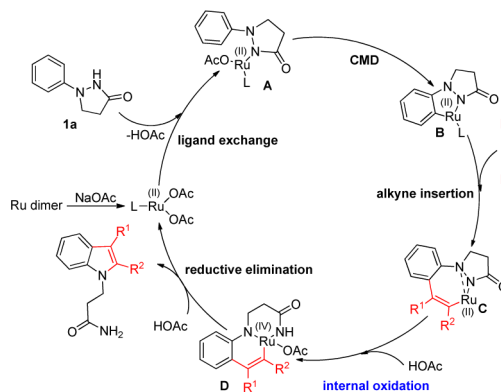


valuable pharmacophores. Amidation using primary and secondary amines led to inhibitors for ZipA–FtsZ protein–protein interaction that is a potential target for antibacterial therapy.<sup>14</sup> Upon treatment with PPA, the resulting acids underwent Friedel–Crafts cyclization to give a fused [6,6,5] tricyclic scaffold that was reported as a SIRT1 activator for the treatment of type II diabetes and other metabolic disorders.<sup>15</sup> The acids also cyclized onto the appending 2-aryl to give a [6,5,7,6]-tetracyclic skeleton that resembles MK-3281, an NS5B inhibitor for HCV.<sup>16</sup> Product 3ac was easily transformed into a useful Pictet–Spengler ligation reagent for site-specific chemical

modification of glyoxyl- and formylglycine-functionalized proteins.<sup>17</sup>

On the basis of the related mechanistic discussions on redox-neutral Rh catalysis in the literature,<sup>4,18</sup> we propose a preliminary Ru(II)–Ru(IV)–Ru(II) catalytic cycle (Scheme 5). The active

Scheme 5. Proposed Catalytic Cycle for the Indole Synthesis



Ru(II) acetate first inserts into the NH bond of the pyrazolidin-3-one to give the Ru(II) amido complex A, which undergoes carboxylate-assisted concerted metalation–deprotonation to give B. Subsequent alkyne insertion generates intermediate C that is further oxidized to the Ru(IV) species D by the cleavage of the cyclic N–N bond. Final reductive elimination releases the product and the Ru(II) acetate.

In summary, we have developed a general regioselective synthesis of polysubstituted indoles. This protocol demonstrates several important advances over existing methods: (1) redox neutral using a cheap Ru catalyst; (2) unprecedented Ru turnover via N–N bond cleavage; (3) suitable for previously incompatible terminal alkynes with excellent regioselectivity; and (4) in situ installation of a pharmacologically significant N-propanamide functionality via internal cleavage of the directing group.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, condition screening table, product characterizations, and copies of all NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) For recent reviews on C–H activation, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) “C–H Activation”:



Topics in Current Chemistry; Yu, J.-Q., Shi, Z.-J., Eds.; Springer: Heidelberg, 2010. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (f) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (g) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (h) White, M. C. *Science* **2012**, *335*, 807. (i) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (k) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (l) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (m) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (n) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(2) Recent reviews on redox neutral C–H activation: (a) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.

(3) For selected examples of redox neutral C–H activation reactions via N–O bond cleavage, see: (a) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (b) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (c) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (d) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (e) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (f) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (g) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (h) Kornhaaf, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190. (i) Hyster, T. K.; Knerr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (j) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (k) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504. (l) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (m) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66. (n) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (o) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6033. (p) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12970. (q) Huckins, J. R.; Bercot, E. A.; Thiel, O. R.; Hwang, T.-L.; Bio, M. M. *J. Am. Chem. Soc.* **2013**, *135*, 14492. (r) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912. (s) Zhao, D.; Lied, F.; Glorius, F. *Chem. Sci.* **2014**, *5*, 2869.

(4) Zhao, D.; Shi, Z.; Glorius, F. *Angew. Chem.* **2013**, *52*, 12426.

(5) (a) Wang, C.; Huang, Y. *Org. Lett.* **2013**, *15*, 5294. (b) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625.

(6) (a) Zheng, L.; Hua, R. *Chem.—Eur. J.* **2014**, *20*, 2352. (b) Muralirajan, K.; Cheng, C.-H. *Adv. Synth. Catal.* **2014**, *356*, 1571. (c) Matsuda, T.; Tomaru, Y. *Tetrahedron Lett.* **2014**, *55*, 3302.

(7) For recent reviews on Ru-catalyzed C–H activation reactions, see: (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (b) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. For recent examples on Ru-catalyzed C–H activation reactions, see: (c) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629. (d) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400. (e) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298. (f) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (g) Chidipudi, S. R.; Khan, I.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 12115. (h) Dong, J.; Long, Z.; Song, F.; Wu, N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 580. (i) Schinkel, M.; Marek, I.; Ackermann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3977. (j) Zhang, J.; Ugrinov, A.; Zhao, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6681. (k) Dooley, J. D.; Chidipudi, S. R.; Lam, H. W. *J. Am. Chem. Soc.* **2013**, *135*, 10829. (l) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. (m) Nan, J.; Zuo, Z.; Luo, L.; Bai, L.; Zheng, H.; Yuan, Y.; Liu, J.; Luan, X.; Wang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 17306.

(8) (a) Wang, C.; Sun, H.; Fang, Y.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5795. (b) Sun, H.; Wang, C.; Yang, Y.-F.; Chen, P.; Wu, Y.-D.; Zhang, X.; Huang, Y. *J. Org. Chem.* **2014**, DOI: 10.1021/jo500807d. (c) Chen, Y.; Wang, D.; Duan, P.; Ben, R.; Dai, L.; Shao, X.; Hong, M.; Zhao, J.; Huang, Y. *Nat. Commun.* **2014**, *5*, 4610.

(9) For direct use of terminal alkynes in Ru catalysis, see: Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309.

(10) (a) Sbit, M.; Dupont, L.; Dideberg, O.; Snoeck, J. P.; Delarge, J. *Acta Crystallogr. Sect. C-Cryst. Struct. Commun.* **1987**, *43*, 718. (b) Ray, J. K.; Mahato, T. K.; Chinnakali, K.; Fun, H.-K. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1997**, *53*, 1621.

(11) (a) Li, Y.; Zhang, J.; Wang, W.; Miao, Q.; She, X.; Pan, X. *J. Org. Chem.* **2005**, *70*, 3285. (b) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416.

(12) El-Desokey, S. I.; Hammad, M.; Grant, N.; El-Telbany, E. M.; Rahman, A. H. A. *Boll. Chim. Farm.* **1996**, *135*, 24.

(13) For therapeutic investigations on aP2, see: (a) Furuhashi, M.; Hotamisligil, G. S. *Nat. Rev. Drug Discovery* **2008**, *7*, 489. (b) Makowski, L.; Boord, J. B.; Maeda, K.; Babaev, V. R.; Uysal, K. T.; Morgan, M. A.; Parker, R. A.; Suttles, J.; Fazio, S.; Hotamisligil, G. S.; Linton, M. F. *Nat. Med.* **2001**, *7*, 699. (c) Furuhashi, M.; Tuncman, G.; Görgün, C. Z.; Makowski, L.; Atsumi, G.; Vaillancourt, E.; Kono, K.; Babaev, V. R.; Fazio, S.; Linton, M. F.; Sulsky, R.; Robl, J. A.; Parker, R. A.; Hotamisligil, G. S. *Nature* **2007**, *447*, 959. (d) Hotamisligil, G. S.; Johnson, R. S.; Distel, R. J.; Ellis, R.; Papaioannou, V. E.; Spiegelman, B. M. *Science* **1996**, *274*, 1377. (e) Shum, B. O.; Mackay, C. R.; Görgün, C. Z.; Frost, M. J.; Kumar, R. K.; Hotamisligil, G. S.; Rolph, M. S. *J. Clin. Invest.* **2006**, *116*, 2183. (f) Makowski, L.; Hotamisligil, G. S. *Curr. Opin. Lipidol.* **2005**, *16*, 543. For medicinal chemistry endeavors using the same scaffold as **4a**, see: (g) Miyanaga, W.; Sugiki, M.; Ejima, C.; Tokumasu, M.; Yoshida, T.; Takeshita, S. WO2014/003158 A1, 2014.

(14) (a) Jennings, L. D.; Foreman, K. W.; Rush, T. S.; Tsao, D. H. H.; Mosyak, L.; Kincaid, S. L.; Sukhdeo, M. N.; Sutherland, A. G.; Ding, W. D.; Kenny, C. H.; Sabus, C. L.; Liu, H. L.; Dushin, E. G.; Moghazeh, S. L.; Labthavikul, P.; Petersen, P. J.; Tuckman, M.; Ruzin, A. V. *Bioorg. Med. Chem.* **2004**, *12*, 5115. (b) Awasthi, D.; Kumar, K.; Ojima, I. *Expert Opin. Ther. Patents* **2011**, *21*, 657.

(15) Layek, M.; Reddy, M. A.; Rao, A. V. D.; Alvala, M.; Arunasree, M. K.; Islam, A.; Mukkanti, K.; Iqbal, J.; Pal, M. *Org. Biomol. Chem.* **2011**, *9*, 1004.

(16) (a) Ding, M.; He, F.; Hudyma, T. W.; Zheng, X.; Poss, M. A.; Kadow, J. F.; Beno, B. R.; Rigat, K. L.; Wang, Y.-K.; Fridell, R. A.; Lemm, J.; Qiu, A. D.; Liu, M.; Voss, S.; Pelosi, L. A.; Roberts, S. B.; Gao, M.; Knipe, J.; Gentles, R. G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2866. (b) Stansfield, I.; Ercolani, C.; Mackay, A.; Conte, I.; Pompei, M.; Koch, U.; Gennari, N.; Giuliano, C.; Rowley, M.; Narjes, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 627. (c) Narjes, F.; Crescenzi, B.; Ferrara, M.; Habermann, J.; Colarusso, S.; Ferreira, M. d. R. R.; Stansfield, I.; Mackay, A. C.; Conte, I.; Ercolani, C.; Zaramella, S.; Palumbi, M.-C.; Meuleman, P.; Leroux-Roels, G.; Giuliano, C.; Fiore, F.; Di Marco, S.; Baiocco, P.; Koch, U.; Migliaccio, G.; Altamura, S.; Laufer, R.; De Francesco, R.; Rowley, M. *J. Med. Chem.* **2011**, *54*, 289.

(17) (a) Agarwal, P.; Kudirka, R.; Albers, A. E.; Barfield, R. M.; de Hart, G. W.; Drake, P. M.; Jones, L. C.; Rabuka, D. *Bioconjugate Chem.* **2013**, *24*, 846. (b) Agarwal, P.; van der Weijden, J.; Sletten, E. M.; Rabuka, D.; Bertozzi, C. R. *Nat. Acad. Sci.* **2013**, *110*, 46.

(18) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. *J. Org. Chem.* **2012**, *77*, 3017.