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Indium(III) Chloride-Catalyzed Isocyanide Insertion Reaction to Construct Complex Spirooxindole

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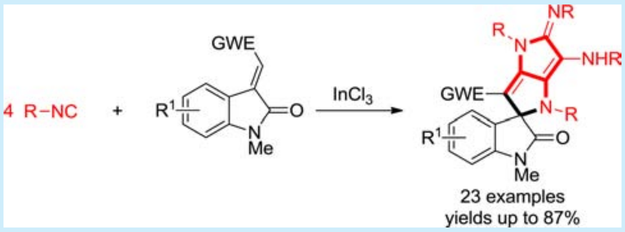
S *Supporting Information*

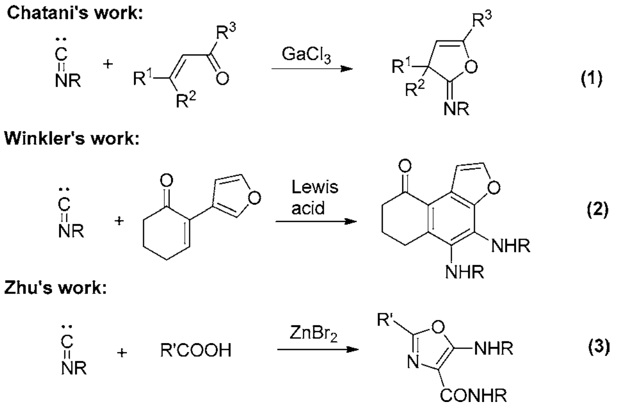
ABSTRACT: An unusual multiple isocyanide insertion reaction with methyleneindolinone using indium(III) chloride as the catalyst has been disclosed. This strategy allows for the rapid construction of structurally complex spirooxindole in an efficient manner. The present protocol features mild conditions, atom economy, and broad substrate scope.



23 examples
yields up to 87%

Isocyanides can serve as highly valuable and versatile C1 building blocks and have been extensively used in various carbon−carbon and carbon−heteroatom bond-forming reactions.[1,2] As such, transformations involving isocyanides have been well documented in the past decades.[3,4] Of note is the isocyanide insertion reaction, which has drawn much attention from the organic community.[5] The history of the isocyanide insertion reaction can be traced back to copper-catalyzed insertion of isocyanide into a series of nucleophiles by Saegusa and Ito.[6] Since then, gallium-,[7] palladium-,[8] aluminum-,[9] ruthenium-,[10] cobalt-,[11] and other metal-catalyzed[12] isocyanide insertions have been widely investigated. To date, the transition-metal-catalyzed and Lewis acid catalyzed isocyanide insertion reactions have become powerful tools in organic synthesis. Despite the achievements in transition-metal-catalyzed reactions, we were particularly interested in Lewis acid catalyzed isocyanide insertions. An extensive literature survey revealed that Lewis acid catalyzed single isocyanide insertion is most common, and numerous reports have been disclosed in this field. For instance, Chatani and co-workers discovered an efficient [4 + 1] cycloaddition reaction with α,β-unsaturated carbonyl compounds to prepare lactone derivatives (Scheme 1, eq 1).[7a,b] In contrast, double-isocyanide insertions are less common, and only a few examples have been reported. In 2006, Winkler and co-workers disclosed a Lewis acid catalyzed novel synthesis of the polycyclic ring using double-isocyanide insertion as the key step (Scheme 1, eqs 2).[13a] In addition, other components including epoxides and 2-ethynylanilines were also proven to be compatible in such transformations.[13b−d] Yet, to our knowledge, examples on Lewis acid catalyzed multiple isocyanide insertions are still very rare. In 2013, Zhu and co-workers reported that in the presence of zinc bromide, reactions of carboxylic acids and isocyanides efficiently afforded polysubstituted oxazoles through a triple-isocyanide insertion process (Scheme 1, eqs 3).[14] As a result, exploring the potential application of Lewis acid catalyzed multiple isocyanide insertion continues to be a challenging and valuable target.

Scheme 1. Lewis Acid Catalyzed Versatile Isocyanide Insertion Reactions



Spirocyclic oxindole represents a privileged synthetic motif that constitutes the core structures of many natural products and clinical pharmaceuticals.[15] In particular, these compounds have exhibited a broad range of biological activities including antitumor, insecticidal, and antibacterial properties.[16] Thus, many efforts have been devoted to the efficient synthesis of such skeletons in a chemo-, regio-, and stereocontrolled fashion.[17] Recently, we have spent much time developing isocyanide-based novel transformations,[18] which included the construction of functionalized spirooxindole from methyleneindolinone using a multicomponent strategy. Following these works, we became interested in exploring Lewis acid catalyzed insertion reactions between isocyanides and methyleneindolinones. As a continuation of our previous research, herein we

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report that methyleneindolinone undergoes an unusual multiple isocyanide insertion reaction to synthesize spirooxindole using indium chloride as catalyst.

We began our research by selecting 2,6-dimethylphenyl isocyanide **1a** and oxindolylideneacetate **2a** as model substrates. In the presence of $InCl_3$ (10 mol %), heating the mixture in toluene under reflux essentially gave rise to unknown compound **3a**. To our surprise, the ^1H NMR of **3a** clearly indicated that four isocyanides participated in the whole conversion. Pleasingly, the structure of compound **3a** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1).[19] Encouraged by this result, we sought to briefly optimize the reaction conditions by varying the solvent, the Lewis acid, and the temperature. The experimental outcome showed that lower yields were observed when reactions were performed in other solvents such as THF, dioxane, and CH_3CN (Table 1, entries 2–5). Notably, decreasing the temperature from reflux to 80 °C could increase the yield of **3a**, which was an extra bonus from the screening (Table 1, entry 6). Of the Lewis acids examined, AgOTf, $FeCl_3$, and $Pd(OAc)_2$ showed no catalytic activity toward the formation of **3a** (Table 1, entries 7, 10, and 12). The replacement of $InCl_3$ with other metal catalysts only led to decreased yields (Table 1, entries 8, 9, and 11).

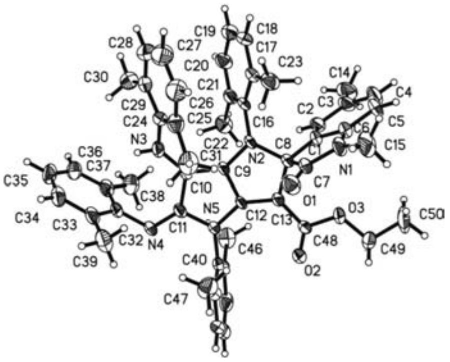
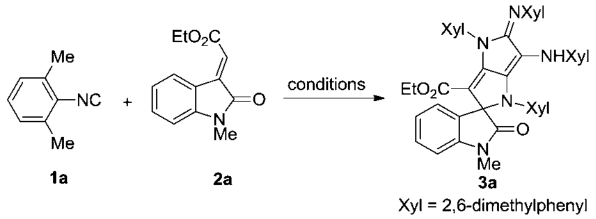


Figure 1. Single-crystal X-ray structure for **3a**.

Table 1. Optimization of Reaction Conditions[a]

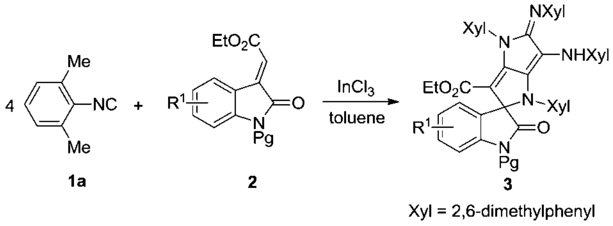


entry	catalyst	solvent	t (°C)	yield[b] (%)
1	$InCl_3$	toluene	reflux	71
2	$InCl_3$	THF	reflux	41
3	$InCl_3$	EtOH	reflux	50
4	$InCl_3$	dioxane	reflux	25
5	$InCl_3$	CH_3CN	reflux	trace
6	$InCl_3$	toluene	80	78
7	AgOTf	toluene	80	
8	$Zn(OTf)_2$	toluene	80	trace
9	$Yb(OTf)_3$	toluene	80	trace
10	$FeCl_3$	toluene	80	
11	$CuCl_2$	toluene	80	10
12	$Pd(OAc)_2$	toluene	80	

[a] Until otherwise noted, 10 mol % of catalyst was used. [b] Yield of product after silica gel chromatography.

After the optimal conditions were established, we then attempted to investigate the feasibility of electron-deficient component **2**. As shown in Table 2, oxindolylideneacetate **2** bearing electron-withdrawing (Table 2, entries 2–5) and electron-donating substituents (Table 2, entries 6 and 7) on the aromatic ring worked well under the standard conditions to afford the desired compounds **3**. All new compounds were characterized by ^1H NMR, ^{13}C NMR, and HRMS (see the Supporting Information for details). Experiments to check the influence of different protecting groups at the nitrogen atom of substrate **2** were subsequently conducted, which revealed that benzyl and acetyl groups were well tolerated under optimized conditions (Table 2, entries 8 and 9).

Table 2. Indium-Catalyzed Reaction of Isocyanide 1a and Oxindolylideneacetate 2[a]



entry	R^1	Pg	product	yield[b] (%)
1	H	Me	**3a**	78
2	5-fluoro	Me	**3b**	82
3	5-bromo	Me	**3c**	77
4	6-bromo	Me	**3d**	72
5	4-bromo	Me	**3e**	53
6	5-methyl	Me	**3f**	65
7	5-methoxyl	Me	**3g**	56
8	H	Bn	**3h**	75
9	H	Ac	**3i**	68

[a] All reactions were carried out with isocyanide **1a** (1.2 mmol), catalyst (10 mol %), and oxindolylideneacetate **2** (0.3 mmol) in 5 mL of toluene under 80 °C unless otherwise noted. [b] Yield of product after silica gel chromatography.

To further demonstrate the utility of the present reaction, reactions using arenacylideneoxindole **4** (derived from isatin and acetophenone) as the electron-deficient component were then performed. As shown in Table 3, a series of substrates **4** with different substituents on the aromatic ring bearing the carbonyl group were first employed to react with isocyanide **1a** (Table 3, entries 1–6). Gratifyingly, all reactions proceeded smoothly to produce the products **5**. Following these encouraging results, changing the substituents on the oxindole ring of arenacylideneoxindoles **4** was then examined (Table 3, entries 7–11), furnishing the corresponding adducts **5** in good performance. In view of the easy availability of methyleneindolinone, the present reaction is significantly distinguished by the broad substrate scope.

The mechanism of this unprecedented isocyanide insertion reaction has not been unequivocally established, but one reasonable mechanistic proposal is depicted in Scheme 2. The beginning of the cascade reaction involves the coordination of $InCl_3$ to the oxygen atom in methyleneindolinone **2** or **4**.[7] The more electrophilic β-carbon in **2** or **4** is then attacked by one

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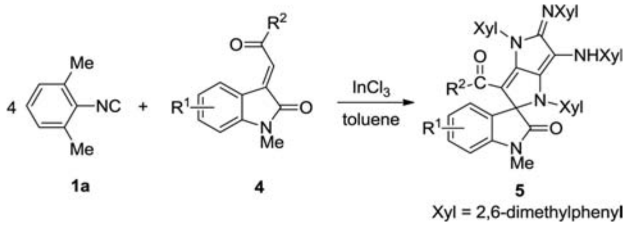
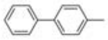
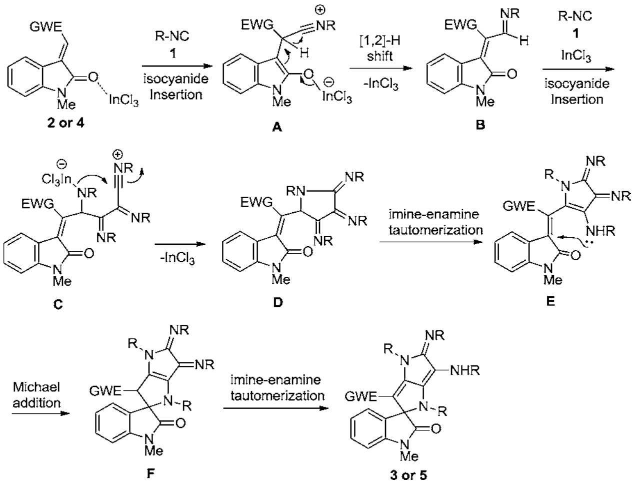
Table 3. Indium-Catalyzed Reaction of Isocyanide 1a and Arenacylideneoxindole 4[a]



entry	R^1	R^2	product	yield (%)[b]
1	H	C_6H_5	**5a**	57
2	H	4-ClC_6H_4	**5b**	58
3	H	3-ClC_6H_4	**5c**	51
4	H	4-BrC_6H_4	**5d**	68
5	H	3-$CH_3OC_6H_4$	**5e**	43
6	H		**5f**	47
7	5-fluoro	C_6H_5	**5g**	70
8	5-chloro	C_6H_5	**5h**	60
9	5-bromo	C_6H_5	**5i**	65
10	4-bromo	C_6H_5	**5j**	53
11	5-methyl	C_6H_5	**5k**	52

[a] Reaction conditions: isocyanide **1a** (1.2 mmol), catalyst (10 mol %), and arenacylideneoxindole **2** (0.3 mmol) in 5 mL of toluene, heated at 80 °C. [b] Yield of product after silica gel chromatography.

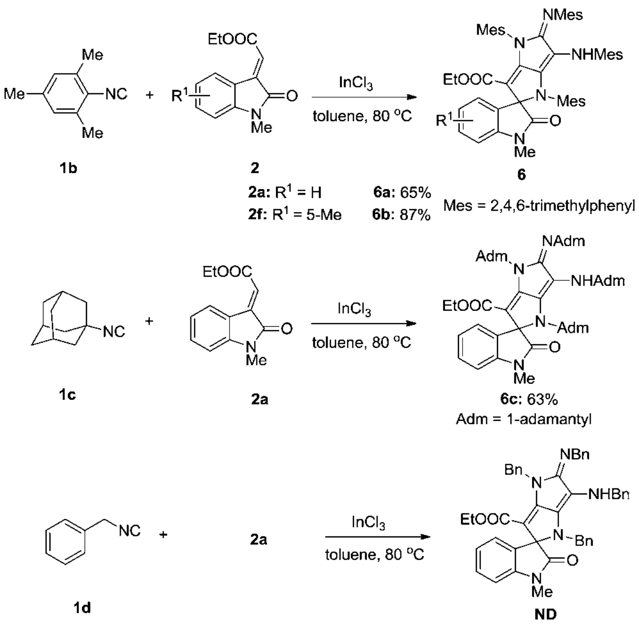
Scheme 2. Proposed Mechanism



molecular isocyanide **1** to form intermediate **A**. The following transformation involves an intramolecular [1,2]-H shift, which is accompanied by the delivery of $InCl_3$. Then $InCl_3$-mediated multiple insertion of isocyanides into imines occurs to produce intermediate **C**, which is believed to be the key step in whole transformation. The following intramolecular cyclization and isomerization essentially leads to the formation of intermediate **E** via **D**. Intermediate **E** undergoes Michael addition to afford **F**, thus furnishing the construction of the second ring. Finally, imine–enamine tautomerization[20] from **F** essentially yields product **3** or **5**.

To further explore the scope and limitation of the present reaction, several aliphatic and aromatic isocyanides **1** were used to experience the standard conditions. The experimental results showed that bulky isocyanides were particularly compatible in this reaction (Scheme 3). Notably, reactions between sterically hindered 2,4,6-trimethylphenyl isocyanide **1b** and methyleneindolinone **2** proceeded smoothly to afford **6a** and **6b** in good yields. Adamantyl isocyanide **1c** was also proven to be good partner in present transformation. Benzyl isocyanide **1d** was also used to experience the standard reaction conditions, yet no reaction occurred in such case.

Scheme 3. Controlled Experiments



In conclusion, we developed a novel multiple isocyanide insertion reaction with methyleneindolinone using indium chloride as the catalyst.[21] The present transformation comprises Michael addition, isocyanide insertion, cyclization, and sequential imine–enamine tautomerization. This reaction allowed for the construction of structurally complex spirooxindole in an efficient fashion. This protocol also features excellent atom economy, high synthetic efficiency, and mild conditions. As a result, the present reaction has the potential to be further applied in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02432.

Experimental procedures and full characterization of all compounds, spectral data, and ^1H and ^{13}C NMR spectra for all products (PDF)

X-ray crystal structure data for compound **3a**(CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent examples, see: (a) Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1293. (b) Buyck, T.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 11524. (c) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708. (d) Mampuys, P.; Zhu, Y.; Vlaar, T.; Ruijter, E.; Orru, R. V. A.; Maes, B. U. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 12849. (e) Basavanag, U. M. V.; Santos, A.; El Kaim, L.; Gámez-Montaño, R.; Grimaud, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 7194.

(2) For reviews, see: (a) *Multicomponent Reactions in Organic Synthesis*; Zhu, J., Wang, Q., Wang, M.-X., Eds.; Wiley-VCH: Weinheim, 2014. (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(3) For synthesis of heterocycles, see: (a) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094. (b) Liao, J.-Y.; Shao, P.-L.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137*, 628. (c) Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270. (d) Li, M.; Lv, X.-L.; Wen, L.-R.; Hu, Z.-Q. *Org. Lett.* **2013**, *15*, 1262. (e) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem. - Eur. J.* **2009**, *15*, 227.

(4) For construction of complex skeletons, see: (a) Janvier, P.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291. (b) Santra, S.; Andreana, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418. (c) Qiu, G.; He, Y.; Wu, J. *Chem. Commun.* **2012**, *48*, 3836. (d) Riva, R.; Banfi, L.; Basso, A.; Cerulli, V.; Guanti, G.; Pani, M. *J. Org. Chem.* **2010**, *75*, 5134. (e) Wang, X.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 1954.

(5) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257.

(6) (a) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Yoshioka, H. *Tetrahedron Lett.* **1966**, *7*, 6121. (b) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K. *J. Am. Chem. Soc.* **1967**, *89*, 2240. (c) Saegusa, T.; Ito, Y.; Kobayashi, S. *Tetrahedron Lett.* **1968**, *9*, 935. (d) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K. *Tetrahedron Lett.* **1967**, *8*, 521.

(7) (a) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812. (b) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. (c) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431. (d) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697.

(8) (a) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 13058. (b) Qiu, G.; Liu, G.; Pu, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 2903. (c) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496. (d) Wang, J.; Luo, S.; Huang, J.; Mao, T.; Zhu, Q. *Chem. - Eur. J.* **2014**, *20*, 11220.

(9) (a) Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741. (b) Tobisu, M.; Yamaguchi, S.; Chatani, N. *Org. Lett.* **2007**, *9*, 3351.

(10) (a) Jones, W. D.; Kosar, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 5640. (b) Hsu, G. C.; Kosar, W. P.; Jones, W. D. *Organometallics* **1994**, *13*, 385.

(11) (a) Zhu, T.-H.; Wang, S.-Y.; Tao, Y.-Q.; Wei, T.-Q.; Ji, S.-J. *Org. Lett.* **2014**, *16*, 1260. (b) Zhu, T.-H.; Wang, S.-Y.; Wei, T.-Q.; Ji, S.-J. *Adv. Synth. Catal.* **2015**, *357*, 823.

(12) (a) Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593. (b) Zhang, M.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 4498. (c) Lazar, M.; Angelici, R. J. *J. Am. Chem. Soc.* **2006**, *128*, 10613. (d) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286. (e) Bocarsly, J. R.; Floriani, C.; Chiesl-VIIIa, A.; Guastinis, C. *Organometallics* **1986**, *5*, 2380.

(13) (a) Winkler, J. D.; Asselin, S. M. *Org. Lett.* **2006**, *8*, 3975. (b) Bez, G.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991. (c) Kobiki, Y.; Kawaguchi, S.; Ogawa, A. *Org. Lett.* **2015**, *17*, 3490. (d) Gao, Q.; Zhou, P.; Liu, F.; Hao, W.-J.; Yao, C.; Jiang, B.; Tu, S.-J. *Chem. Commun.* **2015**, *51*, 9519.

(14) Odabachian, Y.; Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10878.

(15) For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (d) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

(16) (a) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573–3577. (b) Venkatesan, H.; Davis, M. C.; Altas, Y.; Liotta, D. C. *J. Org. Chem.* **2001**, *66*, 3653. (c) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (d) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, *2009*, 165.

(17) (a) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2013**, *15*, 5254. (b) Arai, T.; Ogawa, H.; Awata, A.; Sato, M.; Watabe, M.; Yamanaka, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 1595. (c) Han, Y.; Sheng, Y.-J.; Yan, C.-G. *Org. Lett.* **2014**, *16*, 2654. (d) Wang, C.-S.; Zhu, R.-Y.; Zheng, J.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2015**, *80*, 512.

(18) (a) Jia, S. L.; Su, S. K.; Li, C. J.; Jia, X. S.; Li, J. *Org. Lett.* **2014**, *16*, 5604. (b) Su, S. K.; Li, C. J.; Jia, X. S.; Li, J. *Chem. - Eur. J.* **2014**, *20*, 5905. (c) Li, J.; Su, S. K.; Huang, M. Y.; Song, B. Y.; Li, C. J.; Jia, X. S. *Chem. Commun.* **2013**, *49*, 10694. (d) Li, J.; Wang, N.; Li, C. J.; Jia, X. S. *Chem. - Eur. J.* **2012**, *18*, 9645. (e) Li, J.; Liu, Y. J.; Li, C. J.; Jia, X. S. *Chem. - Eur. J.* **2011**, *17*, 7409.

(19) CCDC 1413865 for compound **3a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) (a) Haibach, M. C.; Seidel, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 5010. (b) Alajarín, M.; Bonillo, B.; Ortín, M.-M.; Sánchez-Andrada, P.; Vidal, Á. *Org. Lett.* **2006**, *8*, 5645. (c) Alajarín, M.; Bonillo, B.; Sánchez-Andrada, P.; Vidal, Á. *J. Org. Chem.* **2010**, *75*, 3737.

(21) For a related multiple insertion of isocyanides with palladium complex, see: Tanase, T.; Ohizumi, T.; Kobayashi, K.; Yamamoto, Y. *Organometallics* **1996**, *15*, 3404.