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Synthesis of Substituted 3-Indolylimines and Indole-3-carboxaldehydes by Rhodium(II)-Catalyzed Annulation

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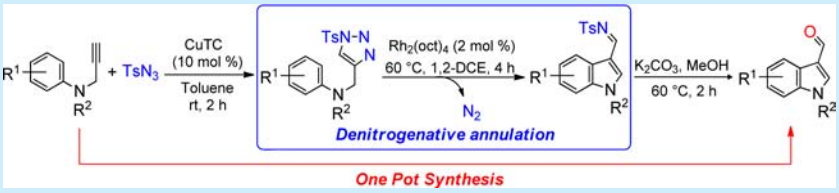
Supporting Information



ABSTRACT: An efficient Cu/Rh-catalyzed method is proposed for the synthesis of 3-indolylimines from *N*-propargylanilines through Rh(II)-catalyzed denitrogenative annulation of *N*-sulfonyl-1,2,3-triazoles. Further combined with hydrolysis or reduction, a one-pot method is developed to enable the direct incorporation of an imine, aldehyde, or amine group into an indole system from an alkyne. A variety of substituted 3-indolylimines, indole-3-carboxaldehydes, and 3-Indolylmethanamines are synthesized in good yields.

Substituted indoles are one of the most abundant and important natural heterocycles. This core alkaloid motif is a key component of a vast number of biologically active natural and synthetic compounds, e.g., serotonin, which is a simple neurotransmitter, and vincristine, which is used clinically in cancer therapy.[1] The naturally occurring amino acid tryptophan, which is a component of proteins in living systems and of many biologically vital natural products, contains the indole core system.[2] The indole skeleton is a pharmacophore in a wide range of medicinal compounds, and numerous drugs containing this skeleton have been reported, such as indomethacin, sumatriptan, tadalal, ondansetron, rizatriptan, and uvastatin.[3] For over 100 years, the prevalence of indole rings in bioactive natural products and pharmaceuticals has inspired chemists to develop the synthesis and functionalization of indoles.

Several classic synthetic strategies are available for the synthesis of indoles from different precursors.[4] The well-known Fischer indole synthesis from phenyl hydrazones,[5a] Bischler indole synthesis from α-bromoacetophenones and aniline,[5b] Hemetsberger indole synthesis by azirine-triggered electrocyclization from β-styryl azides,[5c] Bartoli indole synthesis from *ortho*-substituted nitroarenes and vinyl Grignard reagents,[5d] Leimgruber–Batcho indole synthesis using enamines,[5e] and Gassman indole synthesis[5f] are widely used in modern organic chemistry. Aryl isonitriles and nitrosoarenes are generally used as precursors in the synthesis of biologically interesting indoles.

To expand the range of substrates, transition-metal catalysis is a promising and efficient method in indole synthesis to tolerate a wide range of functionalities, making the synthesis applicable to complex molecules. The electrophilic activation of alkynes in the presence of late-transition-metal complexes is an attractive method of indole synthesis.[6] In recent decades, Pd complexes have proved to be promising catalysts in the construction and functionalization of indoles.[7] Moreover, the rapid growth of the use of Rh catalysts has provided various methods for the preparation of many functionalized, fused, and unusual architectures containing indole motifs.[8−15] Rh-catalyzed cycloisomerization of disubstituted alkynylanilines to indoles was developed by Trost et al.[8] Rh-catalyzed oxidative coupling of *N*-acetylanilines and alkynes was proposed by Fagnou.[9] Glorius et al. successfully used 2-acetyl-1-arylhydrazines as oxidation-directing agents to obtain various indoles.[10] The Rh-mediated formation of nitrenoids in the absence of arylamines has been reported to transform vinyl azides into indoles.[11] On the basis of the amino-Claisen rearrangement, Saito et al. converted *N*-propargylanilines to indoles using a Rh(I) catalyst.[12] However, the preparation of 3-imino- and 3-carboxaldehyde-substituted indoles by these well-established methods using Rh catalysts is still limited. Because the cyclization is usually mediated by highly reactive intermediates such as carbenes/nitrenes, allenes, and Rh-coordinated complexes, the presence of extra electrophilic groups in the structure may result in undesired side reactions.

Recently, metal-catalyzed transformations of *N*-sulfonyl-1,2,3-triazole rings via diazoimino intermediates have been reported. The use of Cu catalysts with these triazoles leads to the formation of ketenimine intermediates, which can be transformed into a range of heterocycles.[15] In a similar approach using Rh complexes as catalysts, Rh carbenoids are formed as the reactive intermediates in the direct denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazoles.[16] Rh carbenoids are versatile precursors, because their high electrophilicity and C–H insertion ability facilitate the production of

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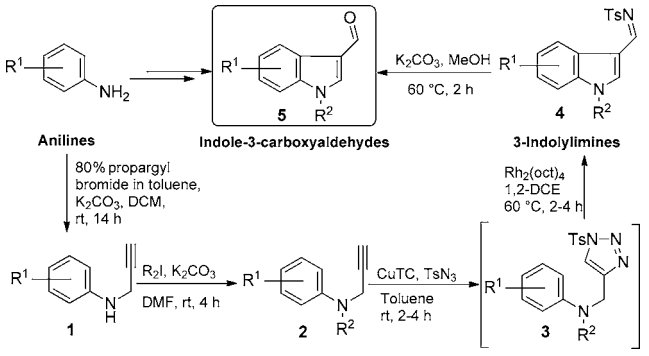
valuable nitrogen-containing heterocyclic compounds from 1,2,3-triazoles. Alford et al. used the denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazoles to convert cyclic ketones to 2,3-fused pyrroles and substituted indoles.[17] Inspired by the reported transformations and our previous work on the Cu(I)-catalyzed synthesis of dihydropyrimidinones,[18] in this research we developed a strategy for converting *N*-propargylanilines to functionalized indoles. The concept is based on the formation of the corresponding *N*-sulfonyl-1,2,3-traizole intermediate, followed by denitrogenative ring opening to form a reactive Rh carbenoid intermediate. The electrophilic property of the resulting Rh carbenoid enables subsequent cyclization, triggered by amino groups, via aromatic electrophilic addition.

As shown in Scheme 1, in the first step of the reaction sequence, substituted anilines were treated with propargyl

Scheme 1. Synthetic Design



bromide to provide *N*-propargylanilines. Conversion of the alkyne functional group to a stable *N*-sulfonyl-1,2,3-triazole was then achieved using tosyl azide (TsN_3) in the presence of copper thiophenecarboxylic acid (CuTC) as the catalyst. Without further purification, in one pot, a rhodium(II) octanoate catalyst was added to the reaction mixture. The desired 3-indolylsulfonylimine was formed, as shown in the X-ray ORTEP diagram (Figure 1). The sulfonylimine can be

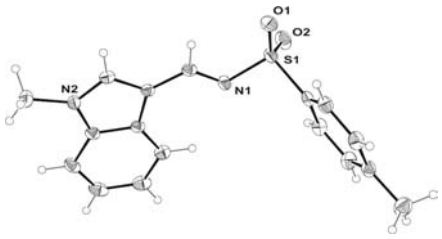
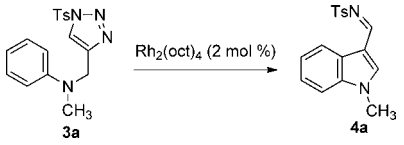


Figure 1. X-ray ORTEP diagram for compound **4a**.

easily hydrolyzed to an aldehyde, so our proposed method enables the cascade synthesis of the core indole unit and formylation at the C-3 position. The C-3-formylation of indoles is a key step in the preparation of biologically active natural products, including homofascaplysin C, FR-9004829 which is a mitomycin-like antitumor agent, and many indole alkaloids.[19a−c] Conventional syntheses of 3-formylindoles are achieved using Vilsmeier−Haack, Friedel−Crafts acylations and Reimer−Tiemann, Rieche, and Duff reactions, which generally require high temperatures and the use of excess strong bases or acids.[20] Because of the harsh reaction conditions, these methods are not appropriate for indoles with labile functional groups. Mild and operationally simple methods have therefore been developed for the formylation of Indoles. Wu et al. reported an efficient method for C-3 formylation of indoles using a Ru catalyst.[21] Recently, $^{n}Bu_4NI$-catalyzed C-3-selective formylation of N−H and N-substituted indoles, using *N*-methylaniline as the formylating reagent, was demonstrated.[22] As mentioned earlier, our proposed transformation of *N*-propargylanilines into C-3-functionalized indoles involves the use of benign reagents in catalytic amounts, providing an advantageous synthetic path.

After confirming formation of the expected product, we optimized the reaction conditions using different solvents and temperatures. *N*-Sulfonyl-1,2,3-triazole formation using CuTC and TsN_3 is well established,[23] so we focused on optimization of the reaction conditions in the triazole decomposition step; the results are summarized in Table 1. The expected

Table 1. Optimization of Conditions



entry	solvent	temp (°C)	time (h)	yield (%)
1	dichloromethane	40	24	NR
2	1,2-dichloroethane	rt	24	NR
3	1,2-dichloroethane	60	4	83
4	toluene	rt	24	NR
5	toluene	60	4	74
6	1,4-dioxane	60	4	68
7	acetonitrile	60	2	*a*

[a]Formation of multiple spots.

transformation was not observed at ambient temperature. However, the conversion was better when 1,2- dichloroethane (DCE) or toluene were used as the solvent with heating. DCE was found to be the optimal solvent for the reaction (entry 3). Conventional silica gel column chromatography cannot be used for the purification of the desired indoles, probably because the sulfonylimines have poor stabilities. However, precipitation purification using a cosolvent system (ethyl acetate in hexane) gave reasonably good results. Furthermore, we observed that the optimized conditions were suitable for performing the reaction on the gram scale (1.1 g of **3a** was converted to **4a** in 83% yield).

To expand the substrate scope, compounds with different substituents on the aromatic rings and amine groups were used under the optimized conditions, and the conversion efficiencies were determined. The electronic effects of the substituents on the benzene rings during cyclization were examined (Table 2). No significant differences were observed between the outcomes of the reaction using electron-donating groups (entries **4b** and **4c**) and electron-withdrawing halogens (entries **4d**−**4h**). The 4-nitro substituent gave good conversion, but the 3-nitro yield was very low (entry **4j**). It appears that an electron-withdrawing nitro group at the *meta* position of the aniline ring considerably reduces the aromatic electron nucleophilicity in attack of the Rh carbenoid intermediate, resulting in low conversion. The formation of two possible regioisomers was expected in the cases of **4e** and **4j**. In terms of regioselectivity, the cyclization site can be at the *ortho* or *para* position to the 3-substituent. However, the formation of single regioisomer with *para*

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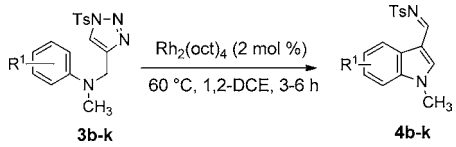
Table 2. Substrate Scope with Different R^1 Groups

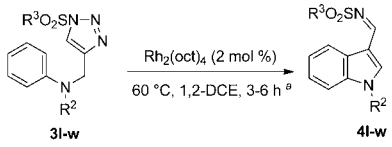


3b-k 4b-k

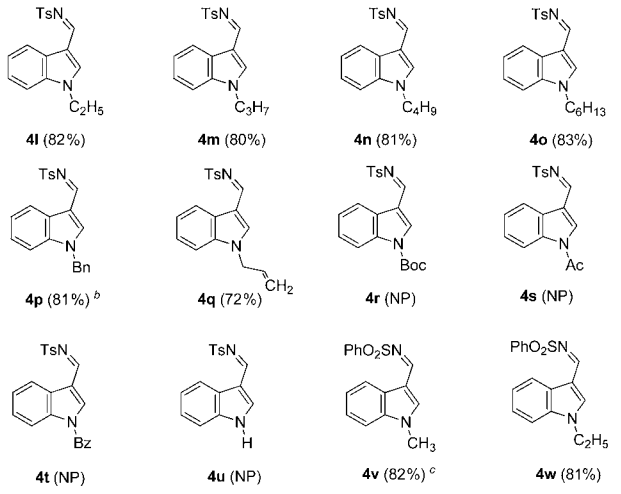
entry	R^1 (3b–k)	time (h)	product	R^1 (4b–k)	yield (%)
1	4-OMe	3	**4b**	5-OMe	87
2	4-^{n}Bu	4	**4c**	5-^{n}Bu	77
3	4-Cl	4	**4d**	5-Cl	82
4	3-Cl	4	**4e**	6-Cl	79
5	4-F	4	**4f**	5-F	74
6	4-Br	4	**4g**	5-Br	80
7	4-I	4	**4h**	5-I	85
8	4-NO_2	6	**4i**	5-NO_2	82
9	3-NO_2	4	**4j**	6-NO_2	25
10	2,3-(Naph)-	4	**4k**	6,7-(Naph)-	77

preference was observed. This specific regioselectivity is probably due to the contribution of the steric effect. A series of *N*-substituents were examined; *N*-alkyl groups (**4l**–**4o**) gave similar results. (Isolated yields 80–83%; Scheme 2) Two

Scheme 2. Substrate Scope Using Different R^2 and R^3 Groups



3l-w 4l-w

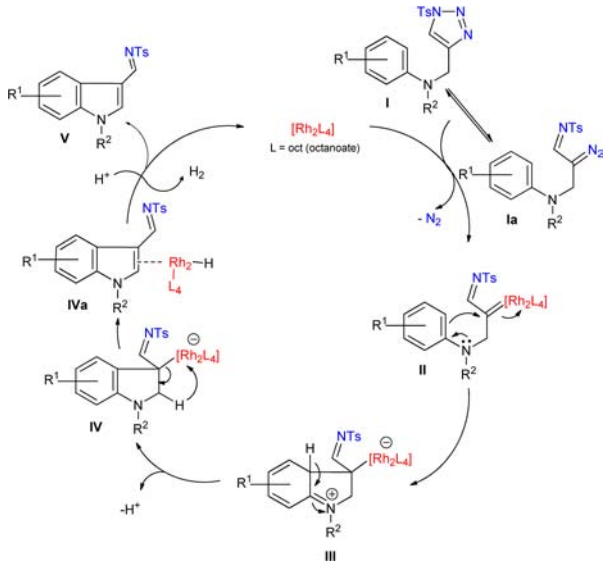


[a]General reaction time 4 h unless noted otherwise. [b]Reaction time 6 h. [c]Reaction time 3 h; NP = no product; multiple spots formation.

popular amine-protecting groups, benzyl and allyl, also gave reasonable yields (**4p**, 81% and **4q**, 72%). However, the desired product was not formed when the amino group was coupled with an electron-withdrawing group; a large number of inseparable products were obtained. Presumably, electron-withdrawing groups on the amino group significantly reduce the nucleophilicity of the nitrogen electron lone pair, resulting in formation of undesired side products from the Rh imino carbenoid intermediates instead of indoles (**4r**–**4t**). Similarly, the synthesis using an unprotected amine (**4u**) was unsuccessful because the Rh imino carbenoid intermediate could be attacked by the free amine intra- or intermolecularly, forming multiple reaction sites. To examine the use of other sulfonyl azides, benzenesulfonyl azide ($PhSO_2N_3$) was used instead of TsN_3. There were no obvious differences among the reaction outcomes (**4v** and **4w**), suggesting that there is scope for further functionalization.

Based on the product formation, a plausible mechanistic pathway is proposed in Scheme 3. Equilibrium is established

Scheme 3. Proposed Mechanistic Cycle



between the *N*-sulfony-1,2,3-triazole **I** and the iminodiazo species **Ia**. Treatment of the *N*-sulfony-1,2,3-triazole with the Rh catalyst generates the reactive Rh imino carbenoid **II**, with the release of molecular nitrogen. The Rh imino carbenoid is then attacked by the nearby aromatic π electrons, triggered by the nitrogen electron lone pair, to produce the cyclic intermediate **III**. A deprotonation step is driven by the reestablishment of aromaticity. The formed intermediate **IV** undergoes β-hydride elimination. In regeneration of the Rh(II) catalyst for the next catalytic cycle, the formation of a double bond furnishes the indole ring **V** with an *N*-sulfonyl imine at the 3-position.

To extend the functionality of indoles obtained by this method, the *N*-sulfonylimine group was converted to the corresponding aldehyde and amine in a one-pot, three-step synthesis. Hydrolysis of the sulfonyl imine using very mild conditions, i.e., K_2CO_3 and MeOH, efficiently afforded substituted 3-indolecarboxaldehydes. With reduced Cu(I) and Rh(II) catalyst loadings, in the absence of bases, tandem reactions were performed sequentially in one pot, giving indole-3-carboxaldehydes from propargylanilines in three steps.[24] The reaction yields were reasonably good (62–72%; Scheme 4). The selective reduction of the sulfonylimine group provided an alternative C-3 functionalization of indoles. Use of standard methods for hydrogenation reduction, such as $NaBH_4$ and Pd on charcoal, provided the desired C-3-amine-functionalized indoles in good overall yields.

In summary, we have developed a new synthetic method for the preparation of C-3-functionalized indoles from propargylanilines and TsN_3, using Cu(I) and Rh(II) catalysts. The developed method uses mild conditions that are efficient and easy to perform. This method combines key indole formation

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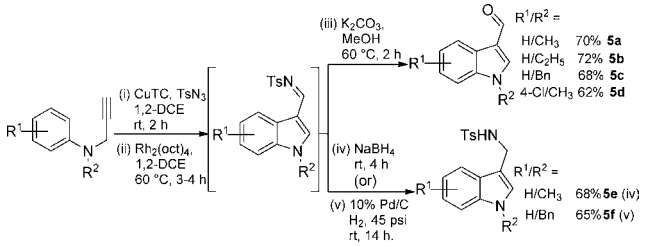
Scheme 4. One-Pot Synthesis of Substituted Indole-3-carboxaldehydes and 3-Indoylimines from Alkynylanilines



and the introduction of a formyl group from easily available *N*-propargylanilines. To the best of our knowledge, this is the first reported one-pot method that enables the direct incorporation of an aldehyde or amine group into an indole system obtained from an alkyne. Indoles are important in medicinal chemistry, and we believe that this method is an attractive option for the construction of molecular libraries for diversity-oriented synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. 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) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (c) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620. (d) Shirinzadeh, H.; Eren, B.; Orhan, H. G.; Suzen, S.; Ozden, S. *Molecules* **2010**, *15*, 2187. (e) Barden, T. C. *Top. Heterocycl. Chem.* **2011**, *26*, 31.

(2) (a) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (b) Biswal, S.; Sahoo, U.; Sethy, S.; Kumar, H. K. S.; Banerjee, M. *Asian J. Pharm. Clin. Res.* **2012**, *5*, 1.

(3) (a) Saxton, J. E. Monoterpenoid indole alkaloids. In *The Chemistry of Heterocyclic Compounds Part 4*; John Wiley & Sons: Hoboken, NJ, 2008. (b) Mehta, R. G.; Liu, J.; Constantinou, A.; Thomas, C. F.; Hawthorne, M.; You, M.; Gerhüser, C.; Pezzuto, J. M.; Moon, R. C.; Moriarty, R. M. *Carcinogenesis* **1995**, *16*, 399. (c) Ferreira, S.; Moncada, S.; Vane, J. *Nat. New Biol.* **1971**, *231*, 237. (d) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761.

(4) For recent reviews of indole synthesis, see: (a) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (c) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195.

(5) (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 373. (b) Bischler, A. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2860. (c) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194. (d) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991**, 651. (e) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214. (f) Gasman, P. G.; Van Bergen, T. J.; Gruetzmacher, O. G. *J. Am. Chem. Soc.* **1973**, *95*, 6508.

(6) (a) Kruger, K.; Tillack, A.; Bellera, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (b) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (c) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844.

(7) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873 and references therein.

(8) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074.

(9) (a) Stuart, D. R.; Laperle, M. B.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (b) Kim, M.; Park, J.; Sharma, S.; Han, S.; Han, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2013**, *11*, 7427.

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

(11) Jones, C.; Nguyen, Q.; Driver, T. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 785.

(12) Saito, A.; Oda, S.; Fukaya, H.; Hanzawa, Y. *J. Org. Chem.* **2009**, *74*, 1517.

(13) Dawande, S. G.; Kanchupalli, V.; Kalepu, J.; Chennamsetti, H.; Lad, B. S.; Katukojvala, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 1.

(14) Zhang, G.; Yu, H.; Qin, G.; Huang, H. *Chem. Commun.* **2014**, *50*, 4331.

(15) Kim, S. H.; Park, S. H.; Choi, J. H.; Chang, S. *Chem.—Asian J.* **2011**, *6*, 2618 and references therein.

(16) (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (c) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (d) Selander, N.; Worrell, B. T.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 13054.

(17) Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 11712.

(18) Rajagopal, B.; Chen, Y.-Y.; Chen, C.-C.; Liu, X.-Y.; Wang, H.-R.; Lin, P.-C. *J. Org. Chem.* **2014**, *79*, 1254.

(19) (a) Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636. (b) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083. (c) Coldham, I.; Dobson, B. C.; Fletcher, S. R.; Franklin, A. I. *Eur. J. Org. Chem.* **2007**, 2676.

(20) (a) Coldham, I.; Dobson, B. C.; Fletcher, S. R.; Franklin, A. I. *Eur. J. Org. Chem.* **2007**, 2676. (b) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287. (c) Rodriguez, J. G.; Lafuente, A.; Almaraz, P. G. *J. Heterocycl. Chem.* **2000**, *37*, 1281.

(21) Wu, W.; Su, W. *J. Am. Chem. Soc.* **2011**, *133*, 11924.

(22) Li, L.-T.; Huang, J.; Li, H.-Y.; Wen, L.-J.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 5187.

(23) (a) Raushel, J.; Fokin, V. V. *Org. Lett.* **2010**, *12*, 4952. (b) Yang, Y.-L.; Rajagopal, B.; Liang, C.-F.; Chen, C.-C.; Lai, H.-P.; Chou, C.-H.; Lee, Y.-P.; Yang, Y.-L.; Zeng, J.-W.; Ou, C.-L.; Lin, P.-C. *Tetrahedron* **2013**, *69*, 2640.

(24) Zhang, L.; Sonaglia, L.; Stacey, J.; Lautens, M. *Org. Lett.* **2013**, *15*, 2128.