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Rhodium Catalyzed Cyanation of Chelation Assisted C−H Bonds

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ABSTRACT

A rhodium-catalyzed cyanation of chelation assisted C−H bonds is described employing *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide as an efficient cyanating reagent. The present method allowed the synthesis of various benzonitirle derivatives in good to excellent yield. A number of chelating groups are also effective in the present cyanation of C−H bonds. In addition, the developed methodology was applied in the formal synthesis of the isoquinoline alkaloid, menisporphine.

Benzonitriles (cyanoarenes) are frequently encountered in both nature and industry, as natural product subunits and as an integral part of herbicides, agrochemicals, pharmaceuticals, natural products, and dyes, respectively.[1] In organic synthesis, cyano functionality serves as a valuable intermediate, which can be readily diversified into various important functionalized products, such as benzoic acid derivatives, aldehydes, amines, heterocycles, etc. Traditionally, direct cyanations were achieved through stoichiometric strategies; this includes the Rosenmund–von Braun reaction[2] and Sandmeyer reaction.[3] In recent decades these methods have been replaced with the transition metal catalyzed cyanation of aryl halides or its equivalents with various nucleophilic cyanating reagents.[4] Nonetheless, general problems in these reactions are the use of expensive aryl halides, highly toxic cyanating reagents, high catalyst loading due to the cyanide poisoning or need for superstoichiometric amounts of additives (generally metal salts), and harsh reaction conditions (Scheme 1).

Selective cyanation of highly abundant C−H bonds with a suitable reagent is probably the most economic and benign route to the synthesis of benzonitrile derivatives. Representative examples on the cyanation of C−H bonds include palladium catalyzed and copper mediated cyanation of directing group assisted C−H cyanation employing nitromethane,[5] DMF/NH_3,[6] and DMF[7] as a "CN" source (Scheme 1).[8] However, these reactions also suffer from the high catalyst loading and need for excess oxidant; thus the development of a corresponding catalytic transformation is highly desirable. Based on the requirement of catalytic cyanation of C−H bonds and inspired by the recent development in the rhodium catalyzed selective functionalization of C−H bonds of various arene derivatives,[9] we herein disclose the rhodium-catalyzed cyanation of chelation assisted C−H bonds.

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: Weinheim, 1989; p 819. (b) Grundmann, C. In *Houben-Weyl: Methoden der Organischen Chemie*, Vol. E5, 4th ed.; Falbe, J., Ed.; Thieme: Stuttgart, 1985; p 1313.

(2) (a) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 1749–1756. (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(3) (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. (b) Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovskii, P. V. *J. Organomet. Chem.* **2004**, *689*, 3810.

(4) For a review on transition metal catalyzed cyanations, see: (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, *2003*, 3513. (c) Schareina, T.; Zapf, A.; Cotte, A.; Muller, N.; Beller, M. *Synthesis* **2008**, *2008*, 3351. (d) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (e) Kim, J.; Kim, H. J.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11948.

(5) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(6) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.

(7) Ding, S.; Jiao, N. *J. Am. Chem. Soc.* **2011**, *133*, 12374.

(8) (a) Jia, X.; Yang, D.; Wang, W.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470. (b) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (c) Xu, H.; Liu, P.-T.; Li, Y.-H.; Han, F.-S. *Org. Lett.* **2013**, *15*, 3354.

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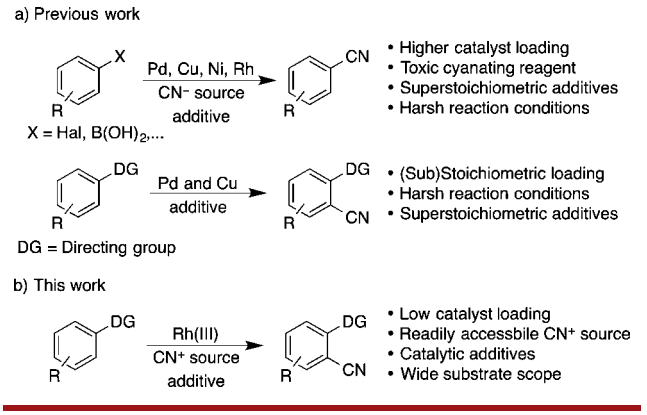
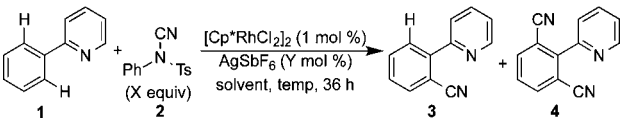
Scheme 1. Different Approaches to the Synthesis of Benzonitrile Derivatives



At the start of our investigation, rhodium catalyzed C−H cyanation of 2-phenyl pyridine was examined with various commercially available and readily accessible electrophilic cyanating reagents to afford the 2-(2-pyridyl)benzonitriles. Interestingly, reaction of 2-phenyl pyridine **1** with $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (40 mol %) in chloroform at 70 °C utilizing *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide **2** (NCTS, 3 equiv),[10] an environmentally benign electrophilic cyanating reagent,[11] only provided the expected product in isolable yield. Having found the target reaction, various other parameters were screened to find the optimized reaction conditions (Table 1).

No reaction was observed when the reaction was performed without either a rhodium catalyst or silver salt. This proves that the present reaction was indeed catalyzed by a rhodium catalyst. Next, increasing the reaction temperature (70 to 120 °C) with 1,2-DCE and toluene as solvent gave a higher conversion and higher yield of **3**; however, a further increase in temperature with xylene did not show a similar trend (Table 1, entries 1−5). In all these reactions, the formation of a precipitate was observed from the homogeneous reaction mixture; we anticipated that might be the cause for the low conversion and yield. Various attempts to isolate and characterize the solid formed were unsuccessful. Furthermore, use of a coadditive such as potassium carbonate also did not improve the yield of the reaction; instead a decrease in the reaction conversion was observed (Table 1, entry 6).

Table 1. Rhodium Catalyzed Cyanation of 2-Phenylpyridine **1**: Optimization[a]



entry	X	Y	solvent	temp (°C)	conversion (%)[b]	yield (%)[c]	ratio[d] **3**:**4**
1	3	40	$CHCl_3$	70	–[e]	22	–[e]
2	3	40	1,2-DCE	90	–[e]	24	–[e]
3	3	40	toluene	100	–[e]	32	–[e]
4	3	40	toluene	120	99	53	4:1
5	3	40	xylene	140	83	38	–[e]
6[f]	3	40	toluene	120	41	30	–[e]
7	1.5	40	toluene	120	96	67	12:1
8	1.5	20	toluene	120	82	73	10:1
9	1.5	10	toluene	120	73	68	9:1
10	2	10	toluene	120	99	91	12:1
11	2	10[g]	toluene	120	99	92	7:1
12	2	10[h]	toluene	120	0	0	0

[a] Reaction conditions: 2-Phenylpyridine (1 equiv), NCTS (*X* equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (Y mol %), solvent (2 mL), temp, 24−36 h. [b] Based on the recovered starting material. [c] Combined isolated yield of **3** and **4**. [d] Based on the isolated product. [e] Not determined. [f] In presence of 2 equiv of K_2CO_3. [g] $AgClO_4$ was used. [h] $NaBF_4$ was used.

Keeping the optimal reaction temperature as 120 °C and solvent as toluene, the influence of equivalents of cyanating reagents and $AgSbF_6$ were studied. Decreasing the equivalents of cyanating reagents to 1.5 equiv and screening the mol % of $AgSbF_6$ (40, 20, and 10 mol %) gave only a marginal change in the selectivity toward the formation of monocyanated products (~10:1), while the overall conversion of the reaction was decreased (Table 1, entires 7−9). Next, a slight increase in the equivalents of the cyanating reagent from 1.5 to 2 equiv gave the best conversion and yield (> 99% and 91%, respectively), where the turnover number of the catalyst is ~50, based on the isolated yield of the product (Table 1, entry 10). The change of the Ag salt to $AgClO_4$ also gave a similar result, while $NaBF_4$ completely ceased the reaction (Table 1, entries 11 and 12). The optimized reaction conditions included NCTS (2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (10 mol %), toluene, 120 °C, and 36 h.

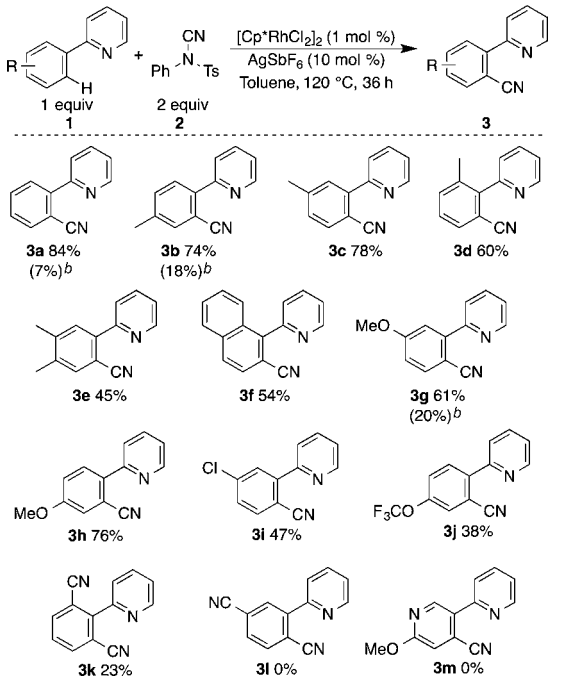
Next, the scope and limitation of aryl groups and chelating groups were investigated. As can be seen in Scheme 2, various substitutions are tolerated under the present rhodium catalyzed cyanation reaction. Alkyl substituted phenyl ring

(9) For reviews on rhodium catalyzed C−H functionalizations, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2009**, *110*, 624. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (d) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2011**, *45*, 814. (e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. For recent examples on rhodium catalyzed C−H functionalization of 2-phenyl pyridine derivatives, see: (f) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706. (g) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869. (h) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014. (i) Schroder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (j) Li, Y.; Zhang, X.-S.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2012**, *14*, 4498. (k) Kwak, J.; Ohk, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 17778. (l) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (m) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (n) Mizuno, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 1251. (o) Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310.

(10) (a) Kurzer, F. *J. Chem. Soc.* **1949**, 1034. (b) Kurzer, F. *J. Chem. Soc.* **1949**, 3029.

(11) (a) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *50*, 519. (b) Anbarasan, P.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 4217. (c) Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5608. During the preparation of this manuscript, Fu et al. reported Rh(III)-catalyzed C−H cyanation of oxime derivatives using NCTS. The author also showed C−H cyanation of 2-phenylpyridine as a substrate; see: Gong, T.-J.; Xiao, B.; Cheng, W.-M.; Su, W.; Xu, J.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630.

Scheme 2. Rhodium(III) Catalyzed Cyanation of 2-Arylpyridine Derivatives with NCTS[a]

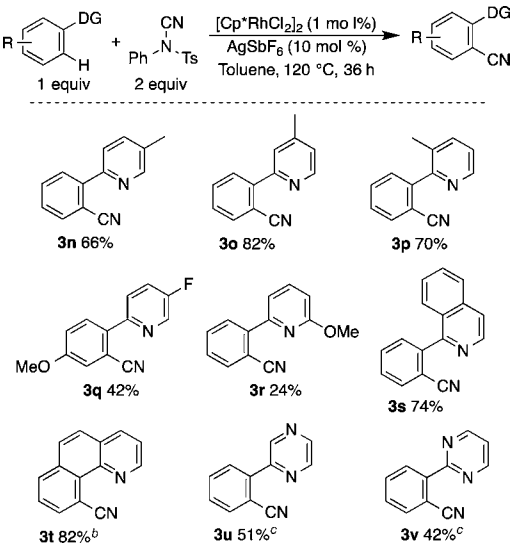


[a] Reaction conditions: 2-Arylpyridine (1 equiv), NCTS (2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (10 mol %), toluene (2 mL), 120 °C, 36 h. All are isolated yields. [b] Isolated yield of dicyano derivative.

gave the corresponding cyanated products (**3a**–**e**) in good to excellent yield, irrespective of its position in the phenyl ring (*ortho*, *meta*, and *para*). Sterically hindered substrates (2-methylphenyl and 1-naphthyl substituted pyridine **3d** and **3f**) also underwent a smooth reaction under the optimized conditions. *meta*-Methoxy substituted phenyl substrates, an electron-donating group containing arenes, gave the corresponding cyanated products **3g** in good yield along with the dicyano derivative. In general, formation of a dicyano derivative was observed for electron-rich arene substituted 2-aryl pyridine derivatives. Interestingly, an electron-withdrawing group containing an arene (*p*-OMe, *m*-Cl, *p*-OCF_3, and *o*-CN) also afforded the expected product (**3h**–**k**) with good to moderate yield. Substrates (**3l**–**m**) having an additional coordination site, such as cyanide, pyridine did not undergo the expected cyanation reaction, and all the starting materials were recovered.[9m]

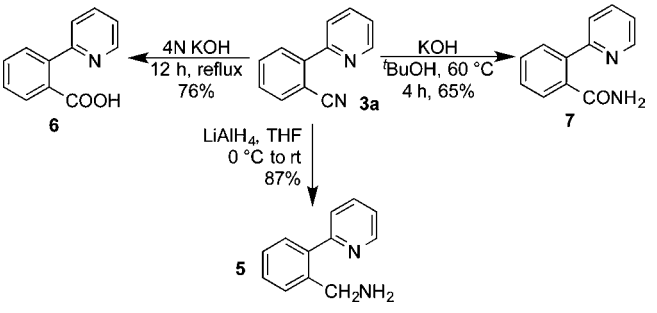
Subsequently, the screening of various nitrogen based chelating groups was also examined under the optimized rhodium catalyzed cyanation conditions (Scheme 3). Both electron-donating and -withdrawing group substitution on the pyridine ring in 2-phenyl pyridine furnished the corresponding cyanated product (**3n**–**s**) in moderate to excellent yield. Substitution at the third and sixth positions of the pyridine gave a lower yield of cyanated product compared to the substitution at the fourth and fifth positions, presumably due to the steric effect. Instead of simple 2-phenyl pyridine, cyanation of 2-phenylisoquinoline and 7,8-benzoquinoline also afforded the products **3s** and **3t** in 74% and 82% yield, respectively. Furthermore, the change of pyridine to other heterocyclic system, such as pyrazine and pyrimidine as chelating groups, also gave the cyanated product (**3u** and **3v**) in good yield.

Scheme 3. Rhodium(III) Catalyzed Cyanation of C–H Bonds: Scope and Limitation of Chelating Group[a]



[a] Reaction conditions: Arene (1 equiv), NCTS (2 equiv), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (10 mol %), toluene (2 mL), 120 °C, 36 h. [b] 48 h. [c] 2 mol % of catalyst.

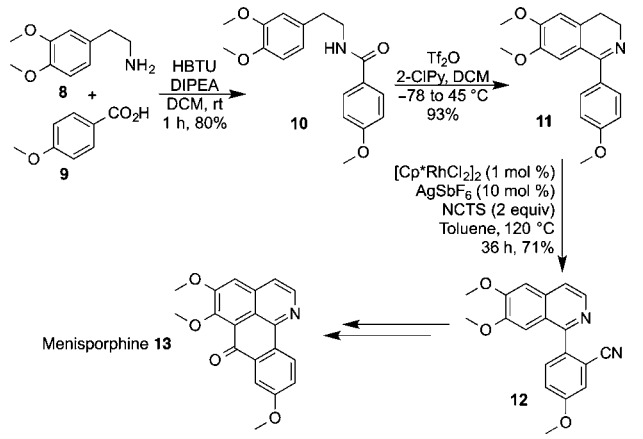
Scheme 4. Synthetic Utility of Benzonitriles



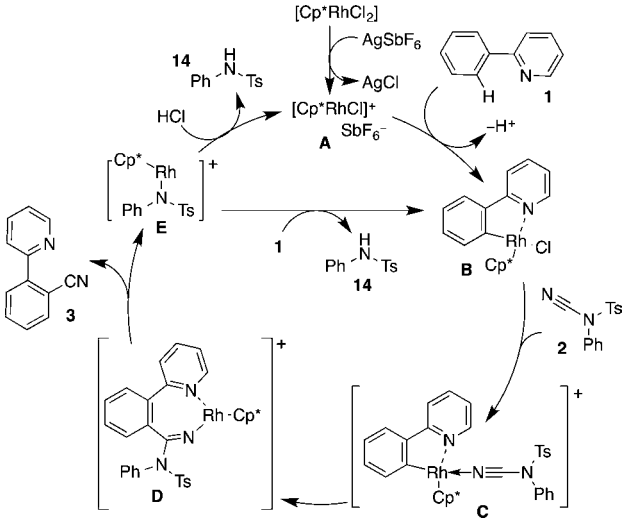
After the scope of arenes and chelating groups was revealed, the utility of the nitrile group was demonstrated by the transformation into various carboxylic acid derivatives and amines. The reduction of a nitrile group in **3a** with lithium aluminum hydride (LAH) afforded benzylamine derivative **5** in excellent yield (Scheme 4). Successively, benzoic acid derivative **6** was achieved in 76% yield through the hydrolysis of nitrile under basic conditions. Furthermore, hydration of nitrile **3a** to corresponding primary amide **7** was achieved on reaction with potassium hydroxide and *tert*-butanol at 60 °C in good yield.

In addition to the elegant conversion of the nitrile group into various functionalities, the key intermediate **12** for the synthesis of menisporphine **13**[12] was synthesized to

Scheme 5. Application of Rhodium Catalyzed Cyanation in the Synthesis of Intermediate for Construction of Menisporphine



Scheme 6. Plausible Mechanism for the Rhodium-Catalyzed Cyanation of C−H Bonds



demonstrate the potential of the present methodology (Scheme 5). Menisporphine **13** is a naturally available alkaloid, isolated from *Menispermum dauricum DC* (Menispermaceae)[13] and shown to possess cytotoxic activity.[14] Structurally menisporphine possesses a unique 7*H*-dibenzo[*de*,*h*]quinolone skeleton, which can be readily accessed from the key intermediate **12**. Synthesis of appropriate precursor **11** for the synthesis of intermediate **12** was achieved in two steps from 3,4-dimethoxyphenylethylamine **8** and 4-methoxybenzoic acid **9** through amide coupling and a cyclization sequence with an overall yield of 75%. Subsequently, the reaction of cyclized product **11** with NCTS under optimized conditions underwent cyanation followed by successive oxidation to afford the key intermediate **12** in 71% yield.

On the basis of previous reports on the rhodium(III)-catalyzed C−H functionalization of 2-phenylpyridine and related compounds,[15] we postulate the following mechanism for the rhodium(III)-catalyzed cyanation of chelation assisted C−H bonds (Scheme 6). Initially, treatment of a rhodium precursor with $AgSbF_6$ generates the reactive cationic rhodium(III) species **A**, which on reaction with **1** affords the cyclic rhodium species **B** through C−H functionalization. Coordination of NCTS **2** with **B** would form the rhodium species **C**. The formation of **D** could be readily envisioned through transfer of the aryl motif to the nitrile carbon atom of the cyanating reagent. Rearrangement of **D** affords the required cyanated product along with the reactive rhodium species **E**. Finally, ligand exchange will furnish the active rhodium species **A** to complete the catalytic cycle. On the other hand, rhodium species **E** can also react directly with **1** to form the cyclic rhodium species **B** to continue the catalytic cycle.

In conclusion, we have demonstrated the direct rhodium catalyzed cyanation of chelation assisted C−H bonds. The use of readily accessible and environmentally benign *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS, **2**) as a cyanating reagent allowed the synthesis of various aryl nitriles having different functional groups from corresponding arenes in good to excellent yield under mild conditions. In addition to the normal pyridine derivative, isoquinoline, benzoquinoline, pyrazine, and pyrimidines were readily employed as a chelating group in the present cyanation reactions. The potential of the developed methodology was further demonstrated by synthesizing the key intermediate for the synthesis of menisporphine **13**, an alkaloid possessing cytotoxic activity.

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Supporting Information Available. Experimental methods, characterizations data, and ^1H and ^{13}C NMR spectra of isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) (a) Kunitomo, J.-I.; Satoh, M. *Chem. Pharm. Bull.* **1982**, *30*, 2659. (b) Kunitomo, J.; Satoh, M.; Shingu, T. *Tetrahedron* **1983**, *39*, 3261.

(13) (a) Kunitomo, J.-I.; Kaede, S.; Satoh, M. *Chem. Pharm. Bull.* **1985**, *33*, 2778. (b) Takani, M.; Takasu, Y.; Takahashi, K. *Chem. Pharm. Bull.* **1983**, *31*, 3091.

(14) (a) Hu, S. M.; Xu, S. X.; Yao, X. S.; Cui, C. B.; Tezuka, Y.; Kikuchi, T. *Chem. Pharm. Bull.* **1993**, *41*, 1866. (b) Yu, B.-W.; Meng, L.-H.; Chen, J.-Y.; Zhou, T.-X.; Cheng, K.-F.; Ding, J.; Qin, G.-W. *J. Nat. Prod.* **2001**, *64*, 968.

(15) (a) Brasse, M. l.; Campora, J.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 6427. (b) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (c) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482.