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Palladium-Catalyzed Debenzylative Cross-Coupling of Aryl Benzyl Sulfides with Aryl Bromides: Synthesis of Diaryl Sulfides

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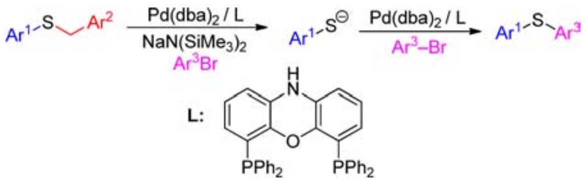
Ⓢ *Supporting Information*

ABSTRACT: A novel debenzylative approach to synthesize diaryl sulfides from aryl benzyl sulfides and aryl bromides in good to excellent yields is reported. Mechanistic studies suggest a single catalyst, derived from Pd(dba)$_2$ and NiXantPhos, efficiently catalyzes α-arylation of sulfides, C−S bond cleavage, and C−S bond formation in a tricatalytic cycle.

Novel metal-catalyzed approaches to break and form carbon−heteroatom bonds provide opportunities to develop new methods and to expand chemists' synthetic repertoire.[1] Along these lines, tandem reactions combining liberation of reactive intermediates and their direct functionalization can streamline classical deprotection−isolation−reaction sequences. Herein, we described an unprecedented approach to synthesize diaryl sulfides from aryl benzyl sulfides and aryl bromides via a tandem palladium-catalyzed S−C(sp^3) bond cleavage/S−C(sp^2) bond formation (Scheme 1).

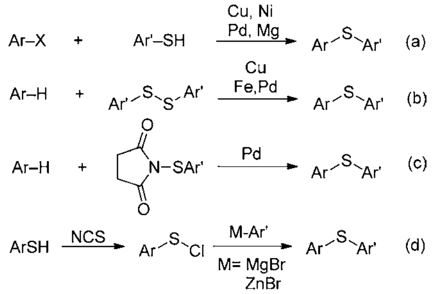
Scheme 1. Diaryl Sulfide Synthesis from Benzyl Aryl Sulfides



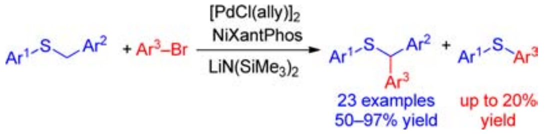
Diaryl sulfides are important scaffolds in natural products,[2] material chemistry,[3] and pharmaceuticals.[4] They have been widely applied as intermediates in organic chemistry.[5] Recently, diaryl sulfides have also found applications as ligands in transition metal catalyzed reactions.[6] Not surprisingly, their synthesis has attracted significant interest.

Recent approaches to construct C−S bonds in diaryl sulfides are generally mediated by transition metals.[7] These reactions fall primarily into four categories (Scheme 2): (a) transition metal catalyzed C−S cross-coupling of thiols with aryl halides and related compounds;[8] (b) transition metal catalyzed direct arylthiolation of C−H bonds employing diaryl disulfides as the thiolating reagents;[9] (c) direct thiolation employing other sulfurating agents, such as *N*-phenylthiosuccinimide;[10] or (d) cross-coupling reactions between sulfenyl chlorides and Grignard or organozinc reagents (Scheme 2d).[11] These approaches use odoriferous starting materials, have a narrow substrate scope, or use exotic sulfurating agents.

Scheme 2. Transition Metal Catalyzed Syntheses of Diaryl Sulfides



Scheme 3. Diarylmethyl Aryl Sulfide Synthesis from Benzyl Aryl Sulfides



Recently, our group initiated a program to arylate weakly acidic C$_{sp^3}$−H bonds via deprotonative cross-coupling processes (DCCP). Current substrates for this approach include diarylmethanes,[12] sulfoxides,[13] sulfones,[14] amides,[15] benzyl phosphine oxides,[16] phosphonates,[17] and benzoxazoles.[18] During our study of the Pd-catalyzed room temperature benzylic arylation of benzyl thioethers[19] (Scheme 3) using van Leeuwen's NiXantPhos ligand[20] (Scheme 1), we

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noticed a diaryl sulfide byproduct was typically generated in trace amounts but was observed in up to 20% yield under more forcing conditions. We decided to optimize this novel debenzylative cross-coupling route to diaryl sulfides.

As a starting point for the debenzylative coupling with 4-tolyl benzyl thioether **1a** and 4-*tert*-butyl bromobenzene (**2a**), we chose $Pd(OAc)_2$/NiXantPhos as the catalyst and cyclopentyl methyl ether (CPME) as the solvent. We screened five different bases [LiO*t*Bu, NaO*t*Bu, KO*t*Bu, $LiN(SiMe_3)_2$, and $NaN(SiMe_3)_2$] at 80 °C for 12 h (Table 1, entries 1−5). This screen led to the identification of $NaN(SiMe_3)_2$ as the lead base, generating the diaryl sulfide **3a** in 67% yield. Other bases either did not promote the transformation (LiO*t*Bu and NaO*t*Bu, entries 1 and 2) or gave low yields of **3a** [KO*t*Bu, and $LiN(SiMe_3)_2$, entries 3 and 4]. We next screened three ethereal solvents [DME (dimethoxyethane), THF, and dioxane] with the lead base, $NaN(SiMe_3)_2$. Unfortunately these solvents led to lower yields of the diaryl sulfide **3a** (26−60%) relative to CPME (entries 5 vs 6−8). CPME was then used to probe the impact of reagent and substrate stoichiometry on the reaction yield. Decreasing the loading of $NaN(SiMe_3)_2$ from 4 to 3 equiv resulted in an increase in the yield of **3a** (74%, entry 9). Decreasing aryl bromide **2a** to 2 equiv improved the yield of **3a** (78%, entry 10). Further lowering the base to 2 equiv, however, had a detrimental impact on the yield (55%, entry 11). Increasing the palladium loading to 5 mol % had no obvious effect on yield (entry 12). Surprisingly, lowering the Pd loading to 1 mol % led to a 77% yield of **3a** (entry 13). Palladium sources $[Pd(OAc)_2$ vs $Pd_2(dba)_3$, $[PdCl(ally)]_2$, and $Pd(dba)_2]$ were also examined, and $Pd(dba)_2$ gave the highest yield of **3a** (80%, entry 16 vs entries 13−15). Therefore, our optimized conditions are 1 equiv of thioether **1a**, 2 equiv of aryl bromide **2a**, 3 equiv of $NaN(SiMe_3)_2$, 1 mol % $Pd(dba)_2$, and 2 mol % NiXantPhos in CPME at 80 °C for 12 h.

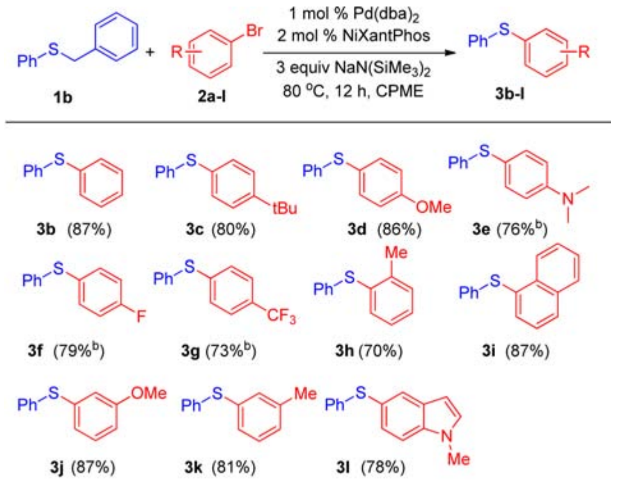
Table 1. Optimization of the Reaction Conditions[a]

entry	base	solvent	1a:2a: base	Pd	yield (%)[b]
1	LiO*t*Bu	CPME	1:3:4	$Pd(OAc)_2$	0
2	NaO*t*Bu	CPME	1:3:4	$Pd(OAc)_2$	0
3	KO*t*Bu	CPME	1:3:4	$Pd(OAc)_2$	5
4	$LiN(SiMe_3)_2$	CPME	1:3:4	$Pd(OAc)_2$	39
5	$NaN(SiMe_3)_2$	CPME	1:3:4	$Pd(OAc)_2$	67
6	$NaN(SiMe_3)_2$	DME	1:3:4	$Pd(OAc)_2$	26
7	$NaN(SiMe_3)_2$	THF	1:3:4	$Pd(OAc)_2$	60
8	$NaN(SiMe_3)_2$	dioxane	1:3:4	$Pd(OAc)_2$	33
9	$NaN(SiMe_3)_2$	CPME	1:3:3	$Pd(OAc)_2$	74
10	$NaN(SiMe_3)_2$	CPME	1:2:3	$Pd(OAc)_2$	78
11	$NaN(SiMe_3)_2$	CPME	1:2:2	$Pd(OAc)_2$	55
12	$NaN(SiMe_3)_2$	CPME	1:2:3	$Pd(OAc)_2$	78[c]
13	$NaN(SiMe_3)_2$	CPME	1:2:3	$Pd(OAc)_2$	77[d,f]
14	$NaN(SiMe_3)_2$	CPME	1:2:3	$Pd_2(dba)_3$	74
15	$NaN(SiMe_3)_2$	CPME	1:2:3	$[PdCl(ally)]_2$	70
16	$NaN(SiMe_3)_2$	CPME	1:2:3	$Pd(dba)_2$	80[f] (80[e])

[a]Reaction performed on a 0.1 mmol scale. [b]Yields determined by ^1H NMR analysis of crude mixtures with CH_2Br_2 as internal standard. [c]5 mol % catalyst was used. [d]1 mol % catalyst was used. [e]Isolated yield. [f]Yields averaged of two experiments.

With the optimized conditions for the debenzylative coupling, we examined the scope of aryl bromides with phenyl benzyl thioether (**1b**, Scheme 4). The parent bromobenzene (**2b**) reacted to give diphenyl sulfide (**3b**) in 87% isolated yield. Aryl bromides bearing electron-donating groups, such as 4-*tert*-butyl, 4-methoxy, and 4-*N*,*N*-dimethylamino, exhibited good reactivity, producing **3c**−**3e** in 76−86% yields. Aryl bromides possessing electron-withdrawing groups are also good coupling partners. 4-Fluorobromobenzene (**2f**) and 4-trifluoromethyl bromobenzene (**2g**) afforded the corresponding products in 79% and 73% yield, respectively. Sterically hindered aryl bromides, such as 2-bromotoluene (**2h**) and 1-bromonaphthalene (**2i**), coupled with **1b** and furnished the products in 70% and 87% yields, respectively. Meta-substituted 3-bromoanisole and 3-bromotoluene were good substrates under our conditions, giving diaryl sulfides in 87% and 81% yield, respectively. Heterocyclic diaryl sulfides could be prepared, as exemplified by the generation of indole-containing sulfide **3l** in 78% yield.

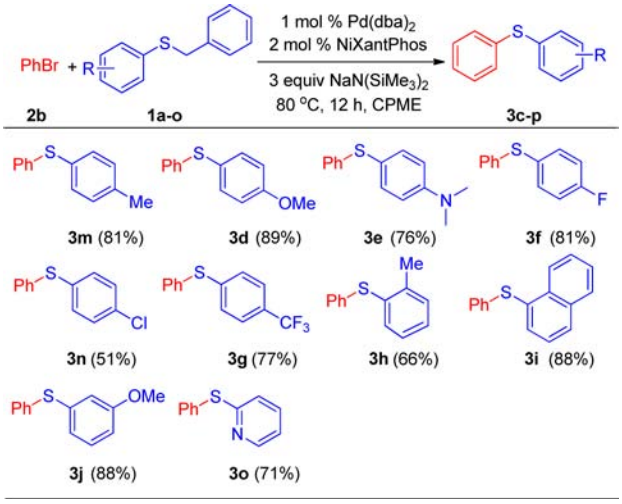
Scheme 4. Substrate Scope of Aryl Bromides in Pd-Catalyzed Diaryl Sulfide Formation with 1b[a]



[a]Reaction performed on a 0.2 mmol scale. [b] 3 equiv aryl bromide were used.

Next, the substrate scope of aryl benzyl sulfides was examined in the debenzylative cross-coupling with bromobenzene (**2b**) (Scheme 5). In general, functional groups were well tolerated. Aryl benzyl sulfides bearing electron-donating groups, such as 4-Me (**1a**), 4-OMe (**1d**), and 4-NMe_2 (**1e**), provided the corresponding products in 81%, 89%, and 76% yield, respectively. Aryl benzyl sulfides with electron-withdrawing 4-F (**1f**) and 4-CF_3 (**1g**) coupled in 81% and 77% yield, respectively. Aryl benzyl sulfide possessing 4-Cl (**1n**) gave only a 51% isolated yield of **3n**, probably due to the cross-coupling at the Ar−Cl.[12b] Hindered 2-tolyl (**1h**) and 1-naphthyl benzyl sulfide (**1i**) afforded the expected products in 66% and 88% yield, respectively. The 3-OMe derivative (**1j**) could also be utilized as a coupling partner, leading to **3j** in 88% yield. Heterocyclic sulfides exhibit various bioactivities.[3] Phenyl 2-pyridyl sulfide (**3o**) was formed in 71% yield under our conditions.

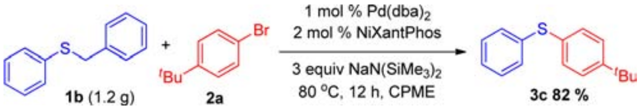
Scheme 5. Substrate Scope of Aryl Benzyl Sulfides in Pd-Catalyzed Diaryl Sulfide Formation with Bromobenzene (2b)[a]



[a]Reaction performed on a 0.2 mmol scale.

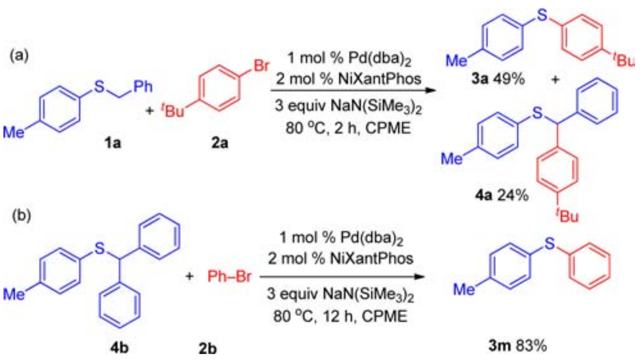
For a method to be useful, it must be scalable. To test the scalability, 6.0 mmol of **1b** (1.2 g) were utilized to cross-couple with **2a**. An 82% yield of **3c** was obtained (Scheme 6).

Scheme 6. Gram Scale Synthesis of 4-*tert*-Butylphenyl Phenyl Sulfide



To generate diaryl sulfides in these debenzylative reactions, the Pd(NiXantPhos)-based catalyst promotes multiple reactions involving C_{sp^3}–S bond cleavage and C_{sp^2}–S bond formation. Based on experiments discussed below, a palladium-catalyzed tricatalytic cycle is proposed in Figure 1. Cycle A is our previously reported α-arylation of aryl benzyl sulfides.[19] Support for cycle A was gained by monitoring the reaction between **1a** and **2a** with a base (Scheme 7a). After 2 h, the α-arylation product (**4a**) was produced in 24% yield as well as 49% yield of the diaryl sulfide **3a**. Intermediate **4a** was absent at longer reaction times, presumably because of conversion to **3a**. Heating **4b** under the conditions used in Schemes 4 and 5 resulted in an 83% yield of the diaryl sulfide **3m**, indicating that **4b** is a viable substrate in the diaryl sulfide synthesis (Scheme 7b).

Scheme 7. Tandem Pd-Catalyzed Synthesis of (4-*tert*-Butylphenyl) (*p*-Tolyl) Sulfide and 4-Tolyl Phenyl Sulfide



In cycle B, a palladium-catalyzed C–S bond cleavage is proposed via an η^3-π-benzyl-palladium intermediate (VII), which is followed by S-arylation of the arylthiolate intermediate with aryl bromide (cycle C). We proposed a similar triple relay mechanism in our related palladium-catalyzed diaryl sulfoxide formation from aryl benzyl sulfoxides and aryl bromides.[21] Unfortunately, attempts to isolate the diarylmethyl containing byproducts failed due to decomposition.

Palladium-catalyzed benzylation reactions have received significant recent attention.[1] However, we are unaware of examples using thiolates as leaving groups.

In summary, we report a novel debenzylative approach to generate diaryl sulfides from aryl benzyl sulfides and aryl bromides. A variety of diaryl sulfides were generated in good to excellent yields. Preliminary studies suggest that the Pd(dba)$_2$/NiXantPhos-based catalyst promotes three distinct

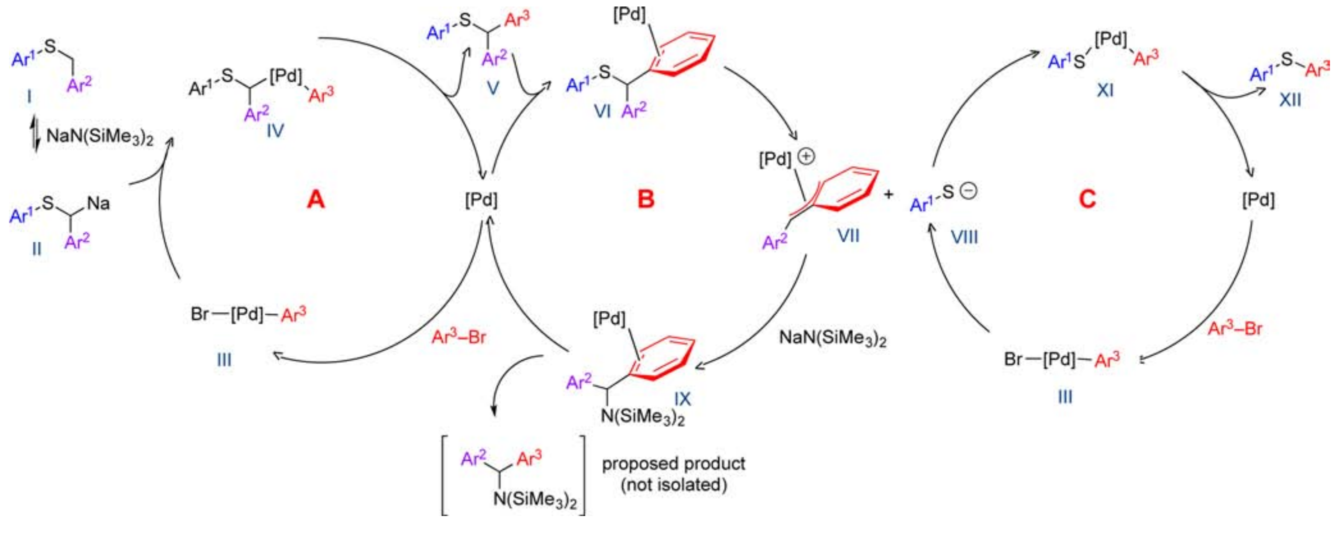


Figure 1. Proposed tricatalytic cycle.

catalytic reactions involving benzyl aryl thioether α-arylation, benzylic C−S bond cleavage, and C−S bond formation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures and full characterization of 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) For a review, see: (a) Trost, B. M.; Czabaniuk, L. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 2826. For leading works, see: (b) Legros, J. Y.; Fiaud, J. C. *Tetrahedron Lett.* **1992**, *33*, 2509. (c) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104. (d) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973. (e) Kuwano, R.; Kusano, H. *Org. Lett.* **2008**, *10*, 1979.

(2) (a) Nakazawa, T.; Xu, J.; Nishikawa, T.; Oda, T.; Fujita, A.; Ukai, K.; Mangindaan, R. E. P.; Rotinsulu, H.; Kobayashi, H.; Namikoshi, M. *J. Nat. Prod.* **2007**, *70*, 439. (b) Liu, H.; Fujiwara, T.; Nishikawa, T.; Mishima, Y.; Nagai, H.; Shida, T.; Tachibana, K.; Kobayashi, H.; Mangindaan, R. E. P.; Namikoshi, M. *Tetrahedron* **2005**, *61*, 8611.

(3) (a) Okamoto, T.; Mitsui, C.; Yamagishi, M.; Nakahara, K.; Soeda, J.; Hirose, Y.; Miwa, K.; Sato, H.; Yamano, A.; Matsushita, T.; Uemura, T.; Takeya, J. *Adv. Mater.* **2013**, *25*, 6392. (b) Mori, T.; Nishimura, T.; Yamamoto, T.; Doi, I.; Miyazaki, E.; Osaka, I.; Takimiya, K. *J. Am. Chem. Soc.* **2013**, *135*, 13900. (c) Takimiya, K.; Shinamura, S.; Osaka, I.; Miyazaki, E. *Adv. Mater.* **2011**, *23*, 4347.

(4) (a) Krapcho, J.; Spitzmiller, E. R.; Turk, C. F. *J. Med. Chem.* **1963**, *6*, 544. (b) Krapcho, J.; Turk, C. F. *J. Med. Chem.* **1966**, *9*, 191.

(5) (a) Bahrami, K.; Khodaei, M. M.; Sohrabnezhad, S. *Tetrahedron Lett.* **2011**, *52*, 6420. (b) Boruah, J. J.; Das, S. P.; Ankireddy, S. R.; Gogoi, S. R.; Islam, N. S. *Green Chem.* **2013**, *15*, 2944. (c) Kamata, K.; Hirano, T.; Mizuno, N. *Chem. Commun.* **2009**, 3958. (d) Rostami, A.; Akradi, J. *Tetrahedron Lett.* **2010**, *51*, 3501. (e) Ruano, J. L. G.; Aleman, J.; Fajardo, C.; Parra, A. *Org. Lett.* **2005**, *7*, 5493.

(6) For a review, see: (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. For recent examples, see: (b) Bu, X.-H.; Chen, W.; Du, M.; Biradha, K.; Wang, W.-Z.; Zhang, R.-H. *Inorg. Chem.* **2002**, *41*, 437. (c) Bu, X.-H.; Chen, W.; Hou, W.-F.; Du, M.; Zhang, R.-H.; Brisse, F. *Inorg. Chem.* **2002**, *41*, 3477. (d) Errington, J.; McDonald, W. S.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1980**, 2309. (e) Li, Y.; Xu, M. H. *Chem. Commun.* **2014**, *50*, 3771. (f) Manojlovic-Muir, L.; Muir, K. W.; Solomun, T. *Inorg. Chim. Acta* **1977**, *22*, 69. (g) Black, J. R.; Champness, N. R.; Levason, W.; Reid, G. *J. Chem. Soc., Dalton Trans.* **1995**, 3439.

(7) For reviews, see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (b) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. For recent examples, see: (d) Dahl, T.; Tornoee, C. W.; Bang-Andersen, B.; Nielsen, P.; Joergensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1726. (e) Fernandez-Rodriguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (f) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (g) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13. (h) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (i) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (j) Osakada, K.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1987**, *28*, 6321. (k) Wang, L.; Zhou, W. Y.; Chen, S. C.; He, M. Y.; Chen, Q. *Adv. Synth. Catal.* **2012**, *354*, 839. (l) Zhao, P.; Yin, H.; Gao, H. X.; Xi, C. J. *J. Org. Chem.* **2013**, *78*, 5001. (m) Zhang, C. P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183. (n) Zhao, J.; Fang, H.; Han, J.; Pan, Y.; Li, G. *Adv. Synth. Catal.* **2014**, *356*, 2719.

(8) (a) Xu, X. B.; Liu, J.; Zhang, J. J.; Wang, Y. W.; Peng, Y. *Org. Lett.* **2013**, *15*, 550. (b) Liu, T. J.; Yi, C. L.; Chan, C. C.; Lee, C. F. *Chem.—Asian J.* **2013**, *8*, 1029. (c) Byeun, A.; Baek, K.; Han, M. S.; Lee, S. *Tetrahedron Lett.* **2013**, *54*, 6712.

(9) Prasad, C. D.; Balkrishna, S. J.; Kumar, A.; Bhakuni, B. S.; Shrimali, K.; Biswas, S.; Kumar, S. *J. Org. Chem.* **2013**, *78*, 1434.

(10) Saravanan, P.; Anbarasan, P. *Org. Lett.* **2014**, *16*, 848.

(11) (a) Cheng, J.-H.; Ramesh, C.; Kao, H.-L.; Wang, Y.-J.; Chan, C.-C.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 10369. (b) Yonova, I. M.; Osborne, C. A.; Morrissette, N. S.; Jarvo, E. R. *J. Org. Chem.* **2014**, *79*, 1947.

(12) (a) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765. (b) Zhang, J.; Bellomo, A.; Trongsiriwat, N.; Jia, T.; Carroll, P. J.; Dreher, S. D.; Tudge, M. T.; Yin, H.; Robinson, J. R.; Schelter, E. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 6276. (c) Bellomo, A.; Zhang, J.; Trongsiriwat, N.; Walsh, P. J. *Chem. Sci.* **2013**, *4*, 849−857.

(13) Jia, T.; Bellomo, A.; El Baina, K.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 3740.

(14) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 1690.

(15) (a) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190. (b) Zheng, B.; Jia, T.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 165.

(16) Montel, S.; Jia, T.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 130.

(17) Montel, S.; Raffier, L.; He, Y.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 1446.

(18) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Commun.* **2014**, *50*, 10661.

(19) Frensch, G.; Hussain, N.; Marques, F. A.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 2517.

(20) van der Veen, L. A.; Keeven, P. H.; Schoemaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 872.

(21) Jia, T.; Bellomo, A.; Montel, S.; Zhang, M.; El Baina, K.; Zheng, B.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 260.