JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Palladium-Catalyzed Asymmetric α-Arylation of Alkylnitriles

Zhiwei Jiao, Kwok Wei Chee, and Jianrong "Steve" Zhou*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore

Supporting Information

ABSTRACT: Asymmetric arylation of alkylnitriles forms quaternary stereocenters in good enantiocontrol for the first time. A lithium heterodimer consisting of an alkylnitrile anion and a disilylamide ion is the actual species responsible for the stereodetermining transmetalation in the catalytic cycle.

In the past 2 decades, significant progress has been gained in transition-metal-catalyzed asymmetric couplings of carbonyl compounds.[1,2] Intermolecular coupling processes offered α-arylation and α-vinylation products in good enantiometric excess (ee) and efficiently formed quaternary stereocenters α to carbonyl groups of cyclic ketones, oxindoles, and lactones (eq 1 in Figure 1).[3] The enantioselective C−C coupling has also been extended to intramolecular arylation and vinylation of aldehydes and amides, and ketones.[4] Asymmetric intermolecular coupling of acyclic enolates is more challenging to achieve, due to the need of *E*/*Z* control of the enolates. We[5] and other groups[6] have also reported metal-catalyzed asymmetric arylation using geometrically defined soft enolates of esters (eq 2), cyclic ketones and lactones, which produced base-sensitive tertiary α-stereocenters.

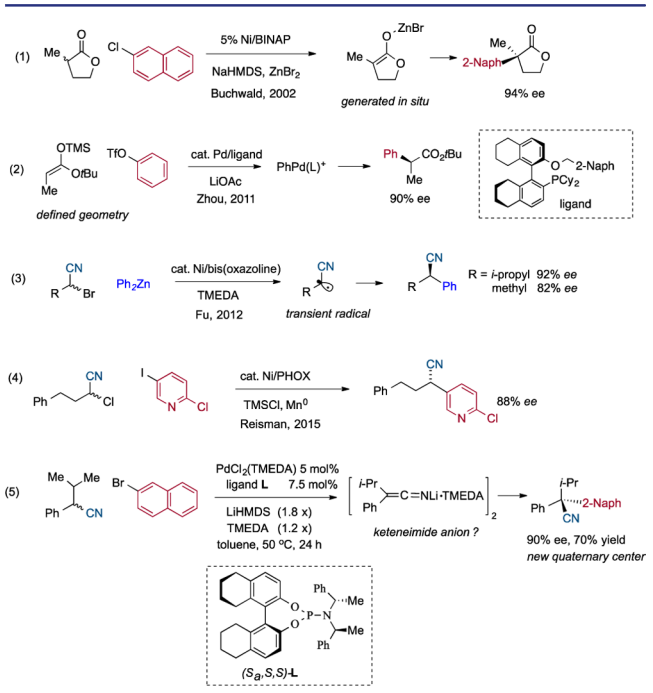


Figure 1. Examples of asymmetric arylation of enolates and arylation of alkyl nitriles.

Alkylnitriles are present in drugs such as verapamil (antiarrhythmic) and anastrozole (advanced breast cancer).[7] Moreover, the nitriles are readily transformed to many useful groups, for example, via hydrolysis,[8] hydrogenation,[9] addition of hydride and organometallic reagents,[10] dipolar cycloaddition,[11] and other processes.[12] Previously, Hartwig[13] and others[14] disclosed Pd-catalyzed procedures for nonstereoselective arylation, which led to achiral or racemic products via in situ deprotonation of alkylnitriles or decarboxylation.[15] Most of the conditions employed strongly donating monophosphines as ancillary ligands to achieve good catalytic activity. However, a catalytic enantioselective arylation of alkylnitriles remained elusive. The challenge is associated with the difficulty in catalyst differentiation of three groups on the α carbon.

At present, catalytic C−C bond forming processes to prepare enantioenriched α-arylated alkylnitriles remain under-developed,[16] examples including nickel-catalyzed coupling of α-bromonitriles and diarylzinc reagents (eq 3),[17] and reductive coupling of α-chloronitriles and heteroaryl iodides (eq 4).[18] In both cases, the nitriles were introduced as electrophiles to produce new tertiary stereocenters, and the structures of products that afforded good ee values remained quite restricted. Moreover, in 2016, Stahl and Liu et al. reported a copper-catalyzed asymmetric cyanation of benzylic C−H bonds to form new tertiary stereocenters.[19]

Herein, we report the first example of Pd-catalyzed asymmetric coupling of aryl halides and alkylnitriles that generated quaternary centers in good ee (eq 5). In a test case of α-isopropyl benzylnitrile and 2-naphthyl bromide, a combination of a palladium complex and a phosphoramidite ligand **L** delivered the desired product in 70% yield and 90% ee. The absolute configuration of the coupling product was determined to be 2*R*, based on single-crystal X-ray diffractional analysis. A strong base, lithium hexamethyldisilylamide (LiHMDS), was used for in situ deprotonation of the alkylnitrile. The reaction also produced a byproduct, naphthalene, via β hydrogen elimination from α-cyanoalkyl group on Pd, which accounted for material balance.

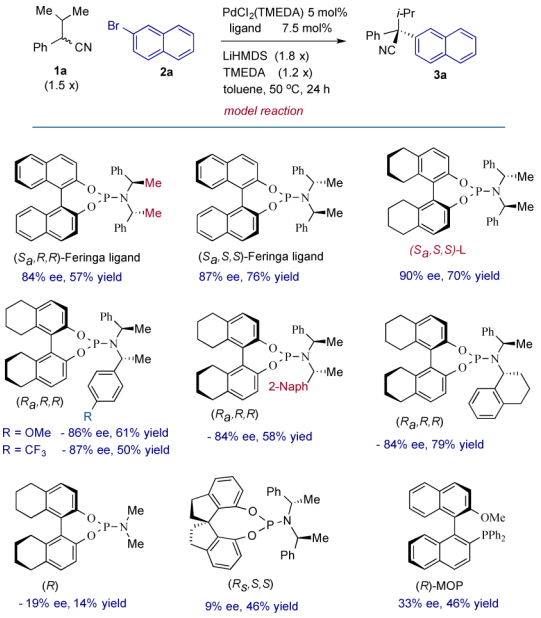
During our catalyst optimization of the model reaction, we initially detected only <10% ee, in the presence of chelating bisphosphines such as binap, difluorphos and segphos. The results were consistent with previous observations by others on the alkylnitrile coupling. After many trials, we were gratified to discover that a Feringa's ligand[20] delivered a significant level of

Received: November 9, 2016
Published: December 7, 2016

DOI: 10.1021/jacs.6b11610
J. Am. Chem. Soc. 2016, 138, 16240−16243

stereoinduction, 84% ee (Scheme 1). We also tested a diastereomeric form of Feringa's ligand and it led to the same

Scheme 1. Influence of Phosphoramidite Ligands in a Model Arylation Reaction



enantiomeric product as the major one (87% ee). Thus, the binaphthyl backbone is the main determinant in setting the absolute configuration of the product, whereas the amine fragment had minor influence.

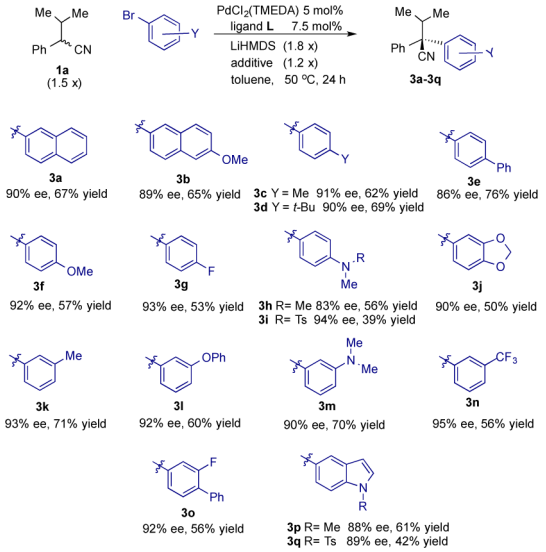
To improve further the stereoselctivity of the coupling reaction, we tested phosphoramidite (*Sa*,*S*,*S*)-**L** on a partially hydrogenated binaphthyl skeleton.[21] To our satisfaction, it led to the coupling product in 90% ee. Furthermore, modification of aryl rings of the amine fragment did not lead to further enhancement of the ee, whereas a small dimethylamine fragment resulted in a much less active and less selective Pd catalyst (19% ee). We observed that Qi-Lin Zhou's phosphoramidite on a spirõ-diindanyl scaffold afforded a very low level of stereoinduction (9% ee).[22]

During condition optimization of the model reaction, an interesting effect of additives emerged (see the Supporting Information). In the presence of tetramethylethylene-1,2-diamine (TMEDA), the ee value of the product increased from 60% to 90%. In comparison, adding (−)-sparteine to the reaction resulted in 75% ee, whereas the additives of *N*,*N*′-dimethylpropyleneurea (DMPU) or hexamethylphosphoric triamide (HMPA) provided ee's slightly below 90%.

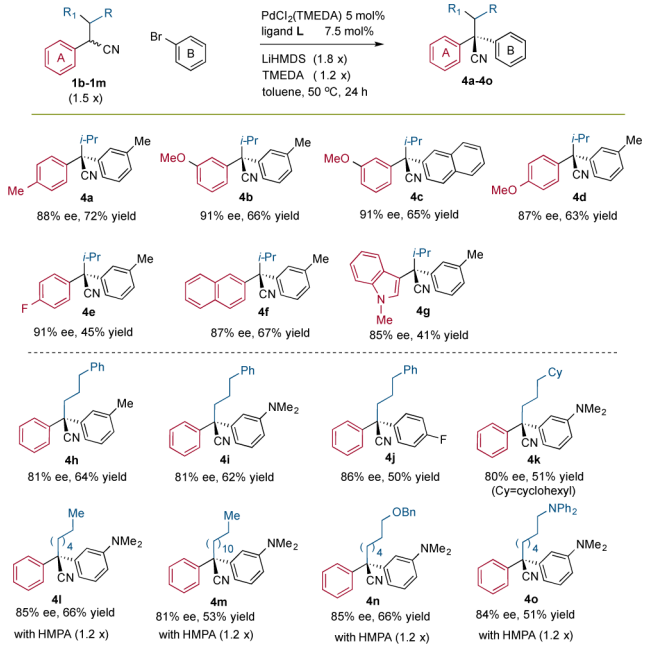
The combination of palladium source and (*Sa*,*S*,*S*)-**L** was successfully applied to asymmetric coupling of other aryl bromides with the model benzylnitrile (Scheme 2). Not only electron-deficient but also electron-rich aryl halides reacted smoothly. Two indolyl bromides were also coupled in good ee values. However, other bromides such as 3-bromobenzothiophene and 3-bromoindole, 2-bromothiophene led to low yields of the products. The reactions of aryl iodides led to low yields. The strong base also caused fast hydrolysis of most aryl triflates.

We also examined the scope of alkylnitriles in couplings with aryl bromides (Scheme 3). Both electron-donating and withdrawing groups were tolerated on α-aryl rings of nitriles. Furthermore, the nitriles can have linear alkyl chains containing

Scheme 2. Examples of Aryl Bromides in Asymmetric Coupling with α-Isopropylbenzylnitrile



Scheme 3. Examples of Alkylnitriles in Asymmetric Couplings of Aryl Bromides



both benzylether and aniline groups, and the enantiomeric ratio of products was generally >9:1. Notably, the last four cases in the presence of TMEDA gave low yields (<40%) of the coupling products and in <80% ee's. The main side reactions were identified to be the reduction of the C−Br bonds to $PhNMe_2$ (35−55%) and bimolecular condensation of an alkylnitrile anion to another molecule of the nitrile (around 10% for isomers of β-ketoalkylnitriles). When TMEDA was replaced by HMPA,[23] the reactions gave reasonable yields of desired products (>50%) along with some $PhNMe_2$ byproduct (25−35%), whereas the condensation of alkylnitriles was prevented. Unfortunately though, benzylnitriles bearing other α groups (e.g., methyl, ethyl, and cyclohexyl) led to low yields.

The ee value of catalytic processes is diagnostic of the stereodetermining step. Therefore, to probe the transmetalating

DOI: 10.1021/jacs.6b11610
J. Am. Chem. Soc. 2016, 138, 16240−16243

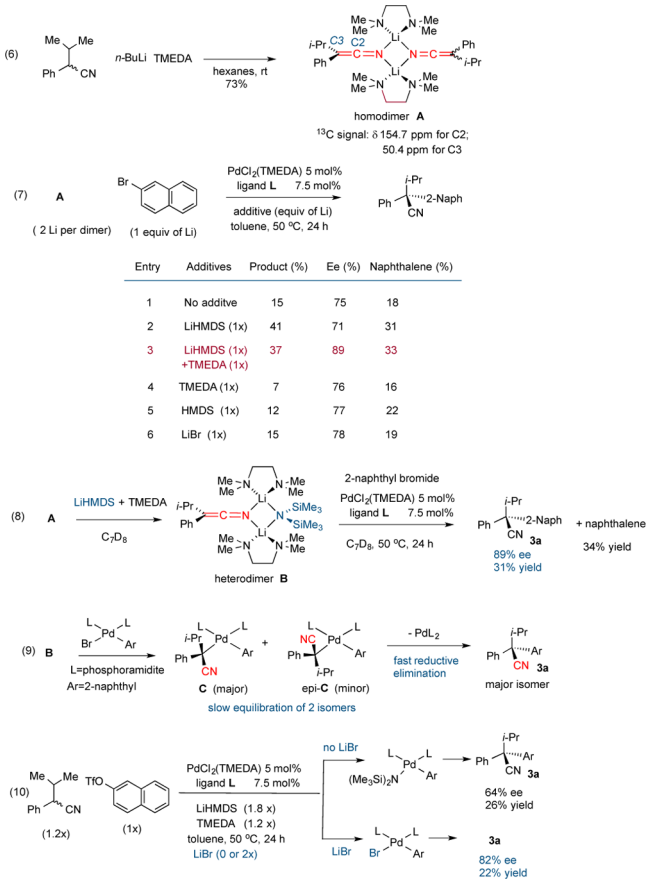


Figure 2. Mechanistic study.

species, we prepared a dimeric complex $[Ph(i\text{-}Pr)C{=}C{=}NLi(TMEDA)]_2$ **A** containing a core of Li_2N_2, using Boche's procedure (eq 6 in Figure 2).[24] The iminyl carbon has distinct ^{13}C signals at 154.7 ppm for C2 and 50.4 ppm for C3, indicative of significant negative charge localizing on C3 and a Li-bound nitrile group at the nitrogen instead of α carbon, in reference to chemical shifts of related compounds in the literature.[25]

When complex **A** was used in the model catalytic reaction of 2-naphthyl bromide, it only gave 75% ee surprisingly (eq 7, entry 1). The value is significantly lower than 90% ee observed under in situ deprotonation conditions (eq 5). Next, we added LiHMDS to the coupling conditions, but the ee remained almost unchanged (entry 2). Interestingly, we found that when both LiHMDS and TMEDA were added, the ee was enhanced to 89% (entry 3). This is almost identical to the value from in situ deprotonation (90% ee). Additionally, TMEDA, LiBr, or $HN(SiMe_3)_2$ alone had little effect on the stereoselectivity of the model reaction (entries 4–6).

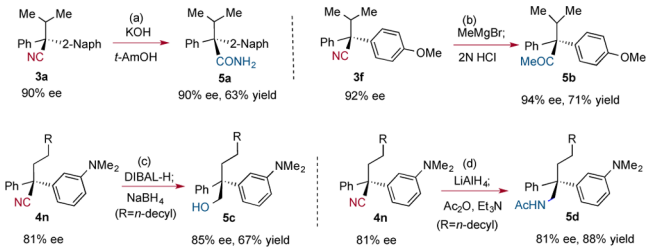
We then allowed complex **A** and LiHMDS and TMEDA in molar ratio (1:2:2) to stand in d_8-toluene overnight, which gave a relatively clean sample of complex **B** (eq 8).[26] The isopropyl methine has a distinct heptet at 2.79 ppm, which is shifted upfield from 2.83 ppm of **A**. When the solution of **B** was used in the catalytic reaction, it indeed gave the product in 89% ee (31% yield). Therefore, we concluded that the active transmetalating species is heterodimer **B** instead of homodimer **A** in the model catalytic reaction.

Recently, Gschwind et al. revealed that *cis*-$(L)_2PdCl_2$ complexes of Feringa-type phosphoramidites are stabilized by extensive CH–π and π–π interactions between two ligands of L, when compared with the trans isomer.[27] Putting all the information together, we conclude that the transmetalation of **B** to *cis*-$(L)_2Pd(aryl)Br$ sets the configuration in the coupling product (eq 9). Two cis ligands **L** formed a C_2-symmetrical pocket around the palladium center. After the transmetalation, the chiral α-cyanoalkyl ligand in complex **C** undergoes very slow epimerization and subsequent C–C reductive elimination is relatively fast.

The result of 2-naphthyl triflate provides additional support for the stereodetermining nature of the transmetalation process. The reaction afforded 64% ee in the absence of LiBr (eq 10). We suggest that the disilylamide occupies the fourth coordination site on the palladium center (instead of the triflate ion). In comparison, the ee increased to 82% in the presence of LiBr (1 equiv). This is probably due to partial conversion of the disilylamide complex to a bromide complex, the latter being more stereoselective toward transmetalation with **B**.

The nitrile groups in the arylation products are readily converted to other functionalities (Scheme 4), for example, an amide after basic hydrolysis, a ketone via Grignard addition, an alcohol via DIBAL-H reduction, an *N*-acetyl protected amine after hydride reduction. In two cases (b and c), the ee value slightly increased after flash chromatography, probably due to accidental partial resolution of dimers or oligomers on silica.[28]

Scheme 4. Transformation of Nitrile Groups



In conclusion, the first examples of enantioselective arylation of benzylnitriles produce quaternary stereocenters in good ee values. To our surprise, heterodimer **B** of a lithium keteneimide, rather than homodimer **A**, is responsible for the stereoselective transmetalation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11610.

Procedure and characterization of compounds (PDF)
^1H and ^{13}C NMR charts (PDF)
Data for $C_{21}H_{20}N$ (CIF)
Crystal structure report for a nitrile product (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*jrzhou@ntu.edu.sg

ORCID

Jianrong "Steve" Zhou: 0000-0002-1806-7436

Notes

The authors declare no competing financial interest.

DOI: 10.1021/jacs.6b11610
J. Am. Chem. Soc. 2016, 138, 16240–16243

■ ACKNOWLEDGMENTS

We thank Singapore Ministry of Education Academic Research Fund (MOE2013-T2-2-057 and MOE2014-T1-001-021) for financial support.

■ REFERENCES

(1) Reviews: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082−1146. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676−707. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587−9652.

(2) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027−3043.

(3) Examples: (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918−1919. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261−1268. (c) Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500−3501. (d) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182−5191. (e) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413. (f) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (g) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900−9901. (h) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16330−16333. (i) Guo, J.; Dong, S.; Zhang, Y.; Kuang, Y.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 10245−10249. (j) Ghosh, A.; Walker, J. A.; Ellern, A.; Stanley, L. M. *ACS Catal.* **2016**, *6*, 2673−2680.

(4) Examples: (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415. (b) García-Fortanet, J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8108−8111. (c) Liu, L.; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666−1669. (d) Nareddy, P.; Mantilli, L.; Guénée, L.; Mazet, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 3826−3831. (e) Humbert, N.; Larionov, E.; Mantilli, L.; Nareddy, P.; Besnard, C.; Guénée, L.; Mazet, C. *Chem. - Eur. J.* **2014**, *20*, 745−751. (f) Liu, R.-R.; Li, B.-L.; Lu, J.; Shen, C.; Gao, J.-R.; Jia, Y.-X. *J. Am. Chem. Soc.* **2016**, *138*, 5198−5201.

(5) Examples: (a) Huang, Z.; Liu, Z.; Zhou, J. *J. Am. Chem. Soc.* **2011**, *133*, 15882−15885. (b) Huang, Z.; Chen, Z.; Lim, L. H.; Quang, G. C. P.; Hirao, H.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 5807−5812. (c) Huang, Z.; Lim, L. H.; Chen, Z.; Li, Y.; Zhou, F.; Su, H.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4906−4911. (d) Yang, J.; Zhou, J. *Org. Chem. Front.* **2014**, *1*, 365−367.

(6) Examples: (a) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640−11641. (b) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (c) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778−13781. (d) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782−13785. (e) Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 9090−9093. (f) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815−10818.

(7) Alnabari, M.; Freger, B.; Arad, O.; Zelikovitch, L.; Seryi, Y.; Danon, E.; Davidi, G.; Kaspi, J. Novel processes for preparing substantially pure anastrozole. Patent US 20060035950 A1, February 16, 2006.

(8) Examples: (a) Parkins, A. W. *Platinum Metals Rev.* **1996**, *40*, 169. (b) Basu, M. K.; Luo, F.-T. *Tetrahedron Lett.* **1998**, *39*, 3005−3006.

(9) Examples: (a) Mukherjee, A.; Srimani, D.; Chakraborty, S.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2015**, *137*, 8888−8891. (b) Elangovan, S.; Topf, C.; Fischer, S.; Jiao, H.; Spannenberg, A.; Baumann, W.; Ludwig, R.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2016**, *138*, 8809−8814.

(10) (a) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771−1802. (b) Turnbull, B. W. H.; Evans, P. A. *J. Am. Chem. Soc.* **2015**, *137*, 6156−6159.

(11) Examples: (a) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2003**, *125*, 9983−9987. (b) Cantillo, D.; Gutmann, B.; Kappe, C. O. *J. Am. Chem. Soc.* **2011**, *133*, 4465−4475.

(12) Examples: (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904−13905. (b) Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 2428−2429. (c) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874−12875. (d) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594−12595.

(13) (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330−9331. (b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330−9331. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245. (d) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824−15832.

(14) Examples: (a) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051−5053. (b) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690−1693. (c) Todorovic, N.; Awuah, E.; Albu, S.; Ozimok, C.; Capretta, A. *Org. Lett.* **2011**, *13*, 6180−6183.

(15) Examples: (a) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470−4474. (b) Velcicky, J.; Soicke, A.; Steiner, R.; Schmalz, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 6948−6951. (c) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 2912−2915.

(16) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524−2525.

(17) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102−9105.

(18) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480−10483.

(19) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. *Science* **2016**, *353*, 1014−1018.

(20) Reviews: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (b) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375−1378. (c) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179−188. (d) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039−1075. (e) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486−2528.

(21) van Zijl, A. W.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2004**, *346*, 413−420.

(22) (a) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2003**, *68*, 1582−1584. (b) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581−593.

(23) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201−7210.

(24) Boche, G.; Marsch, M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 373−374.

(25) Purzycki, M.; Liu, W.; Hilmersson, G.; Fleming, F. F. *Chem. Commun.* **2013**, *49*, 4700−4702.

(26) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602−11603.

(27) (a) Mikhel, I. S.; Bernardinelli, G.; Alexakis, A. *Inorg. Chim. Acta* **2006**, *359*, 1826. (b) Hartmann, E.; Gschwind, R. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2350−2354.

(28) Matusch, R.; Coors, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 626−627.

DOI: 10.1021/jacs.6b11610
J. Am. Chem. Soc. 2016, 138, 16240−16243