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Synthesis of 7,7′-Dihydroxy-8,8′-biquinolyl (azaBINOL) via Pd-Catalyzed Directed Double C−H Functionalization of 8,8′-Biquinolyl: Emergence of an *Atropos* from a *Tropos* State

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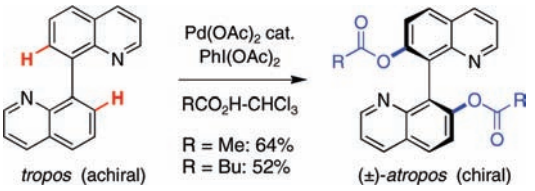
ABSTRACT



7,7′-Dihydroxy-8,8′-biquinolyl (azaBINOL) was prepared from 2-chloroaniline in four steps: (1) the Skraup reaction, (2) Ni-catalyzed reductive coupling of 8-chloroquinoline, (3) Pd(II)-catalyzed double C−H functionalization of 8,8′-biquinolyl mediated by $PhI(OAc)_2$, and (4) saponification. During the third step, an axially chiral (*atropos* type) biaryl molecule was directly generated from an essentially achiral (*tropos* type) biaryl starting material.

Providing that it can be achieved with a high level of selectivity, direct oxidation of C−H bonds is likely to offer the most efficient and step-economical path to functional materials. Innate heightened reactivity of certain types of C−H bonds may allow for their selective transformation in special cases,[1] but in general an engineered mechanism is required to ensure the required degree of regiocontrol. An attractive strategy for C−H functionalization that recently emerged to prominence involves electrophilic metalation processes as directed by coordination sites intrinsic to the substrate.[2] Of particular note, Sanford and co-workers,[3] among others,[4] have shown that Pd(II) species formed in situ via internal ligand assisted palladation can be used to introduce nontrivial functional groups via oxidation of the metal center to a higher valence state.[5] Crucially, the key bond forming event involves reductive elimination and this serves to return active Pd(II) salts to the reaction mixture, thus closing a catalytic cycle. Herein, we report exploitation of this C−H functionalization paradigm to the synthesis of

(1) For a recent survey of innate C−H bond reactivity, see: Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374.

(2) Reviews: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (b) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84.

(3) Representative and salient examples: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (b) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149–4152. (c) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523–2526. (d) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–1935. (e) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285–13293. (f) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584–4587.

(4) Selected examples: (a) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048. (b) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882–4886. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061. (d) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270–8272. (e) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648–3649. (f) Xiao, F.; Shuai, Q.; Baslé, O.; Deng, G.; Li C.-J. *Org. Lett.* **2011**, *13*, 1614–1617. (g) Guo., H.-M.; Rao, W.-H.; Niu, H.-Y.; Jiang, L.-L.; Meng, G.; Jin, J.-J.; Yang, X.-N.; Qu, G.-R. *Chem. Commun.* **2011**, *47*, 5608–5610. See ref 2a for more examples.

(5) For discourse on the role that Pd(IV) and Pd(III) intermediates play in these reactions, see: (a) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530–14536. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824–889. (c) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241. (d) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974–10983.

(6) For background on *tropos* vs *atropos* biaryl ligand systems, see: Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561–1578.

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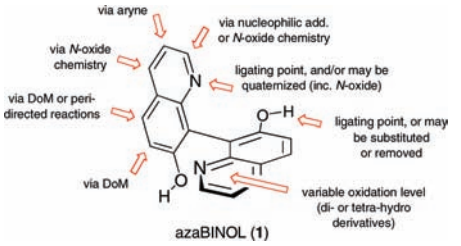


Figure 1. 7,7′-Dihydroxy-8,8′-biquinolyl ("azaBINOL", **1**) with indication of metal ion ligation sites and position specific derivatization tactics. DoM = Directed ortho Metalation.

an axially chiral (*atropos*) heterocyclic biaryl molecule from an achiral (*tropos*) biaryl precursor.[6]

7,7′-Disubstituted 8,8′-biquinolyls were identified as a useful class of axially chiral molecules for the exploration of novel interannular proximity effects in ambifunctional catalysis.[7] It was further recognized that 7,7′-dihydroxy-8,8′-biquinolyl ("azaBINOL", **1**), a formal aza-analog of the biaryl ligand BINOL,[8] might prove useful as a metal ligand (or chiral catalyst) in its own right and that this material could serve as a pivotal intermediate en route to other 8,8′-biquinolyls of interest. Methods to derivatize biquinolyl **1** at all positions are available, rendering the framework amenable to any kind of decoration desired (Figure 1). In earlier work, we developed synthetic routes to 7,7′-dioxygenated 8,8′-biquinolyls,[7a,c] devised methods for their resolution into enantiopure atropisomers,[7b,c] and investigated key properties of such azaBINOL molecules, including racemization kinetics,[7b,c] chiroptical behavior,[7b] and the dependence of basicity on conformation.[7d] More recently, Loh and Xiao prepared and resolved the *N*,*N*′-dimethylated derivative of octahydro azaBINOL.[9]

Further investigation of azaBINOL systems is hindered by the cumbersome nature of the reported syntheses of **1** which proceed via 7-hydroxyquinoline (**3**), a compound of limited commercial availability and best obtained from 3-aminophenol (**2**) by the four step Fukuyama quinoline synthesis (Scheme 1).[10] The shortest current approach to azaBINOL requires a total of 7 steps,[7a] key among them an $FeCl_3$ mediated homocoupling of the 8-quinolyllithium derived from directed ortho-metalation of carbamate **4** to afford the biquinolyl system of **5** (alternatively, **5** is also available from **4** by a two step sequence of iodination and Ullmann coupling).[7a,9]

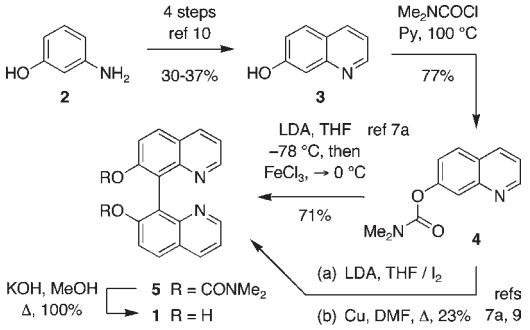
(7) (a) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373–376. (b) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2006**, *71*, 8212–8218. (c) Blakemore, P. R.; Milicevic, S. D.; Zakharov, L. N. *J. Org. Chem.* **2007**, *72*, 9368–9371. (d) Blakemore, P. R.; Milicevic, S. D.; Perera, H.; Shvarev, A.; Zakharov, L. N. *Synthesis* **2008**, 2271–2277.

(8) For reviews of 1,1′-binaphthyl systems, including 1,1′-bi-2-naphthol (BINOL) derivatives, see: (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405–2494. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3211.

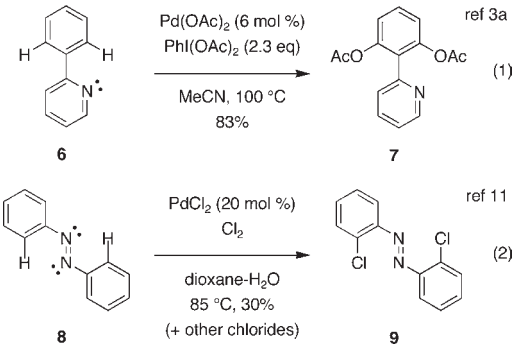
(9) Xiao, J.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 2876–2879.

(10) Tokuyama, H.; Sato, M.; Ueda, T.; Fukuyama, T. *Heterocycles* **2001**, *54*, 105–108.

Scheme 1. Existing 7/8 Step Synthesis of AzaBINOL (**1**) via 7-Hydroxyquinoline (**3**) Originating from 3-Aminophenol (**2**)

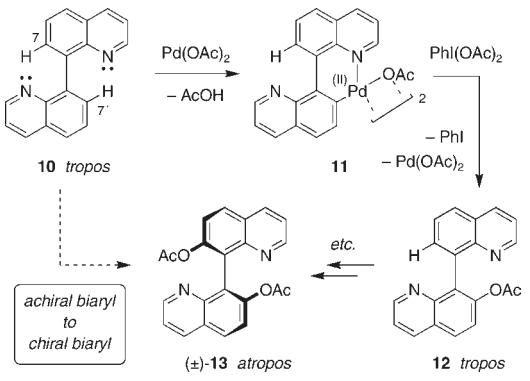


The aforementioned advances in substrate directed C−H functionalization prompted reevaluation of the azaBINOL synthesis. This axially chiral heterocyclic biaryl material could conceivably be accessed in a single step from 8,8′-biquinolyl (**10**) via a double C−H functionalization along similar lines to Sanford's conversion of 2-phenylpyridine (**6**) to bisacetoxylated product **7** (eq 1).[3a] Another



suggestive example, and one that is closer to the intended transformation in a topological sense at least, is seen in Fahey's chlorination of azobenzene (eq 2).[11] Thus, it was envisioned that each quinolyl N-atom in **10** could direct functionalization of the spatially proximal peri C−H bond on the opposing fused ring system (i.e., N1

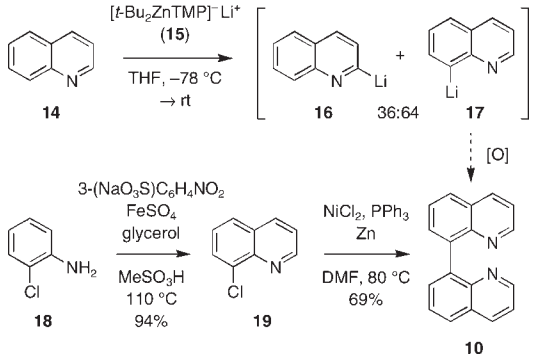
Scheme 2. Proposed Direct Route to Axially Chiral 7,7′-Dioxygenated 8,8′-Biquinolyls via Directed Double C−H Functionalization of Achiral 8,8′-Biquinolyl (**10**)



directs to C7′ and N1′ directs to C7). In this manner (Scheme 2), a configurationally labile (effectively achiral) *tropos* type biaryl system **10** would be initially converted via putative palladacycle **11** into a 7-oxygenated biquinolyl (**12**) and then further transformed in an identical fashion to the configurationally stable *atropos* type chiral biaryl system found in azaBINOL diester **13**. Realization of this concise approach to azaBINOLs began with identification of the most practical means to access 8,8′-biquinolyl (**10**).

A one-pot synthesis of biquinolyl **10** directly from quinoline (**14**) was initially pursued. Kondo et al. reported regioselective C8 lithiation of quinoline using a complex zincate base (**15**) generated in situ from lithium 2,2,6,6-tetramethylpiperide (LiTMP) and di-*tert*-butyl zinc.[12] The desired target is potentially available by homocoupling of 8-lithioquinoline (**17**) with a suitable oxidant; however, in our hands, lithiation of quinoline could not be achieved with a regioselectivity of higher than 64:36 (**17**:**16**)[13] and this fact precluded a satisfactory entry to **10** (Scheme 3).

Scheme 3. Synthesis of 8,8′-Biquinolyl (**10**)

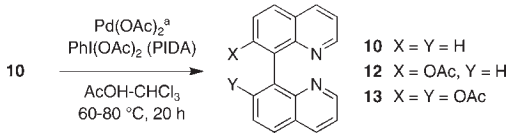


Furthermore, the ease of conducting such chemistry on a large scale is doubtful. Before abandoning the possibility of an efficient direct conversion of **14** to **10**, this feat was attempted by the Cu(II)-mediated intermolecular biaryl coupling procedure recently disclosed by Miura et al.[14] The original report described an azole coupling with an arylazine counterpart, and so it was perhaps not surprising that the desired azine/azine homocoupling reaction failed to occur and quinoline (an electron-deficient ring system) was recovered unchanged after protracted heating (> 24 h) in the presence of $Cu(OAc)_2$ and pivalic acid.[15]

Previous routes to biquinolyls have involved reductive homocoupling of haloquinolines,[16] and this tack was next successfully implemented using optimized procedures. 8-Chloroquinoline (**19**) was obtained in a pure form and in significant quantity (ca. 0.5 mol) by Skraup reaction from 2-chloroaniline (**18**). Next, Ni(0)-mediated coupling of **19** using Zn as a terminal reductant[17] furnished the desired biquinolyl **10** in excellent yield over a range of practical scales (5−50 mmol). Precipitation of biquinolyl **10** during workup obviated the need for chromatography; however, a little further processing of this material was required to remove traces of inorganic chlorides and quinoline that were inimical to subsequent Pd(II) catalyzed oxidation.[18]

Initial attempts to oxidize biquinolyl **10** to diacetate **13** in the presence of $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ (2.5 equiv) in AcOH (at 80 °C), a protocol previously reported by Sanford and co-workers,[3a] resulted in a low conversion to monoacetoxylated adduct **12** (≤10%, Table 1, entry 1).

Table 1. Directed Double C−H Functionalization of 8,8′-Biquinolyl (**10**) with $Pd(OAc)_2$/$PhI(OAc)_2$



no.	%AcOH in $CHCl_3$	**10** mmol	Pd(II) mol %	PIDA equiv	temp °C	% of biquinolyl distrib[b] **10**	**12**	**13**
1	100	0.5	5.0	2.5	80	88	10	<2
2	50	0.5	5.0	2.5	74	28	60	10
3	37.5	0.5	5.0	2.5	68	13	62	23
4	25	0.5	5.0	2.5	67	<2	22 (20)	62 (48)
5	12.5	0.5	5.0	2.5	64	<2	20 (12)	68 (51)
6	0	0.5	5.0	2.5	61	<2	31	42
7	12.5	2.0	5.0	2.5	64	<1	28	59 [48]
8	12.5	2.0	7.5	3.0	64	<1	22	61 [52]
9	12.5	2.0	7.5	1.2	64	16	68 (53)	11 (8)
10	12.5	10.0	5.0	2.5	64	<1	18	76 [51][c]

[a] Reactions conducted in open vessels using 0.15 M solutions of **10**. [b] Distribution of biquinolyl components (relative mol %) in the crude product mixture as quantified by ^{1}H NMR (400 MHz) spectral analysis; where determined, isolated % yields appear in parentheses indicating purification by SiO_2 chromatography and in square brackets indicating that pure product was obtained by EtOAc trituration only. [c] Reaction time of 36 h; an additional 13% yield of **13** was obtained from the EtOAc triturant residue by SiO_2 chromatography (total yield = 64%).

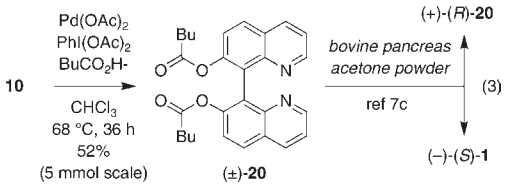
A significant majority of known C−H functionalizations of a similar nature involve 5-membered palladacycles rather than the kind of 6-membered variant required to access **12** and **13** (e.g., **11**).[2a,19] It was therefore suspected that tether geometry might hamper cyclometalation in this case, and we also speculated that the quinoline rings involved may lack sufficient nucleophilicity to be readily palladated at C7.[20] Since the protonation state would affect the ability of the basic azacycle to

(11) Fahey, D. R. *J. Organomet. Chem.* **1971**, *27*, 283–292.
(12) Lithiation of quinoline reported with a regioselectivity of 70:30 in favor of 8-lithio- versus 2-lithioquinoline, see: Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539–3540.
(13) Determined by conversion of lithiated quinolines to a mixture of 8- and 2-iodoquinolines by treatment with I_2 (47% isolated yield of 8-iodo-quinoline, 26% isolated yield of 2-iodoquinoline).
(14) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160–2162.

experience electrophilic substitution, a series of oxidations were conducted using varied blends of AcOH and $CHCl_3$ as the reaction solvent (entries 2−6). Under the chosen test conditions, an acceptable level of conversion was charted using a 1:7 mixture of AcOH and $CHCl_3$ (entry 5). It is likely that an acid cosolvent assists with catalyst turnover but, at a high concentration, inhibits both initial binding of Pd(II) to the biquinolyl and subsequent intramolecular electrophilic palladation.

With an optimal solvent composition so identified, the oxidation was investigated on larger scales (entries 7−10). Little was gained by increasing the reagent loading (entry 8), and monoacetate **12** could be deliberately targeted by appropriate adjustment to the stoichiometry of $PhI(OAc)_2$ (entry 9). Reactions on ≥10 mmol scale benefitted from a longer reacton time (entry 10). Significantly, it was found that diester **13** (a highly crystalline material) could be isolated in pure form by direct evaporation of the reaction solvent followed by trituration of the residue with EtOAc. Saponification of **13** with methanolic KOH (2 h, rt) gave azaBINOL (**1**) in high yield (>85%).[21]

It was previously demonstrated that racemic divalerate **20** is effectively resolved into (+)-(*R*)-**20** and (−)-(*S*)-**1** by a practical enzymatic hydrolysis using bovine pancreas acetone powder.[7c] Substitution of valeric acid for acetic acid in the solvent blend used for Sanford oxidation was the only change required to access this valuable precursor to scalemic azaBINOLs in good yield directly from **10** on a multigram scale (eq 3).



In summary, a concise synthesis of azaBINOL (**1**) from 2-chloroaniline (in 35% overall yield) has been developed that utilizes a Pd(II)-catalyzed directed double C−H functionalization. The key step is notable for several reasons: (1) an achiral (*tropos*) biaryl (**10**) is converted to a chiral (*atropos*) biaryl ligand system (**13**/**20**), and as such the reaction provides a viable platform for the study of enantioselective Pd(II)-catalyzed oxidations;[22] (2) the reaction progresses via putative 6-membered palladacycles rather than the more commonly encountered 5-membered examples; and (3) in this case, electrophilic metalation of an electron-deficient azine occurs without resort to an activation tactic (e.g., *N*-oxide formation).[23] In comparing the original 7/8 step synthesis of azaBINOL (**1**) with the new route described herein the improvement is marked. The C−H functionalization based approach is shorter and higher yielding overall; none of the steps involved require special precautions or awkward experimental procedures, and chromatography can be avoided.

The ready availability of azaBINOL (**1**) (and its easily resolved diester derivative **20**) made possible by this work will facilitate further investigation of biquinolyl templates in a wide variety of contexts, including: organocatalysis, metal mediated synthesis, and materials chemistry. Work along these lines will be reported in due course.

Acknowledgment. The National Science Foundation (CHE-0722319) and Murdock Charitable Trust (2005265) are thanked for support of the OSU NMR facility.

Supporting Information Available. All experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra. CIF file for 7-chloro-8,8′-biquinolyl. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Regioselective rhodation of the C8 position of quinoline may offer an alternative means to directly access **10** from **14**, see: Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780–3783.

(16) For the Ni(0) mediated reductive coupling of 8-bromoquinoline to give 8,8′-biquinolyl (**10**), see: (a) Benito, Y.; Canoira, L.; Rodriguez, J. G. *Appl. Organomet. Chem.* **1987**, *1*, 535–540. Biquinolyl **10** has also been prepared via pyrrolytic deauration of 8-quinolylgold(I) complexes: (b) Vaughan, L. G. *J. Organomet. Chem.* **1980**, *190*, C56–C58.

(17) Colon, I.; Kelsey *J. Org. Chem.* **1986**, *51*, 2627–2637.

(18) If residual $NiCl_2/ZnCl_2$ were not removed from the precipitated **10**, a significant quantity of 7-chloro-8,8′-biquinolyl was generated in the Sanford oxidation step (established by XRD). Nonproductive reduction of **19** to quinoline (**14**) occurs to a limited extent during its conversion to **10**. The Pd(II) catalyzed acetoxylation of samples of **10** contaminated by traces of quinoline proceeded sluggishly and failed to give an acceptable yield of **13**. Inorganic salts were removed from **10** by its redissolution in EtOAc−CH_2Cl_2 followed by filtration/concentration; trace quinoline was removed by trituration with *t*-BuOMe. See Supporting Information.

(19) A six-membered palladacycle somewhat related to **11** and generated by cyclometallation of 2-(diphenylphosphino)-1,1′-binaphthyl is known; however, see: Huang, X.-J.; Mo, D.-L.; Ding, C.-H.; Hou, X.-K. *Synlett* **2011**, 943–946.

(20) Simple pyridines and quinolines are often used as directing groups for palladation but are seldom metalated themselves (e.g., see ref 2a). For a recent review of cyclopalladation, see: Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.

(21) Monoacetate **12** was similarly hydrolyzed to yield 7-hydroxy-8,8′-biquinolyl, a potentially useful new *tropos* N,O-ligand. See Supporting Information for details of both saponification reactions.

(22) Enantioselective Pd(II)-catalyzed C−H functionalization reactions are in their infancy; for a particularly significant example by Yu and co-workers, see ref 4b. Other types of Pd(II)-catalyzed enantioselective transformations have been reported, for an example, see: Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476.

(23) For use of *N*-oxide derivatives to activate azines toward metal catalyzed C−H functionalization, see: (a) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749–759. (b) Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180–8189. (c) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56.