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COMMUNICATION

Copper-Catalysed Cross-Coupling of Arylzirconium Reagents with Aryl and Heteroaryl Iodides

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An unprecedented Cu^I-catalysed cross-coupling of arylzirconium reagents with aryl and heteroaryl iodides is reported. Mechanistic studies with a Cp₂Zr(Ar)(Cl) complex revealed that Cp₂Zr(Ar)(Cl) is the reactive species that undergoes transmetalation with (PN-1)CuI. In addition, experiments with radical probes indicated that the reaction proceeds via a non-radical pathway.

Cross-couplings represent one of the most widely utilised organic reactions for carbon-carbon (C–C) bond formation.^{1,2} These transformations, typically catalysed by Pd complexes, have been extensively utilised in the synthesis of a variety of molecular targets, pharmaceuticals and building blocks.³ Despite remarkable success over the last three decades and the maturity of the transformation with regard to its substrate scope, catalytic turnover and application, low abundance of Pd in nature remains a major concern for the long term sustainability of cross-couplings.

In this regard, Cu can be considered as an ideal alternative not only because of its abundance in nature but also due to its low cost and low toxicity to human health. As such, Cu has attracted a tremendous attention in its potential application to cross-coupling reactions.⁴ Early investigations undoubtedly showed improved effects of using Cu-salts in Pd- and Ni-catalysed cross-couplings.⁵ Cu-salts have remained instrumental in catalysing the coupling of Grignard reagents with organic electrophiles.⁶ However, the reactions only work with alkyl electrophiles, which proceed via a traditional S_N2 type mechanism. In 1996, Liebeskind and Allred demonstrated that stoichiometric amounts of Cu-salts alone could promote the coupling of aryltin reagents with aryl iodides.⁷ Since the disclosure of this seminal work, a number of stoichiometric and catalytic reactions have emerged and further increased hope to develop Cu as a viable alternative to Pd.⁸

Despite these early signs of optimism, the scope of the reaction remained limited as it typically required less functional group tolerant and highly reactive Grignard reagents and proceeded mainly with primary alkyl electrophiles.⁹ Subsequent reaction protocols that focused on more stable organometallic coupling partners such as organoboron reagents were only able to couple a limited number of arylboronic acids with aryl iodides.¹⁰

Recently, we¹¹ and others¹² have demonstrated that Cu-salts can catalyse the couplings of a variety of organoboron reagents and other organometallic coupling partners, such as organosilicon¹³ and organoindium reagents,¹⁴ with alkyl, aryl and heteroaryl halides. In our quest to demonstrate further the versatility of Cu-based catalytic systems, we have begun to search for reaction conditions that would enable us to utilise organozirconium reagents as coupling partners. Transmetalation of organozirconium reagents to Cu has been documented in Cu-mediated transformations of zirconacyclopentadienes to different molecules.^{4a} In 1996, Takahashi and coworkers further demonstrated that dicopper-diene complexes, generated via transmetalation of zirconacyclopentadienes with 2 equivalents of CuCl, could react with 1,2-dihaloarenes to afford fused aromatic rings.¹⁵ Aside from this literature precedent and subsequent reports with stoichiometric Cu-salts,¹⁶ we are unaware of any general and practical Cu-catalysed cross-coupling of arylzirconium reagents with aryl halides leading to the formation of biaryl compounds. Herein, we report one such reaction protocol that allows us to cross-couple a variety of arylzirconium reagents with aryl and heteroaryl iodides.

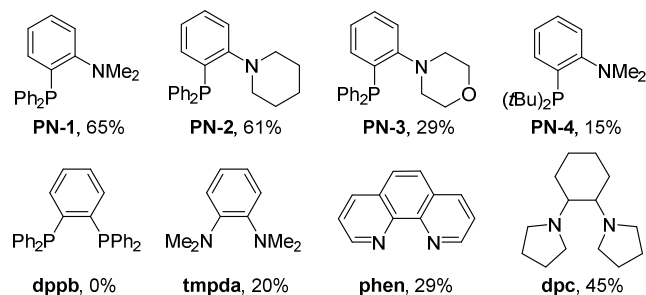
Our recent investigations have revealed that Cu-catalysed cross-coupling of organoboron¹¹ and organosilicon^{13c} reagents with aryl halides affords products in optimal yields when the reactions are conducted in DMF in the presence of a fluoride source or a base. Unfortunately, however, the cross-coupling of Cp₂Zr(Ph)(Cl),

generated *in situ* from a 1:1 mixture of Cp_2ZrCl_2 and PhLi ,³⁷ afforded the product in trace amounts under the previously established reaction conditions both with and without CsF in DMF (Table 1, entries 1-2). Further studies of the coupling under a variety of different conditions indicated that the reaction furnished the product in highest yield when conducted in THF without CsF and bases (entry 3). The fact that the reaction proceeds under neutral condition in an easily removable solvent THF should tender a wide synthetic benefit. While the reaction did not proceed in DMSO, the coupling can be conducted in 2-Me-THF, dioxane and toluene despite lower product yields (entries 4-7). Addition of bases or CsF did not improve the yield (entry 8). The reaction also proceeds in the absence of the added ligand PN-1 but only with 15% yield (entry 9). No product was observed in the absence of CuI (entry 10). Replacement of CuI with $[\text{CuOtBu}]$, purified by sublimation, also furnished the product in a reasonable yield (entry 11). PN-1 could also be replaced with a similar PN-2 ligand (Scheme 1). However, the reaction furnished the product in lower yields when PN-1 was replaced with morpholine-based and sterically hindered ligands PN-3 and PN-4. Bidentate phosphine ligand, 1,2-bis(diphenylphosphino)benzene (dppb), did not afford the product at all. Other bidentate nitrogen ligands, such as *N,N,N',N'*-tetramethyl-*o*-phenylenediamine (tmpda), phenanthroline (phen) and 1,2-dipyrrolidinocyclohexane (dpc), furnished the product in lower yields signifying the crucial role played by the PN-1 ligand in the current Cu-catalysed coupling of arylzirconium reagents with aryl iodides.

Table 1. Optimization of Reaction Conditions^a

entry	modified conditions	yield (%) ^b
1	1.5 equiv CsF , DMF instead of THF	trace
2	DMF instead of THF	trace
3	none	65 (60) ^c
4	DMSO	0
5	toluene	20
6	2-Me-THF	53
7	dioxane	35
8	CsF , Cs_2CO_3 , K_3PO_4 , NaOMe , or NaOAc	34-61
9	without PN-1	15
10	without CuI	0
11	CuOtBu (sublimed) instead of CuI	55

^aReactions were run on 0.20 mmol scale in 1 mL THF in a sealed tube. CuI (99.999%) was used. ^bCalibrated GC yields using 2-nitrophenyl as a standard. ^cThe number in parenthesis is the isolated yield from a 1.0 mmol scale reaction in 5 mL THF.



Scheme 1. Comparison of product yields with various ligands

After optimizing the conditions, we examined the substrate scope of the new coupling protocol. The current conditions allow the reactions to proceed between a variety of arylzirconium reagents and aryl iodides, affording the products in good to excellent yields (Table 2). Fortunately, the reaction can be conducted using both electron-deficient and electron-rich aryl iodides, and electron-neutral and electron-rich arylzirconium reagents.¹⁸ The cross-coupling also tolerates sterically hindered substrates (entries 13-14), and a wide range of functional groups including OMe, Cl, CF_3 , CN and OTBS in aryl iodides, further demonstrating its wide synthetic utility.

Table 2. Coupling of arylzirconium reagents with aryl iodides^a

entry	Ar in $\text{Cp}_2\text{Zr}(\text{Cl})\text{Ar}$	$\text{Ar}'\text{-I}$	$\text{Ar}'\text{-Ar}$	yield (%) ^b
1				
2			2, <i>p</i> - CF_3	75
3			3, <i>p</i> -CN	60
4			4, <i>p</i> -OMe	84
5			5, <i>p</i> -Cl	60
6			6, <i>p</i> -OTBS	40
			7, 3,5-di- CF_3	68
7				
8			8, <i>o</i> -OMe	56
			9, 3,5-di-F	69
9				
10			10, <i>p</i> -CN	80
11			11, <i>p</i> -OMe	74
			12, 3,4-di-Cl	68
12				77
13			13	
14			14, R = H	40
			15, R = Me	69
15				
16			16, R = 3-Cl	54
17			17, R = 3,5-di- CF_3	65
			18, R = 4-Me	70
18				
19			19, R = 3,5-di- CF_3	45
			20, R = 3-Cl	57
20				
			21	47

^aReactions were run on 1.0 mmol scale in a sealed tube. CuI (99.999%) was used. ^bIsolated yields.

The current reaction protocol can also be extended to the coupling of heteroaryl iodides (Table 3). Gratifyingly, the cross-coupling proceeds without the PN-1 ligand and affords the product in good yields. The reaction tolerates alkoxides on arylzirconium reagents and chloride on heteroaryl iodides.

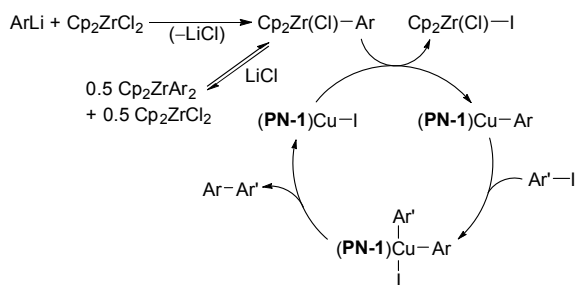
Table 3. Coupling of arylzirconium reagents with heteroaryl iodides^a

entry	Ar in Cp ₂ Zr(Cl)Ar	(Het)Ar-I	(Het)Ar-Ar	yield (%) ^b
1				22, R = H 66
2				23, R = Me 75
3				24, R = OMe 57
4				25, R = H 75
5				26, R = Me 62
6				27, R = OMe 65
7				28 63

^aReactions were run on 1.0 mmol scale in a sealed tube. CuI (99.999%) was used. ^bIsolated yields.

Based on literature reports^{11, 13-16, 19} and our own mechanistic studies, we now propose a catalytic cycle for this process (Scheme 2). In the catalytic reaction, arylzirconium reagents are prepared *in situ* by mixing a 1:1 ratio of ArLi and Cp₂ZrCl₂. However, the exact nature of the reactive ArZr-complex has not been known because the formation of both Cp₂Zr(Ar)(Cl) and Cp₂ZrAr₂ are possible at the reaction temperature. In order to determine the potential reactive species, we synthesized and characterized Cp₂Zr(C₆H₄-*p*Me)₂ (**29**) (Scheme 3). The structure of **29** was further confirmed by X-ray crystallography (Figure 1).²⁰ We then attempted the reaction of **29** with PhI, which revealed that this species has low reactivity both in the absence and presence of LiCl (Scheme 4).²¹ However, when one equivalent of Cp₂ZrCl₂ was added in the presence of LiCl, the reaction proceeded affording the product in 35% yield.²² Based on these experiments, we believe that Cp₂ZrCl₂ and the Cp₂ZrAr₂ complex compropionate to generate Cp₂Zr(Ar)(Cl), an intermediate that is also generated from a 1:1 mixture of ArLi and Cp₂ZrCl₂, as a reactive species that transmetalates with (PN-1)CuI to form (PN-1)CuAr. (PN-1)CuAr then reacts with ArI to afford the cross-coupled product and regenerates the catalyst.

The reaction of [RCu] species with ArI is generally considered to proceed via a radical or non-radical process.²³ In order to determine if aryl radicals were involved in the reaction, we performed radical clock experiments with **30** and **31** (Scheme 5), which produced only the coupled products.²⁴ We also conducted the standard reaction in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger, which formed the coupled product in significant amounts (Scheme 5). These experiments indicate that the current reaction does not involve aryl free radicals.



Scheme 2. Proposed catalytic cycle

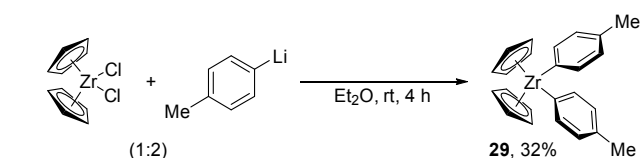
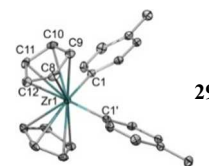
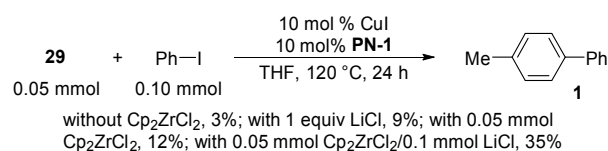
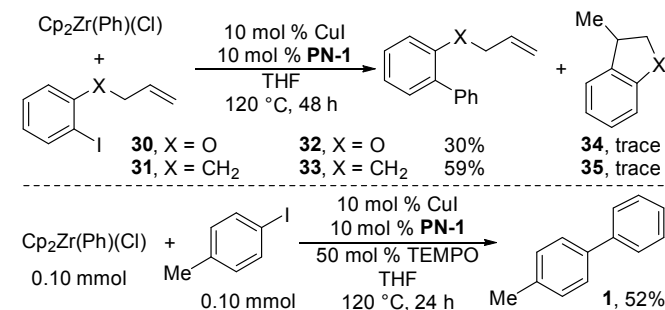
Scheme 3. Synthesis of Cp₂Zr(C₆H₄-*p*Me)₂

Fig. 1. X-ray structure of **29**. Selected bond lengths (Å) and angles (°): C1-Zr1, 2.3020(12), C8-Zr1, 2.5257(13); C1-Zr1-C1', 103.45(6), C1-Zr1-C8, 81.58(4), C1-Zr1-C11, 135.20(4).

Scheme 4. Reaction of Cp₂Zr(C₆H₄-*p*Me)₂ with PhI

Scheme 5. Radical clock and radical trap experiments

Conclusions

We have developed a Cu^I-catalysed coupling of arylzirconium reagents with aryl- and heteroaryl iodides that generates biaryl products in good to excellent yields. The reaction for the formation of aryl-heteroaryl products proceeds without the requirement for the addition of an external ligand. We have also conducted preliminary mechanistic studies *via* the synthesis and *in situ* generation of arylzirconium intermediates, and proposed a possible catalytic cycle. We further showed by experiments with radical probes and scavengers that the current Cu-catalysed cross-coupling does not involve aryl radical intermediates.

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization and crystallographic data, and the ^1H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c000000x/

- (a) R. F. Heck, in *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, 1991, 833; (b) F. Diederich, P. J. Stang, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, 1998; (d) E.-i. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71.
- For reviews, see: (a) T.-Y. Luh, M.-k. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187; (b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; (c) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555; (d) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669; (e) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508; (f) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; (g) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461; (h) T. J. Hiyama, *Organomet. Chem.* **2002**, *653*, 58; (i) C. J. Handy, A. S. Manoso, W. T. McElroy, W. M. Seganish, P. DeShong, *Tetrahedron* **2005**, *61*, 12201.
- (a) A. M. Rouhi, *Chem. Eng. News* **2004**, *82*, 49; (b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651.
- For reviews, see: (a) B. H. Lipshutz, *Acc. Chem. Res.* **1997**, *30*, 277; (b) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; (c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; (d) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632; (e) P. Wipf, *Synthesis* **1993**, *1993*, 537.
- (a) X. X. Liu, M. Z. Deng, *Chem. Commun.* **2002**, 622; (b) J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer, C. S. Burgey, *Org. Lett.* **2009**, *11*, 345; (c) B. H. Lipshutz, D. M. Nihan, E. Vinogradova, B. R. Taft, Z. V. Bogkovic, *Org. Lett.* **2008**, *10*, 4279.
- G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748.
- (a) T. Takeda, K.-i. Matsunaga, Y. Kabasawa, T. Fujiwara, *Chem. Lett.* **1995**, *24*, 771; (b) J. R. Falck, R. K. Bhatt, J. Ye, *J. Am. Chem. Soc.* **1995**, *117*, 5973; (c) Y. Wang, D. J. Burton, *Org. Lett.* **2006**, *8*, 1109; (d) S. Mohapatra, A. Bandyopadhyay, D. K. Barma, J. H. Capdevila, J. R. Falck, *Org. Lett.* **2003**, *5*, 4759; (e) S.-K. Kang, T. Yamaguchi, T.-H. Kim, P.-S. Ho, *J. Org. Chem.* **1996**, *61*, 9082; (f) E. Piers, M. A. Romero, *J. Am. Chem. Soc.* **1996**, *118*, 1215; (g) S.-K. Kang, J.-S. Kim, S.-C. Choi, *J. Org. Chem.* **1997**, *62*, 4208; (h) J.-H. Li, B.-X. Tang, L.-M. Tao, Y.-X. Xie, Y. Liang, M.-B. Zhang, *J. Org. Chem.* **2006**, *71*, 7488.
- (a) G. Cahiez, O. Gager, J. Buendia, *Angew. Chem. Int. Ed.* **2010**, *49*, 1278; (b) J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2003**, *125*, 5646; (c) C.-T. Yang, Z.-Q. Zhang, J. Liang, J.-H. Liu, X.-Y. Lu, H.-H. Chen, L. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 11124; (d) D. H. Burns, J. D. Miller, H.-K. Chan, M. O. Delaney, *J. Am. Chem. Soc.* **1997**, *119*, 2125.
- For reactions with alkynyl halides, see: 8a. For a few examples of reactions with secondary alkyl electrophiles, see: 8c-d.
- (a) M. B. Thathagar, J. Beckers, G. Rothenberg, *J. Am. Chem. Soc.* **2002**, *124*, 11858; (b) J.-H. Li, J.-L. Li, D.-P. Wang, S.-F. Pi, Y.-X. Xie, M.-B. Zhang, X.-C. Hu, *J. Org. Chem.* **2007**, *72*, 2053; (c) J. Mao, J. Guo, F. Fang, S.-J. Ji, *Tetrahedron* **2008**, *64*, 3905; (d) Y.-M. Ye, B.-B. Wang, D. Ma, L.-X. Shao, J.-M. Lu, *Catal. Lett.* **2010**, *139*, 141. For reactions of arylboronic acids with ArBr, see: 10c-d.
- S. K. Gurung, S. Thapa, A. Kafle, D. A. Dickie, R. Giri, *Org. Lett.* **2014**, *16*, 1264.
- (a) C.-T. Yang, Z.-Q. Zhang, Y.-C. Liu, L. Liu, *Angew. Chem. Int. Ed.* **2011**, *50*, 3904; (b) Y. Zhou, W. You, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed.* **2014**, *53*, 3475; (c) T. W. Liwosz, S. R. Chemler, *Org. Lett.* **2013**, *15*, 3034.
- (a) S. K. Gurung, S. Thapa, B. Shrestha, R. Giri, *Synthesis* **2014**, *46*, 1933; (b) H. Ito, H.-o. Sensui, K. Arimoto, K. Miura, A. Hosomi, *Chem. Lett.* **1997**, *26*, 639; (c) S. K. Gurung, S. Thapa, A. S. Vangala, R. Giri, *Org. Lett.* **2013**, *15*, 5378; (d) A. Tsubouchi, Muramatsu, T. Takeda, *Angew. Chem. Int. Ed.* **2013**, *52*, 12719; (e) J. R. Herron, Z. T. Ball, *J. Am. Chem. Soc.* **2008**, *130*, 16486; (f) V. Russo, J. R. Herron, Z. T. Ball, *Org. Lett.* **2009**, *12*, 220; (g) J. R. Herron, V. Russo, E. J. Valente, Z. T. Ball, *Chem. Eur. J.* **2009**, *15*, 8713; (h) L. Cornelissen, M. Lefrancq, O. Riant, *Org. Lett.* **2014**, *16*, 3024; (i) L. Cornelissen, V. Cirriez, S. Vercruyssen, O. Riant, *Chem. Commun.* **2014**, *50*, 8018.
- S. Thapa, S. K. Gurung, D. A. Dickie, R. Giri, *Angew. Chem. Int. Ed.* **2014**, *53*, 11620.
- T. Takahashi, R. Hara, Y. Nishihara, M. Kotora, *J. Am. Chem. Soc.* **1996**, *118*, 5154.
- (a) T. Takahashi, W.-H. Sun, C. Xi, U. Haruka, Z. Xi, *Tetrahedron* **1998**, *54*, 715; (b) Y. Ni, K. Nakajima, K.-i. Kanno, T. Takahashi, *Org. Lett.* **2009**, *11*, 3702; (c) T. Takahashi, Y. Li, P. Stepnicka, M. Kitamura, Y. Liu, K. Nakajima, M. Kotora, *J. Am. Chem. Soc.* **2002**, *124*, 576; (d) T. Takahashi, W.-H. Sun, Z. Duan, B. Shen, *Org. Lett.* **2000**, *2*, 1197; (e) Y. Liu, C. Xi, R. Hara, K. Nakajima, A. Yamazaki, M. Kotora, T. Takahashi, *J. Org. Chem.* **2000**, *65*, 6951; (f) Y. Yamamoto, T. Ohno, K. Itoh, *Chem. Commun.* **1999**, 1543.
- PhLi was generated from *n*BuLi and PhI. PhLi generated *in situ* from PhI and Li gave low product yields. See the supporting information for details.
- Reaction of (*E*)-stryrylzirconocene chloride with *p*-iodotoluene did not afford the cross-coupled product. Attempts to generate other functionalised arylzirconocene chlorides failed potentially due to functional group incompatibility in generating aryllithium species.
- (a) C. Chen, C. Xi, Y. Jiang, X. Hong, *J. Am. Chem. Soc.* **2005**, *127*, 8024; (b) Y. Zhou, X. Yan, C. Chen, C. Xi, *Organometallics* **2013**, *32*, 6182.
- For the X-ray structure of a similar complex, see: G. W. Margulieux, S. P. Semproni, P. J. Chirik, *Angew. Chem. Int. Ed.* **2014**, *53*, 9189.
- LiCl (1 equiv) is formed when $\text{Cp}_2\text{Zr}(\text{Ar})\text{Cl}$ is generated *in situ* from a 1:1 mixture of Cp_2ZrCl_2 and ArLi. Therefore, 1 equiv of LiCl was added in order to imitate the actual catalytic reaction conditions.
- For the role of LiI in stabilizing [RCu], see: (a) J. Wei, Z. Wang, W.-X. Zhang, Z. Xi, *Org. Lett.* **2013**, *15*, 1222; (b) W. Geng, J. Wei, W.-X. Zhang, Z. Xi, *J. Am. Chem. Soc.* **2014**, *136*, 610.
- (a) R. Giri, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 15860; (b) G. O. Jones, P. Liu, K. N. Houk, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 6205.
- The aryl radicals generated from the radical probes **30** and **31** are known to cyclize in DMSO and DMF at 23 and 50 °C to give the cyclized products **34** and **35** with k_{obs} of $9.6 \times 10^9 \text{ s}^{-1}$ and $5.0 \times 10^8 \text{ s}^{-1}$, respectively. See: (a) A. Annunziata, C. Galli, M. Marinelli, T. Pau, *Eur. J. Org. Chem.* **2001**, 1323; (b) A. N. Abeywickrema, A. L. J. Beckwith, *J. Chem. Soc. Chem. Commun.* **1986**, 464.

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