

Synthetic Methods

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Practical Direct α -Arylation of Cyclopentanones by Palladium/Enamine Cooperative Catalysis

Yan Xu, Tianshun Su, Zhongxing Huang, and Guangbin Dong*

Abstract: Direct arylation of cyclopentanones has been a long-standing challenge because of competitive self-aldol condensation and multiple arylations. Reported herein is a direct mono- α -C–H arylation of cyclopentanones with aryl bromides which is enabled by palladium/amine cooperative catalysis. This method is scalable and chemoselective with broad functional-group tolerance. Application to controlled sequential arylation of cyclopentanones has been also demonstrated.

The Buchwald–Hartwig–Miura (BHM) arylation represents a cornerstone in functionalizing carbonyl compounds through transition metal catalyzed cross-coupling with aryl halides.^[1,2] While broad substrate scope has been established for this transformation, simple or less substituted cyclopentanones have been known as problematic substrates^[3] despite α -arylated cyclopentanones being widely found in pharmaceuticals and bioactive compounds (Figure 1). The challenge is attributed to the side reactions of the cyclopentanones, for example, self-aldol condensation^[3a,c] and multiarylation,^[3b] which result from the basic reaction media and more acidic α -hydrogen atoms in singly arylated products (Scheme 1 a).^[4]

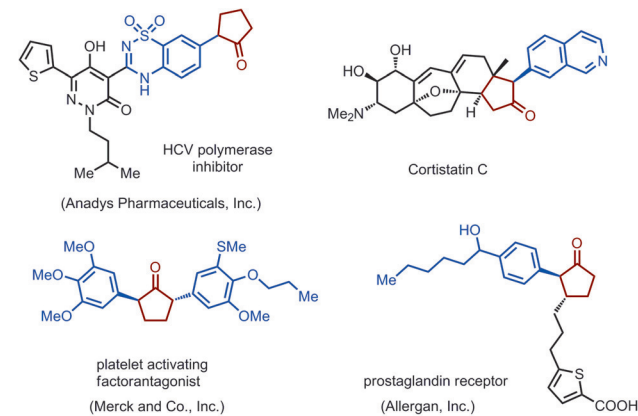


Figure 1. Representative examples of bioactive α -arylated cyclopentanones.

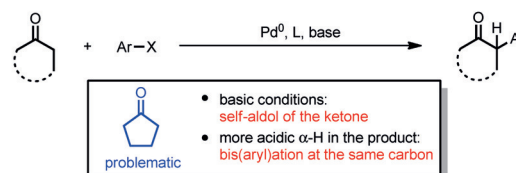
[*] Y. Xu, Z. Huang, Prof. Dr. G. Dong
 Department of Chemistry, University of Texas at Austin
 100 East 24th street, Austin, TX 78712 (USA)
 E-mail: gbdong@cm.utexas.edu
 Homepage: <http://gbdong.cm.utexas.edu/>

T. Su

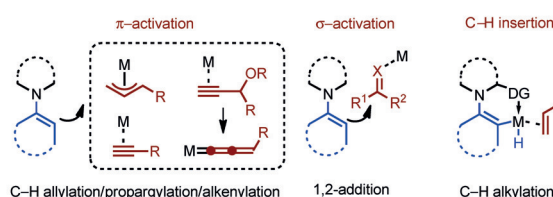
Department of Chemistry, University of Science and Technology of China (USTC), Hefei, Anhui 230026 (China)

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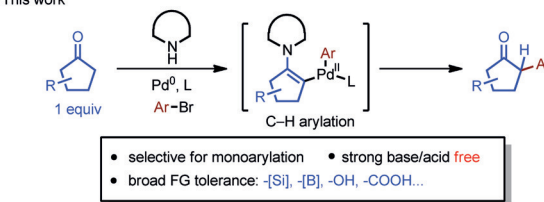
a) Buchwald–Hartwig–Miura α -arylation



b) Previous C–C bond formation at ketone α -position via metal–enamine catalysis



c) This work



Scheme 1. α -Functionalization of ketones. DG = donating group.

Consequently, only few examples^[5] have been reported wherein either excess^[6] or specialized cyclopentanones are used.^[3a,7] More often, indirect multistep approaches are employed to access α -arylated cyclopentanones.^[8–10] Thus, a general solution to the cyclopentanone arylation problem remains to be discovered. Complementary to the BHM reaction, herein, a direct α -C–H arylation strategy between readily available aryl bromides and normal cyclopentanones is described using palladium/enamine cooperative catalysis. This method is highly selective for monoarylation, operationally simple, and exceptionally chemoselective.

Merging transition-metal and enamine catalysis has enabled a number of powerful C–C bond-forming transformations at the α -position of carbonyl compounds.^[11,12] The mode of activation generally includes 1) nucleophilic attack of enamines on metal-activated allyl, benzylic, propargyl, and alkynyl electrophiles; 2) 1,2- or 1,4-addition to polar π bonds activated by Lewis-acidic metals (Scheme 1 b).^[11c] In addition, we recently reported a directed C–H insertion/metalation approach for ketone α -alkylation^[13a–c] and alkenylation^[13d] with olefins and alkynes. Moreover, through combining enamine and copper catalysis, elegant trifluoromethylation,^[14a] arylation,^[14b] and vinylation^[14c] of more reactive

aldehyde substrates were reported by MacMillan and co-workers using hypervalent iodonium salts. However, to the best of our knowledge, direct catalytic ketone α -arylation by transition metal/enamine catalysis has not been reported to date (Scheme 1c).

To address the challenge of the α -arylation of cyclopentanones, a palladium/enamine cooperative catalysis strategy was conceived (Figure 2). Starting with a secondary amine and a palladium(0) catalyst, an enamine and a $X\text{-Pd}^{\text{II}}$ -aryl species can be formed, respectively, with cyclopentanone and the aryl halide (steps A and B). Subsequently, C–H metalation of the enamine would afford an enaminyll-arylpalladium(II) intermediate (steps C and D),^[15] which can undergo reductive elimination and hydrolysis to provide the arylated ketone and regenerate the catalysts (step E). This strategy avoids the use of strong bases (or acids), thus self-aldol reactions should be less favorable. In addition, over arylation can be minimized because enamine formation is highly sensitive to the sterics of the ketone substrate. Furthermore, because of the redox-neutral and mild pH conditions, high chemoselectivity and broad functional-group tolerance are expected.

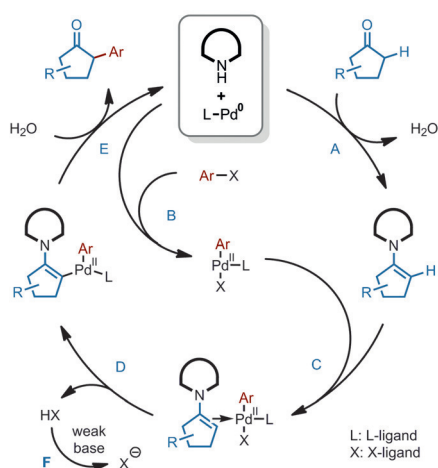


Figure 2. Proposed strategy.

Nevertheless, the challenges of the proposed strategy are twofold: 1) In palladium catalysis, amines are known to either reduce aryl halides to arenes^[16] or cross-couple to form anilines,^[17] thus, the compatibility between the two catalytic processes would be one concern. 2) The kinetics of forming the enamine and $X\text{-Pd}^{\text{II}}$ -aryl species need to match each other. Otherwise, known side reactions, such as enamine-aldol,^[18] ketone dehydrogenation,^[19] and aryl dimerization^[20] can compete. Hence, to test the feasibility of this strategy, cyclopentanone and PhBr were employed as model substrates. After investigating various reaction parameters, using pyrrolidine as the amine catalyst and $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tol})_3$ provided the desired monoarylation product in 75% yield (Table 1).^[21] Interestingly, lowering the palladium loading (down to 2.5 mol%) increased the yield up to 85% (entries 18–20). Control experiments were then conducted,

Table 1: Selected optimization studies.

Entry	Variation on the reaction conditions given above	Yield [%] ^[a]
1	none	75
2	no pyrrolidine	0
3	no $\text{Pd}(\text{OAc})_2$	0
4	no $\text{P}(\text{o-tol})_3$	9
5	PPh_3 instead of $\text{P}(\text{o-tol})_3$	48
6	$\text{P}(1\text{-naphthyl})_3$ instead of $\text{P}(\text{o-tol})_3$	58
7	$\text{P}(\text{tBu})_3$ instead of $\text{P}(\text{o-tol})_3$	73
8	$\text{P}(\text{iPr})_3$ instead of $\text{P}(\text{o-tol})_3$	0
9	$[\text{Pd}^0\{\text{P}(\text{o-tol})_3\}_2]$ instead of $\text{Pd}(\text{OAc})_2/\text{P}(\text{o-tol})_3$	77
10	no amine 4	59
11	NEt_3 instead of 4	54
12	no NaOAc	27
13	NaHCO_3 instead of NaOAc	57
14	Na_2CO_3 instead of NaOAc	52
15	4 (1 equiv)/PivOH (1 equiv) instead of 4 (30 mol%)/NaOAc (1 equiv)	67
16	80 °C, 26 h ^[b]	75
17	60 °C, 48 h, with $\text{P}(\text{tBu})_3$ ^[b]	60
18	with 5 mol% $\text{Pd}(\text{OAc})_2/10$ mol% $\text{P}(\text{o-tol})_3$	79
19	with 2.5 mol% $\text{Pd}(\text{OAc})_2/5$ mol% $\text{P}(\text{o-tol})_3$	82
20	with 2.5 mol% $\text{Pd}(\text{OAc})_2/5$ mol% $\text{P}(\text{o-tol})_3$ ^[b]	85 (80)
21	PhBr (1 equiv) ^[c]	80
22	H_2O (1 equiv) was added ^[c]	74
23	under air ^[c]	50

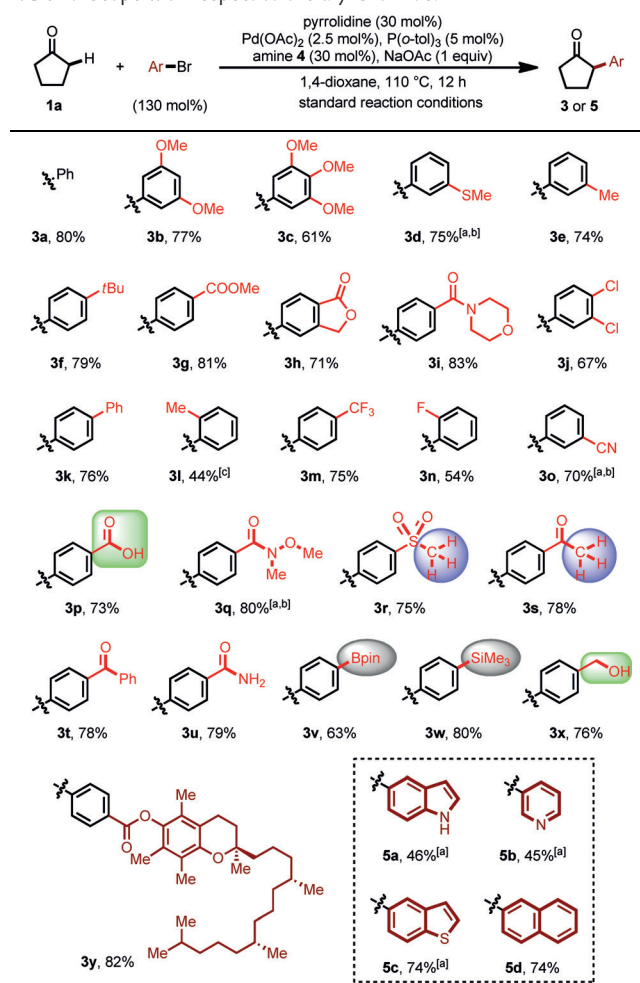
[a] Determined by GC analysis using dodecane as the internal standard.

[b] 30 mol% pyrrolidine was used. [c] Change was made based on entry 20.

and both pyrrolidine^[22] and $\text{Pd}(\text{OAc})_2$ were found to be pivotal (entries 2 and 3). Among various ligands, $\text{P}(\text{o-tol})_3$ proved to be excellent, although $\text{P}(\text{tBu})_3$ worked almost equally as well (entries 4–8). The amine 4 was found to be an important additive, although its role remains to be defined (entries 10 and 11).^[13b] One equivalent of a weak base is required to neutralize the HBr generated from the reaction (see step F in Figure 2). While NaOAc proved to be optimal, other weak bases, such as NaHCO_3 , were also effective (Table 1, entries 12–14). Note that near-neutral conditions can be adopted when NaOAc is replaced with a 1:1 4/PivOH buffer (entry 15). Lower temperatures are also possible but longer reaction times are required (entries 16 and 17). In addition, 1 equivalent of PhBr can be used without significant loss of yield (entry 20). Finally, high compatibility with water (entry 22) and moderate tolerance of air (entry 23) were observed.

The substrate scope was subsequently examined (Table 2). Various aryl bromides having different electronic properties were efficiently coupled in good to excellent yields. Substitutions at the *ortho*-, *meta*-, or *para*-positions were all tolerated. Functional groups (FGs), such as aryl chlorides (3j), fluorides (3n), esters (3g and 3h), nitriles (3o), amides (3i, 3q and 3u), thioethers (3d), and even a tocopherol moiety (3y), were compatible. Substrates bearing enolizable protons, such as methyl sulfones (3r), or FGs which are

Table 2: Scope with respect to the aryl bromide.

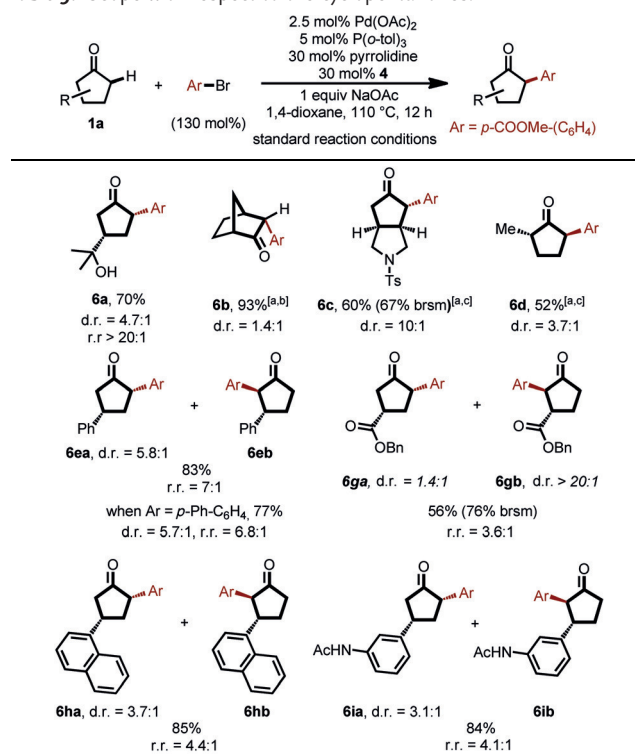


Yields shown are those of the isolated product. [a] With 10 mol% Pd(OAc)₂, 20 mol% P(o-tol)₃. [b] 24 h. [c] With 2 equiv of ArBr, 18 h. pin = pinacol.

sensitive to nucleophiles, for example, benzophenones (**3t**) and Weinreb amides (**3q**), all worked well. Remarkably, free carboxylic acids (**3p**) and alcohols (**3x**) remained intact. In addition, this transformation is highly chemoselective for cyclopentanones. For example, the methyl aryl ketone **3s** was well tolerated, and is likely attributed to the rate difference in enamine formation.^[23] Encouragingly, aryl silanes (**3w**) and boronic esters (**3v**), well known partners for palladium-catalyzed cross couplings, remained untouched because of the lack of strong bases. Furthermore, both electron-rich and electron-deficient heteroarenes and polyarenes, such as unprotected indole (**5a**), pyridine (**5b**), benzothiophene (**5c**) and naphthalene (**5d**) can also be introduced. Altogether, this arylation method offers distinct and complementary features to those of the BHM reaction.

Cyclopentanones with different substitution patterns were tested (Table 3).^[24] Substitutions at α - or β -positions, including alkyl, aryl, and carbonyl groups, were all tolerated. Both bridged (**6b**) and fused cycles (**6c**) are suitable substrates. Interestingly, tertiary alcohol moiety was also competent

Table 3: Scope with respect to the cyclopentanones.

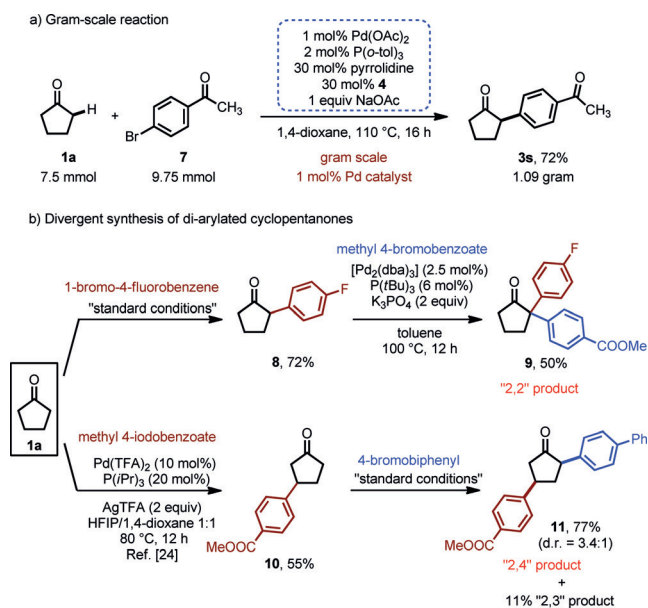


Yields shown are those of the isolated product. The d.r. and r.r. values were determined by NMR analysis of the crude reaction mixture. [a] With 10 mol% Pd(OAc)₂, 20 mol% P(o-tol)₃ and 50 mol% of pyrrolidine. [b] 18 h. [c] Without **4**, 24 h. Ts = 4-toluenesulfonyl.

(**6a**). For substrates with an existing stereocenter, moderate to good diastereoselectivity was observed. The thermodynamically more stable isomers were favored, which is likely controlled by the rapid keto–enol tautomerization under the reaction conditions.

A gram-scale preparation was demonstrated using 1 mol% palladium (Scheme 2a). Given the relatively low costs of each reagent used and the tolerance of moisture/air, this protocol is expected to be practical for larger scales. Further applications were illustrated in the synthesis of multiarylated cyclopentanones (Scheme 2b), which are challenging to prepare by other methods. While the previous attempt only offered the bis(aryl)ated product in spite of using excess cyclopentanone,^[4] under the current reaction conditions the monoarylated product was smoothly obtained. Further conversion into the 2,2-diarylated product **9** was achieved with a regular BHM reaction. In contrast, by using our previously developed β -arylation methods,^[25] followed by the current α -arylation protocol, the 2,4-diarylated compound **11** was rapidly synthesized in two steps from cyclopentanones.

In conclusion, the long-standing challenge of mono- α -arylation of cyclopentanones is addressed by palladium/enamine cooperative catalysis. The unique mode of activation should have further implications on developing other ketone α -functionalization reactions. Efforts on elucidating detailed reaction mechanism are ongoing.



Scheme 2. Synthetic applications. dba = dibenzylideneacetone, TFA = trifluoroacetate.

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- [1] For seminal works of the α -arylation of carbonyl compounds, see: a) M. Kosugi, M. Suzuki, I. Hagiwara, K. Goto, K. Saitoh, T. Migita, *Chem. Lett.* **1982**, 939; b) M. Kosugi, I. Hagiwara, T. Sumiya, T. Migita, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242; c) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108; d) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382; e) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740; *Angew. Chem.* **1997**, *109*, 1820.
- [2] For recent reviews, see: a) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234; b) C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, *49*, 676; *Angew. Chem.* **2010**, *122*, 686; c) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; d) D. Prim, S. Marque, A. Gaucher, J.-M. Campagne in *Organic Reactions*, Vol. 76 (Ed.: S. Denmark), Wiley, Hoboken, **2012**, p. 49.
- [3] a) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; b) J. Chae, J. Yun, S. L. Buchwald, *Org. Lett.* **2004**, *6*, 4809; c) J. M. Knapp, J. S. Zhu, D. J. Tantillo, M. J. Kurth, *Angew. Chem. Int. Ed.* **2012**, *51*, 10588; *Angew. Chem.* **2012**, *124*, 10740.
- [4] Even with excess cyclopentanone, *gem*-diarylation instead of monoarylation can still be preferred. See: A. Thaher, P. Koch, V. Del Amo, P. Knochel, S. Laufer, *Synthesis* **2008**, 225.
- [5] For a unique transition-metal-free ketone α -arylation, see: Q. Xu, H. Gao, M. Yousufuddin, D. H. Ess, L. Kürti, *J. Am. Chem. Soc.* **2013**, *135*, 14048, and references therein.
- [6] For examples of α -arylation of simple cyclopentanone, see: a) R. Mutter, I. B. Campbell, E. M. Martin De La Nava, T. Merritt, M. Wills, *J. Org. Chem.* **2001**, *66*, 3284; b) J. L. Rutherford, M. P. Rainka, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 15168; c) M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem. Int. Ed.* **2005**, *44*, 403; *Angew. Chem.* **2005**, *117*, 407. For a recent example of mono- α -arylation of acetone, see: d) W. C. Fu, C. M. So, W. K. Chow, O. Y. Yuen, F. Y. Kwong, *Org. Lett.* **2015**, *17*, 4612.
- [7] For selected examples of α -arylation of specialized cyclopentanones, see: a) J. Åhman, J. P. Wolfe, M. V. Troutman, M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 1918; b) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261; c) X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195; d) S. Ge, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 16330; e) G. Chen, F. Y. Kwong, H. O. Chan, W.-Y. Yu, A. S. C. Chan, *Chem. Commun.* **2006**, 1413.
- [8] For representative examples of coupling of premade enol ethers with aryl halides, see: a) ref. [3b]; b) H. Yang, R. Larock, E. Yum, *Tetrahedron* **1994**, *50*, 305; c) P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* **2003**, *125*, 3430; d) G. K. Datta, M. Larhed, *Org. Biomol. Chem.* **2008**, *6*, 674; e) A. Trejos, J. Sävmarker, S. Schlummer, G. K. Datta, P. Nilsson, M. Larhed, *Tetrahedron* **2008**, *64*, 8746; f) A. Martínez, M. J. Webber, S. Müller, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 9486; *Angew. Chem.* **2013**, *125*, 9664.
- [9] For representative examples of ring-expansion rearrangement of four-membered rings, see: a) J. W. Seo, H. J. Kim, B. S. Lee, J. A. Katzenellenbogen, D. Y. Chi, *J. Org. Chem.* **2008**, *73*, 715; b) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878; c) J. A. Dabrowski, D. C. Moebius, A. J. Wommack, A. F. Kornahrens, J. S. Kingsbury, *Org. Lett.* **2010**, *12*, 3598; d) Y.-M. Shen, B. Wang, Y. Shi, *Angew. Chem. Int. Ed.* **2006**, *45*, 1429; *Angew. Chem.* **2006**, *118*, 1457; e) Z. Chai, T. J. Rainey, *J. Am. Chem. Soc.* **2012**, *134*, 3615; f) F. Romanov-Michailidis, L. Guénée, A. Alexakis, *Angew. Chem. Int. Ed.* **2013**, *52*, 9266; *Angew. Chem.* **2013**, *125*, 9436; g) Q. Yin, S.-L. You, *Org. Lett.* **2014**, *16*, 1810; h) F. Romanov-Michailidis, M. Romanova-Michaelides, M. Pupier, A. Alexakis, *Chem. Eur. J.* **2015**, *21*, 5561.
- [10] For representative examples of 1,2-addition of aryl nucleophiles to cyclopentanones followed by elimination/oxidation sequence, see: Ref. [4] and M. Góra, M. K. Łuczynski, J. J. Sepioł, *Synthesis* **2005**, 1625.
- [11] For reviews, see: a) Z. H. Shao, H.-B. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; b) C. Zhong, X.-D. Shi, *Eur. J. Org. Chem.* **2010**, 2999; c) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633; d) Z.-T. Du, Z.-H. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337; e) Y. Deng, S. Kumar, H. Wang, *Chem. Commun.* **2014**, *50*, 4272; f) D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, *Acc. Chem. Res.* **2014**, *47*, 2365.
- [12] For a review on ketone-based C–H functionalization, see: Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764.
- [13] a) Z. Wang, B. J. Reinius, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 13954; b) F. Mo, G. Dong, *Science* **2014**, *345*, 68; c) H. N. Lim, G. Dong, *Angew. Chem. Int. Ed.* **2015**, *54*, 15294; *Angew. Chem.* **2015**, *127*, 15509; d) Z. Wang, B. J. Reinius, G. Dong, *Chem. Commun.* **2014**, *50*, 5230.
- [14] a) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986; b) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260; c) E. Skucas, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 9090.
- [15] For examples on related C–H metalation with Ar–Pd^{II} species, see: Ref. [3c], D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172.

- [16] E. Brenner, Y. Fort, *Tetrahedron Lett.* **1998**, 39, 5359.
- [17] For selected reviews, see: a) J. F. Hartwig, *Acc. Chem. Res.* **1998**, 31, 852; b) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, 47, 6338; *Angew. Chem.* **2008**, 120, 6438; c) J. F. Hartwig, *Acc. Chem. Res.* **2008**, 41, 1534; d) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, 2, 27.
- [18] For a recent review, see: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, 107, 5471.
- [19] J. Muzart, *Eur. J. Org. Chem.* **2010**, 3779.
- [20] For selected examples, see: a) D. D. Hennings, T. Iwama, V. H. Rawal, *Org. Lett.* **1999**, 1, 1205; b) T. D. Nelson, R. D. Crouch, *Org. React.* **2004**, 265.
- [21] The diarylated product was only observed in a trace amount (ca. 2%).
- [22] Attempts to use various chiral secondary amines resulted in no enantiomeric induction, and is likely attributed to the rapid formation of conjugated enol or enamine (racemization) during the reaction.
- [23] D. Sánchez, D. Bastida, J. Burés, C. Isart, O. Pineda, J. Vilarasa, *Org. Lett.* **2012**, 14, 536.
- [24] In a preliminary investigation, mono α -arylation was also observed with cycloheptanone (20% yield) and cyclooctanone (ca. 10% yield) using 4-bromobiphenyl under standard reaction conditions.
- [25] Z. Huang, G. Dong, *J. Am. Chem. Soc.* **2013**, 135, 17747.
- [26] CCDC 1437119 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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