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Regioselectivity Switch Achieved in the Palladium Catalyzed α-Arylation of Enones by Employing the Modified Kuwajima–Urabe Conditions

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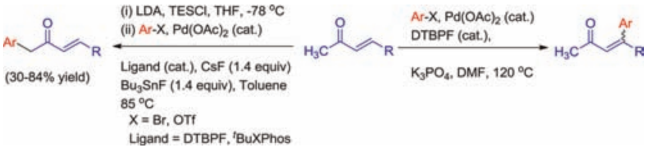
ABSTRACT



A new regioselective approach to the synthesis of α-aryl enones is reported. This represents an important application of the Kuwajima–Urabe protocol toward the synthesis of this simple albeit complex functional array. Several α-aryl enones were synthesized by the palladium catalyzed arylation of triethylsilylenol ethers of enones with high regioselectivity and broad scope, utilizing sterically encumbered electron-rich phosphine ligands to drive the reaction.

Transition metal catalyzed, and in particular Pd-catalyzed, α-arylation of ketones and other enolizable carbonyl compounds is a versatile reaction of tremendous synthetic utility.[1] This reaction belongs to a rather rare class of the few cross-coupling reactions that form an sp^2–sp^3 C–C bond. Several catalyst systems and variations of this reaction have been reported in the past few decades, and this class of reaction has been very well reviewed recently.[2,3] The reaction is essentially base catalyzed and involves a transmetalation/nucleophilic substitution step involving the oxidatively inserted aryl halide or triflate and the ketone enolate.[3,4]

In the course of the synthesis of a resorcylic acid lactone, we were confronted with the synthesis of an α-aryl enone. The most common methods of syntheses of this functional array include aldol condensations, cross-metathesis, and elimination reactions. Given the sensitive nature of other functional groups in our target molecule, a mild and simple synthesis for this functional array is needed. An obvious contemplation was the base-mediated, transition metal catalyzed α-arylation reaction. However, an apparent expected outcome was the possibility of a Heck reaction involving the olefin of the enone, which has been well documented and reviewed.[5] The regioselectivity for arylation would depend upon which of the two reactions is more feasible, the transmetalation with the enolate or the migratory insertion of the enone double bond.[6] Research groups of Buchwald[7] and Hartwig[8] have reported

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[1] Schlummer, B.; Scholz, U. In *Modern Arylation Methods* (Ed. Ackermann, L.), Wiley-VCH: Weinheim, 2009, pp 69–120.

[2] (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (b) Llyod-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953–956. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. (d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707. (e) Novák, P.; Martin, R. *Curr. Org. Chem.* **2011**, *15*, 3233–3262.

[3] Kulkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.

[4] For seminal work on palladium catalyzed direct α-arylation of ketones with bromides, see: (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740–1742. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (c) Harmann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.

[5] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

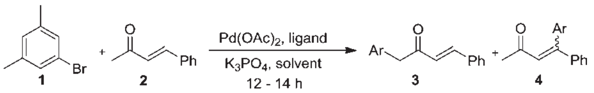
[6] Huang, D. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 5757–5761.

[7] (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370. (b) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919.

[8] Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

10.1021/ol300401c

Table 1. Attempts toward Base Catalyzed α-Arylation of Enones[a]



ligand	THF	dioxane (ratio of **3**:**4**)	toluene	DMF
S-Phos	60:40 (50)	23:77 (40)	21:79(50)	1:99 (80)
X-Phos	79:21 (58)	51:49(55)	55:45 (60)	3:97 (70)
XantPhos	NR	1:99 (70)	1:99 (45)	1:89 (75)
BINAP	NR	9:91 (65)	8:92 (50)	1:99 (70)
*t*Bu-XPhos	NR	Messy	Messy	1:99 (75)
DTBPF	30:70 (30)	4:96 (30)	5:95 (30)	1:99 (95)

[a] Ratios determined by GCMS; NR = Less than 10% conversion after 14 h; numbers in parentheses denote conversions after 14 h.

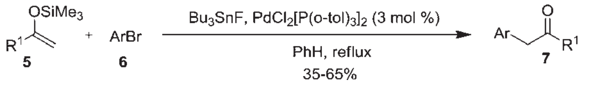
enantioselective α-arylation of exocyclic cycloalkenones using aryl bromides and triflates, respectively. Several groups have also reported γ-arylations and related reactions.[9−12]

On careful search of the literature it was realized that the α-arylation of enones was not general, and very few instances of the same have been reported and are substrate specific.[13] Here we report our results on studies related to the regioselective α-arylation of enones using a broad spectrum of aryl bromides and triflates. This protocol resulted in moderate to good yields of the α-arylated products. A variety of enones were scanned, and the reaction was found to be fairly general. Our studies began by examining the feasibility of the base mediated, Pd-catalyzed α-arylation reaction with simple acyclic enones.

In most of the cases we ended up with a mixture of products arising out of a combination of base mediated α-arylation and the Heck reaction (Table 1). The loss of stereocontrol in the Heck reaction was probably a result of steric crowding at the β-position of the enone. When the enone was substituted with an alkyl chain instead of the phenyl ring at the β-position, a complex mixture of products was obtained which could not be analyzed accurately. Use of stronger bases such as NaHMDS led mostly to polymeric products. Other palladium sources led to mostly similar results.

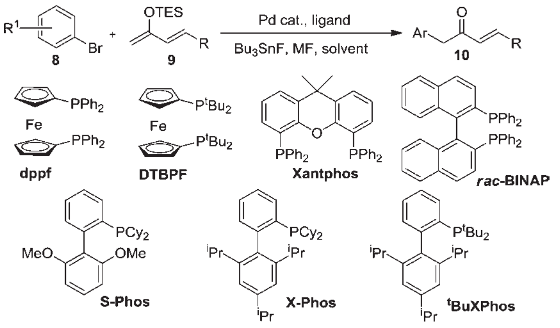
Having failed in getting any single catalyst system to result in the regioselective α-arylated product, we came up with the idea of utilizing Kuwajima and Urabe's method for Pd-catalyzed α-arylation of simple ketones wherein they utilized trialkyltin fluoride for the *in situ* generation of α-stannyl ketones via silyl−stannyl exchange (Scheme 1).[14]

Scheme 1. Kuwajima−Urabe Protocol for α-Arylation of Methyl Ketones



Consequently, many reports utilizing silyl enol ethers in Pd-catalyzed arylation have appeared.[15−18] An important outcome of Hartwig's study was the synergistic effect of the use of two fluorides, tributyltin fluoride and cesium fluoride.[17] This method has an advantage over base-mediated α-arylation in that the functional group tolerance is much higher and regiochemistry can be very well controlled. This variant of the α-arylation has been used on ketones and to the best of our knowledge has never been tried with enone systems. We attempted to apply this strategy to enone systems (Scheme 2).

Scheme 2. Ligands Scanned for This Transformation



Several catalyst systems were initially scanned, and since the outcome with simple phosphine ligands was quite disappointing, we turned to scanning bulky, electron-rich phosphine ligands. It has been well documented by several research groups that the use of bulky, electron-rich phosphines promotes the stabilization of the metal center by decreasing the energy of the low coordinate Pd(0) species.[19] It is also postulated that the increase in the electron density at the metal enhances the rate of oxidative

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(9) (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203–6206. (b) Terao, T.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967–5974.

(10) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236–7239.

(11) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881–3884.

(12) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690–1693.

(13) Zhao, Y.; Zhou, Y.; Liang, L.; Yang, X.; Du, F.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 555–558.

(14) (a) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831–6833. (b) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181–187.

(15) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809–4812.

(16) (a) Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725–5728. (b) Johnson, P. D.; Sohn, J.-H.; Rawal, V. H. *J. Org. Chem.* **2006**, *71*, 7899–7902.

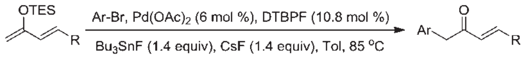
(17) Su, W. P.; Raders, S.; Verkade, J. G.; Liao, X. B.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 5852–5855.

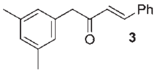
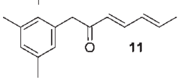
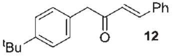
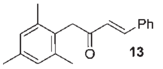
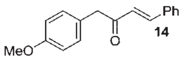
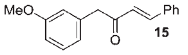
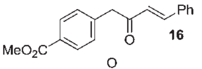
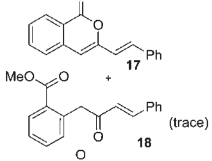
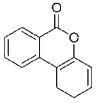
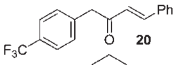
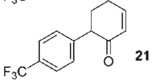
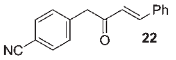
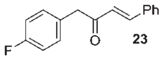
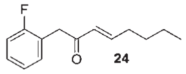
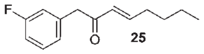
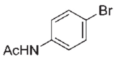
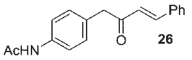
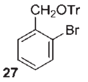
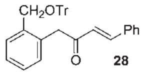
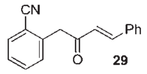
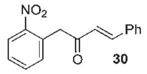
(18) (a) Guo, Y.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583–3585. (b) Chobanian, H. R.; Liu, P.; Chioda, M. D.; Guo, Y.; Lin, L. S. *Tetrahedron Lett.* **2007**, *48*, 1213–1216. (c) Shigeshisa, H.; Jikihara, T.; Takizawa, O.; Nagase, H.; Honda, T. *Tetrahedron Lett.* **2008**, *49*, 3983–3986. (d) Guo, Y.; Twamley, B.; Shreeve, J. M. *Org. Biomol. Chem.* **2009**, *7*, 1716–1722. (e) Guo, Y.; Tao, G.-H.; Blumenfeld, A.; Shreeve, J. M. *Organometallics* **2010**, *29*, 1818–1823.

insertion and also serves to increase turnover numbers by suppressing side reactions such as phosphine cleavage.

Our attempts with electron-rich phosphines succeeded in giving a regioselective reaction in the form of the α-arylated product. Although the reaction worked fairly well with $Pd_2(dba)_3$/BINAP or $PdCl_2$(DTBPF)[19i] systems, the cleanest conversions were obtained with $Pd(OAc)_2$/DTBPF. The substrate scope with bromides was found to be quite general and is shown in Table 2. The use of cesium fluoride was found to be necessary for this reaction; the reaction was very sluggish in the absence of it. Other sources of fluorides that were scanned were not as effective as CsF. At this point, the exact role of CsF is not understood. The best yields were obtained in nonpolar solvents. In particular, toluene was found to be the solvent of choice.[20] The reaction with the DTBPF system was very fast at 85 °C and required at most 2−3 h to complete. The reaction worked well with neutral alkyl substituted aromatic bromides, and the yields with ortho substituted bromides were notably good. In particular, the mesityl bromide (Table 2, entry 4) resulted in the highest yield among all the substrates scanned. The yields with electron-rich aromatic bromides were expectedly moderate (Table 2, entries 5, 6). The reaction condition was tolerated by a wide variety of functional groups such as esters (Table 2, entry 7) and nitriles (Table 2, entry 12). Entries 8 and 9 (Table 2) expectedly resulted in isocoumarin formation.[18b] The formation of the isocoumarin could not be circumvented. The reaction with 2-bromobenzonitrile (Table 2, entry 18) resulted in low yield presumably for the same reason. In all cases, the regioselectivity was excellent (>90:10), and the reaction worked well with all the enone systems that we tried, although the reactions with the cyclohex-2-enone system were slightly sluggish as compared to the acyclic versions. The yields with triflates were rather low with this catalyst system. Thankfully for us, the $Pd(OAc)_2$/^{t}BuXPhos system worked well for triflates. The substrate scope for triflates is depicted in Table 3. The reaction with triflates required ~12 h to complete and worked well for most triflates and enones that were attempted.[21] Only a couple of exceptions were

Table 2. Substrate Scope with Aryl Bromides



entry	bromide	product	yield[a]
1.	3,5-dimethylbromobenzene	 **3**	75%
2.	3,5-dimethylbromobenzene	 **11**	83%
3.	4-(*tert*-butyl)bromobenzene	 **12**	78%
4.	Mesityl bromide	 **13**	84%
5.	4-methoxybromobenzene	 **14**	54%
6.	3-methoxybromobenzene	 **15**	51%
7.	methyl 4-bromobenzoate	 **16**	48%
8.	methyl 2-bromobenzoate	 **17** + **18** (trace)	64%
9.	methyl 2-bromobenzoate	 **19**	30%
10.	4-(trifluoromethyl)bromobenzene	 **20**	52%
11.	4-(trifluoromethyl)bromobenzene	 **21**	70%
12.	4-bromobenzonitrile	 **22**	48%
13.	4-fluorobromobenzene	 **23**	66%
14.	2-fluorobromobenzene	 **24**	68%
15.	3-fluorobromobenzene	 **25**	62%
16.		 **26**	40%
17.	 **27**	 **28**	64%
18.	2-bromobenzonitrile	 **29**	35%
19.	2-nitrobromobenzene	 **30**	67%

[a] All yields are isolated yields.

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(19) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388. (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *33*, 617–620. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478. (d) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370. (e) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002. (f) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817. (g) Rataboul, F.; Zapf, A.; Jackstell, Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2983–2990. (h) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398–3416. (i) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489–5492. (j) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555–1564. (k) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (l) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (m) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141–8154. (n) Hill, L. L.; Crowell, J. L.; Tutwiler, S. L.; Massie, N. L.; Hines, C. C.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H.; Grasa, G. A.; Johansson Seechurn, C. C. C.; Li, H.; Colacot, T. J.; Chou, J.; Woltermann, C. J. *J. Org. Chem.* **2010**, *75*, 6477–6488. (o) Johansson Seechurn, C. C. C.; Parisel, S. L.; Colacot, T. J. *J. Org. Chem.* **2011**, *76*, 7918–7932. (p) Liu, L.; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666–1669. (q) Cao, C.; Wang, L.; Cai, Z.; Zhang, L.; Guo, J.; Pang, G.; Shi, Y. *Eur. J. Org. Chem.* **2011**, 1570–1574. (r) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194–5197.

(20) The reaction works best with freshly prepared TES-enol ethers, which were prepared by methods reported in the literature. TMS-enol ethers were not very stable upon prolonged storage, and therefore the reaction was performed with TES-enol ethers. See ref 18e. The arylation reaction was performed without a glovebox or dry box, in a sealed tube. See Supporting Information for all experimental details.

Scheme 3. Suggestive Pathway for the Reaction with Enones

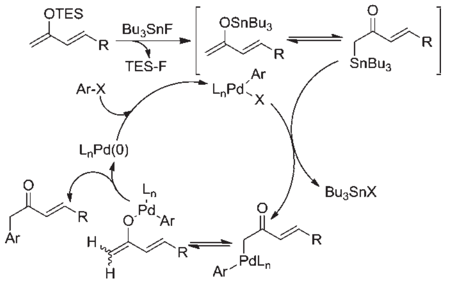
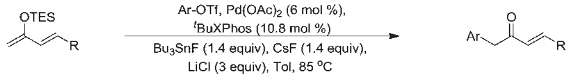
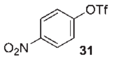
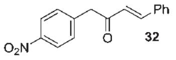
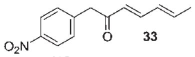
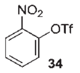
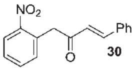
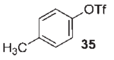
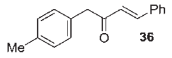
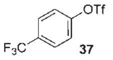
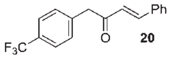
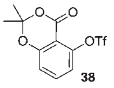
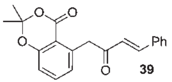
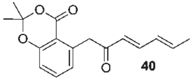
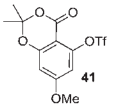
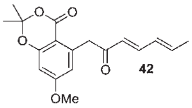
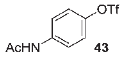
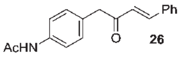
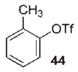
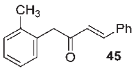
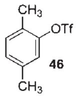
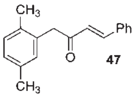


Table 3. Substrate Scope with Aryl Triflates

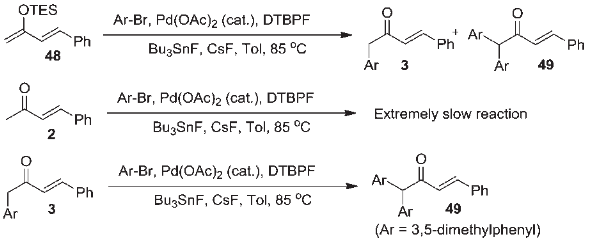


entry	aryl triflate	product	yield[a]
1.	 31	 32	66%
2.		 33	62%
3.	 34	 30	70%
4.	 35	 36	60%
5.	 37	 20	62%
6.	 38	 39	74%
7.		 40	75%
8.	 41	 42	75%
9.	 43	 26	Messy[b]
10.	 44	 45	Messy[b]
11.	 46	 47	Messy[b]

[a] All yields are isolated yields. [b] Product obtained could not be completely purified.

observed (Table 3, entries 9−11). The regioselectivity of the reaction was probably governed by the faster *in situ* silyl−stannyl exchange and consequent transmetalation vs the slower migratory insertion of the olefin of the α,*β*-unstaturated system (Scheme 3).

Scheme 4. Fluoride Mediated Arylation of the Monoaryl Enone



The absence of a strong base to mediate the *β*-H elimination for the competing Heck reaction could also be a contributing factor to the regioselectivity.

Another interesting observation was that of the diarylation product in the reaction mixture[17] and the yield of this product was substrate dependent. This product was not expected, given the proposed reaction mechanism in which the diarylation product would be expected only in a base-mediated reaction. In this case it seemed that the fluoride anion in the anhydrous solvent was acting as a base.[22] To test this hypothesis, the arylation reaction was attempted with the parent enone with the Pd(OAc)$_2$/DTBPF catalyst system in the presence of the added fluoride additives (Scheme 4). Almost no reaction was observed even after 24 h. Monoaryl product **3**, when subjected to the same conditions, resulted in the diarylation product **49** in about 30% yield after about 14 h at 85 °C. This more or less confirmed the fact that the fluoride anion was basic enough to promote the arylation of the monoarylated product due to the substrate's enhanced acidity as compared to the parent enone.

In summary, we have developed a new method for the regioselective synthesis of α-aryl enones by employing sterically encumbered, electron-rich phosphine ligands in a modified Kuwajima−Urabe protocol of arylation of silylenol ethers with a wide range of aryl bromides and triflates. The reaction is of general scope and is expected to have excellent synthetic utility. The application of this protocol in the synthesis of macrocyclic natural products is currently in progress.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) LiCl as an additive was necessary in case of the triflates; see (a) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434–5444.

(22) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429–452.