Synthetic Methods

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Direct Copper-Catalyzed α-Arylation of Benzyl Phenyl Ketones with Aryl Iodides: Route towards Tamoxifen**

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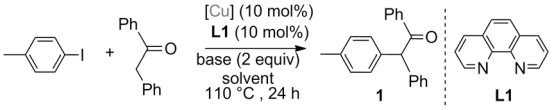
The direct and simple transition-metal-catalyzed α-arylation of ketone enolates is the most general and efficient strategy to access compounds possessing a benzylic carbonyl moiety. This methodology thus constitutes an indispensable tool for the organic chemist, as the molecules obtained are often structural motifs of prime importance in pharmaceutical, agrochemical, or fine chemistry. The first example of such direct α-arylation was reported in the early 1970s by Semmelhack et al., who described an intramolecular nickel-catalyzed α-arylation serving as a key step of the total synthesis of the cephalotaxinone.[1] Twenty years later there was a breakthrough in this field with the independant discovery of practical and efficient palladium-based catalysts by the groups of Miura,[2] Buchwald,[3] and Hartwig.[4] These elegant systems proved their efficiency in the intermolecular coupling of aryl halides with enolates generated in situ from the corresponding ketones in basic conditions. Since then, the α-arylation of ketones based on palladium, mainly associated with phosphines,[5] but also with other ligands such as N-heterocyclic carbenes[6] or cyclic alkyl aminocarbenes,[7] has been investigated.[8,9] Various types of ketones have been used with palladium systems and among them are cyclic ketones, dialkyl- or alkylaryl(or heteroayl) ketones, or aryl benzyl ketones.[8,9] Notably, the challenge of the selective mono α-arylation of acetone was recently performed by Stradiotto et al.[10] and Ackermann et al.[11] in the presence of palladium/phosphine systems. However, although palladium catalysis remains the method of choice, it suffers from several shortcomings, particularly from the perspective of its use in commercial syntheses because of the high cost, toxicity of the metal, and the necessity of using expensive ligands.

As part of our studies on copper-catalyzed arylation of nuclophiles,[12] we report herein the first efficient method for which the direct α-arylation of a non-activated or non-protected family of enolizable ketones (the deoxybenzoin derivatives) with simple aryl iodides can also be achieved using a copper-based catalytic system,[13] wherein the less toxic and inexpensive metal is used together with 1,10-phenanthroline or diketone-type ligands.[14] The potential of the method is illustrated by its application in the total synthesis of tamoxifen, the world's most-prescribed drug for treatment of breast cancer.

First, a set of experiments was performed using 4-iodotoluene and deoxybenzoin as model substrates. The latter and its derivatives constitute the ketone family of choice in this study, as their structure is present in numerous bioactive compounds.[15,16] The preliminary survey, carried out at 110 °C with various solvents, bases, and copper sources, helped us to evaluate the most efficient catalytic system for the desired transformation (Table 1). When copper iodide (10 mol %), 1,10-phenantroline (**L1**; 10 mol %), and Cs_2CO_3 were used in solvents such as *N*,*N*′-dimethylformamide (DMF), acetonitrile (CH_3CN), or dimethyacetamide (DMA), we observed for the first time the expected α-arylated product **1** in low yield (Table 1, entries 1 and 2). The first significant result was obtained when the reaction was performed in *tert*-butyl alcohol, as 52 % of **1** was detected under these reaction conditions (Table 1, entry 3). Moreover, we were pleased to find that this yield could reach a satisfying value (70 %) when 1,4-dioxane was used instead of *t*BuOH (Table 1, entry 4). Under these reaction conditions, replacing Cs_2CO_3 by several organic and inorganic bases only led to

Table 1: Copper-catalyzed α-arylation of deoxybenzoin with 4-iodotoluene in the presence of 1,10-phenantroline (**L1**): parametric study.[a]



Entry	Solvent	[Cu]	Base	Yield [%][b]
1	DMF or CH_3CN	CuI	Cs_2CO_3	10
2	DMA	CuI	Cs_2CO_3	17
3	*t*BuOH	CuI	Cs_2CO_3	52
4	1,4-dioxane	CuI	Cs_2CO_3	70
5	1,4-dioxane	–	Cs_2CO_3	0
6	1,4-dioxane	CuI	Et_3N or CsOH	0
7	1,4-dioxane	CuI	KOAc or K_3PO_4	3
8	1,4-dioxane	CuI	Rb_2CO_3 or K_2CO_3	20
9	1,4-dioxane	$[Cu(acac)_2]$	Cs_2CO_3	30
10	1,4-dioxane	$Cu(OTf)_2$ or Cu_2O	Cs_2CO_3	44
11	1,4-dioxane	CuCl, $Cu(OAc)_2$, $CuBr_2$, or CuCN	Cs_2CO_3	50

[a] Reactions performed on 1 mmol scale (ketone/ArI = 1.5:1).[b] Yield determined by ^{1}H NMR spectroscopy using 1,3-dimethoxybenzene as an internal standard. acac = acetylacetonate, Tf = trifluoromethansulfonyl.

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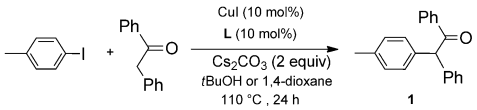
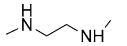
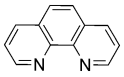
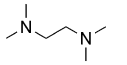
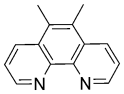
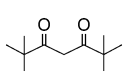
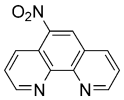
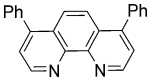
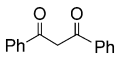
disappointing results (Table 1, entries 6–8). Additionally, several different copper sources (oxidation state I or II) were screened but only low to modest conversions were detected even in the most favorable cases (Table 1, entries 9–11). It is worth noting that the blank experiments showed that the presence of the copper catalyst is necessary in our protocol (Table 1, entry 5).

We then examined, either in *t*BuOH or in 1,4-dioxane, the influence of the ligand upon the course of the reaction (Table 2). Diamine (**L5**, **L6**) and β-diketone (**L7**, **L8**, **L9**) ligands were ineffective, except for β-acetylcyclohexanone (**L8**) in *t*BuOH (58% yield of **1**). Finally, the 1,10-phenantroline-type ligands (**L1**, **L2**, **L3**, **L4**) offered the best solution, with the use of bathophenantroline (**L4**) in *t*BuOH affording **1** in very good yield (84%). These reaction conditions were used with bromobenzene but the cross-coupling failed (8% of product and no reaction with PhCl). As it was the case for the copper source, the presence of a ligand was necessary to obtain satisfying results, as attested by the yields obtained from PhI (6–8%) in its absence (Table 2). In addition, it proved difficult to establish a relationship between the structure or the solubility of the ligand and the reactivity observed, even for the same structural family.

Table 2: Copper-catalyzed α-arylation of deoxybenzoin with 4-iodotoluene in 1,4-dioxane or *t*BuOH using the ligands **L**.[a]



L		Yield [%][b] in 1,4-dioxane	Yield [%][b] in *t*BuOH	L		Yield [%][b] in 1,4-dioxane	Yield [%][b] in *t*BuOH
–		8	6		**L5**	29	5
	**L1**	70	52		**L6**	23	8
	**L2**	27	46		**L7**	20	17
	**L3**	3	47		**L8**	24	58
	**L4**	68	84		**L9**	11	8

[a] Reactions performed on 1 mmol scale (ketone/ArI = 1.5:1). [b] Yields determined by ^{1}H NMR spectroscopy using 1,3-dimethoxybenzene as an internal standard.

Next, the scope of the reaction with respect to various aryl iodides and deoxybenzoin derivatives was investigated. Two scenarios were observed, depending on the nature of the aryl iodide substituents.

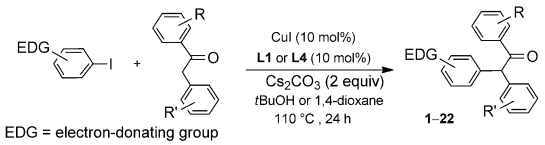
In the case of electron-rich aryl iodides bearing one or two electron-donating groups (Me or OMe), a simple tuning of the copper catalytic system allowed us to obtain numerous α-arylated deoxybenzoins in good to excellent yields upon isolation (Table 3). Although the **L4**/*t*BuOH system used for 4-iodotoluene (Table 2) was applicable to all the substrates tested, improved conversions were obtained using the **L1**/1,4-dioxane couple highlighted in our preliminary studies (Table 3, entries 3, 10, 13, 14, and 16–18). The ligand **L1** (cheaper than **L4**) was also found to be efficient in combination with *t*BuOH for some examples (Table 3, entries 5, 7, and 9). In the case of *ortho*-substituted aryl iodides, which are traditionally poor substrates in copper-catalyzed arylation of C, N, and O nucleophiles, low to fair amounts of the α-arylated products were obtained.

Electron-poor aryl iodides were then considered and reacted with several deoxybenzoin derivatives (Table 4, entries 1–14). Note that for α-arylation catalytic systems based on other metals than copper, this case has been less explored than those of electron-rich aryl halides. Applying the conditions of Table 3 led to poor yields of the coupling products. For example, only 37% of the α-arylated compound **23** (see Table 4, entry 1 for structure) was obtained using the standard system CuI/**L4**/*t*BuOH with 4-iodofluorobenzene (the main by-product was the result of the homocoupling of deoxybenzoin). However, a simple optimization led to an increase in the yield to 52% by using the β-acetylcyclohexanone ligand (**L8**) in *t*BuOH at 110°C (reaction conditions previously employed for the α-arylation from 4-iodotoluene). Finally the selectivity was improved by lowering the reaction temperature to 70°C, thus producing **23** in 75% yield (Table 4, entry 1). By using these reaction conditions, 15 differently substituted arylated deoxybenzoine derivatives were obtained (Table 4) with yields ranging from low (Table 4, entry 13) to excellent (Table 4, entry 14). In some cases, the final compounds feature one or two halides (Br, Cl, F) on the aromatic rings, available for further functionalization at the corresponding positions.

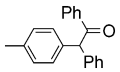
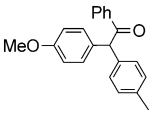
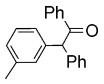
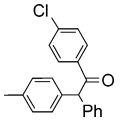
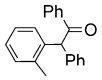
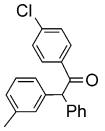
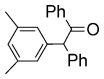
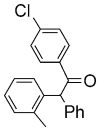
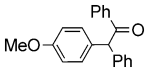
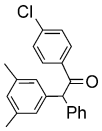
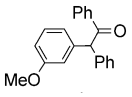
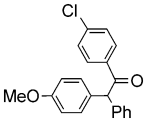
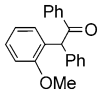
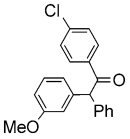
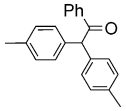
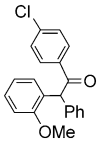
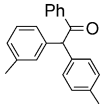
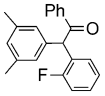
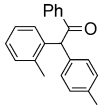
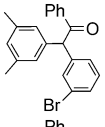
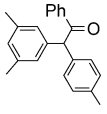
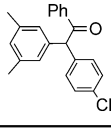
The scope of this methodology was demonstrated by its simple and efficient application to the synthesis of Tamoxifen (TAM). Marketed under the trade name Nolvadex, this molecule has for a long time been the world's most commonly administrated drug for management of breast cancer.[15b,16]

We considered two new and original routes for the total synthesis of this molecule, which belongs to the triphenylethylene class of compounds. In the first pathway, the synthesis starts with the copper-catalyzed α-arylation of deoxybenzoin with 4-Iodophenol (Scheme 1, Route A). The latter is a suitable substrate as evidenced by the good yield obtained for the α-arylated deoxybenzoin derivative **37**. For this step the most efficient catalytic system was CuI/**L8**. *t*BuOH was preferred over 1,4-dioxane because of the greater solubility of the phenolic reagent in alcohols. Compound **37** then underwent an alkylation/elimination/isomerization[17] sequence and the resulting intermediate **38** was directly reacted with 2-chloro-*N*,*N*-dimethylethylamine to give tamoxifen in an overall yield of 70% (over 4 steps) upon isolation.

Table 3: Copper-catalyzed α-arylation of deoxybenzoin derivatives by aryl iodides substituted by electron-donating groups.[a]

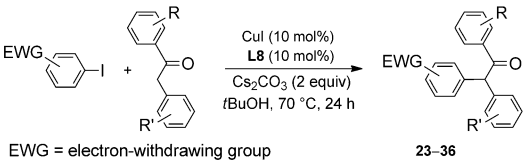


EDG = electron-donating group

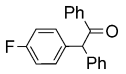
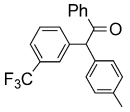
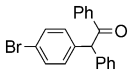
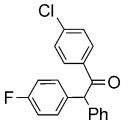
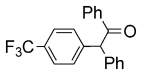
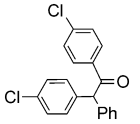
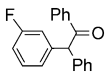
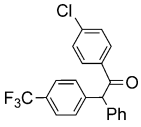
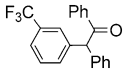
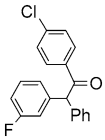
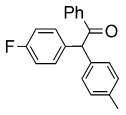
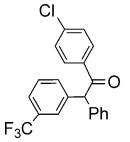
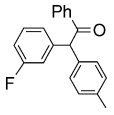
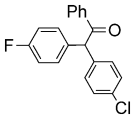
Entry	Product		Yield [%][b]	Entry	Product		Yield [%][b]
1		**1**	84[c]	12		**12**	60[c]
2		**2**	99[c]	13		**13**	89[e]
3		**3**	48[d,e]	14		**14**	99[e]
4		**4**	99[c]	15		**15**	37[d,e]
5		**5**	74[f]	16		**16**	99[e]
6		**6**	75[c]	17		**17**	71[e]
7		**7**	51[f]	18		**18**	74[e]
8		**8**	70[c]	19		**19**	56[e]
9		**9**	56[f]	20		**20**	94[c]
10		**10**	21[d,e]	21		**21**	81[d,c]
11		**11**	88[c]	22		**22**	99[c]

[a] Reactions performed on 1 mmol scale (ketone/ArI: 1.5/1). [b] Yield of isolated product. [c] *t*BuOH/**L4**. [d] Yields determined by ^{1}H NMR spectroscopy. [e] 1,4-Dioxane/**L1**. [f] *t*BuOH/**L1**.

Table 4: Copper-catalyzed α-arylation of deoxybenzoin derivatives by aryl iodides substituted by electron-withdrawing groups[a]

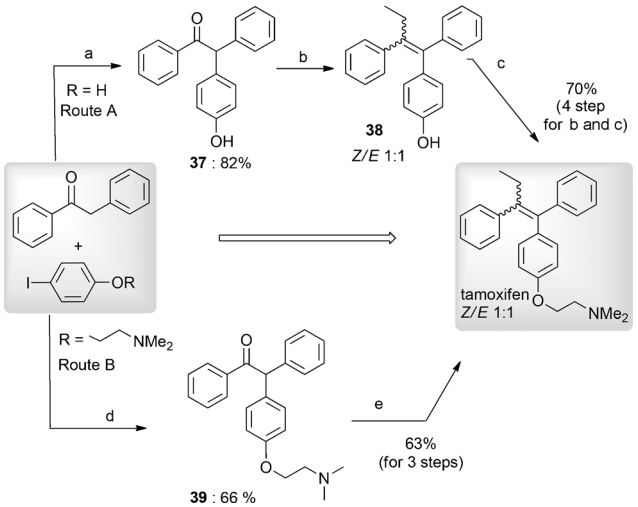


EWG = electron-withdrawing group

Entry	Product		Yield [%][b]	Entry	Product		Yield [%][b]
1		**23**	75	8		**30**	40[c]
2		**24**	60	9		**31**	90
3		**25**	57	10		**32**	75
4		**26**	48	11		**33**	33
5		**27**	60	12		**34**	49
6		**28**	57[c]	13		**35**	17
7		**29**	54[c]	14		**36**	99

[a] Reactions performed in *t*BuOH (1 mL) at 70 °C with 1 mmol of iodoarene, 1.5 mmol of ketone, 2 mmol of Cs_2CO_3, 0.1 mmol of CuI and 0.1 mmol of **L8**. [b] Yield of isolated product. [c] Reaction performed at 90 °C.

We also developed a second route based on a reverse strategy involving, in the first step, the iodoarene already substituted by the dimethylethylamino substituent present on tamoxifen (Scheme 1, Route B).[18] This electron-donating group proved to be a suitable substituent. The coupling of the corresponding aryl iodide with deoxybenzoin gave the expected α-arylated intermediate **39** in good yield. For this step the most efficient catalyst system was **L1**/CuI (10 mol%) in 1,4-dioxane. The same alkylation/elimination/isomerization sequence was used for **39** to yield tamoxifen in a satisfying 63% (3 steps). These two synthetic pathways show that our method is easily applicable for the synthesis of major targets and that it could constitute an efficient tool for the synthesis of a library of tamoxifen derivatives.



Scheme 1. a) CuI (10 mol%), **L8** (10 mol%), Cs_2CO_3 (4 equiv), *t*BuOH, 70°C, 24 h; b) 1. EtMgBr (3 equiv), THF, 25°C, 5 h, 2. HCl (37%), MeOH, 65°C, 15 h, 3. *t*BuOK (4 equiv), DMSO, 50°C, 2 h; c) NaH (3 equiv), $ClC_2H_4NMe_2$ (2 equiv), DMF, 50°C, 3 h. d) CuI (10 mol%), **L1** (10 mol%), Cs_2CO_3 (4 equiv), dioxane, 110°C, 24 h. e) 1. EtMgBr (3 equiv), THF, 25°C, 5 h, 2. HCl (37%), MeOH, 65°C, 15 h, 3. *t*BuOK (5 equiv), DMSO, 50°C, 2 h.

In conclusion, we have discovered the first efficient method in which the direct α-arylation with simple aryl iodides of a non-activated or nonprotected family of enolizable ketones (the deoxybenzoin derivatives) is possible by using a copper catalyst system. The method is selective towards other halides (Br, Cl or F) thus allowing further functionalization of aromatic cycles without any protection/deprotection sequence. This method is complementary to the palladium systems which catalyze the reaction using aryl chlorides. The use of copper in association with commercially available and inexpensive phenanthroline or diketone-type ligands is an advantage in line with sustainable development.[14] Finally this method demonstrated its potential in the easy and step-economical synthesis of tamoxifen, the most commonly administrated drug for treatment of breast cancer. Work is in progress to generalize its application field, to understand the mechanism,[19] and to develop an asymmetric version.

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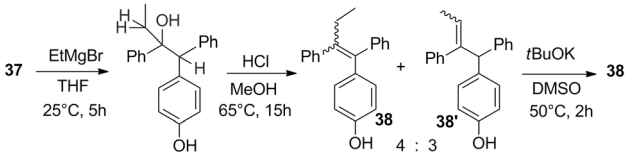

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