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An atom efficient synthesis of Tamoxifen

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ABSTRACT

The direct carbolithiation of diphenylacetylenes and their cross coupling procedure is presented taking advantage of the intermediate alkenyllithium reagents. Employing our recently discovered highly active palladium nanoparticle based catalyst, we were able to couple an alkenyllithium reagent with high (Z/E) selectivity (10:1) and good yield to give breast cancer drug Tamoxifen in just 2 steps from commercially available starting materials and with excellent atom economy and reaction mass efficiency.

Keywords: Organolithium Palladium Atom economy E-Factor Reaction Mass Efficiency The continuous improvement of synthetic routes towards medicinal relevant and/or biologically active compounds has drawn the attention of synthetic chemists for decades.¹ In order to reduce waste and increase yields and cost efficiency or to simplify the procedures towards relevant structures, transition metal catalysis has been a game changer to the field.² Since the emergence of the Suzuki (B), Stille (Sn), Negishi (Zn) and Hiyama-Denmark (Si) reactions, the trend in cross coupling methodology³ has been to transmetallate highly polar (but straightforward to synthesize) organometallic reagents (RMgX, RLi) to softer nucleophiles in order to gain stability, functional group tolerance and reduce the overall sensitivity of the reaction. Despite their major role in our modern synthetic toolbox, drawbacks of these additional synthetic steps are longer reaction times, the production of stoichiometric (sometimes toxic) waste, and a decrease in cost efficiency.⁴ Nonetheless, the direct coupling of organometallic reagents arising from a deprotonation or umpolung reaction has shown great advances in recent years.^{2,5} Since these reagents have an intrinsically higher reactivity, the corresponding cross coupling reactions generally require shorter reaction time, and can be performed at significantly lower temperatures.⁴ As part of our effort to expand the synthetic application of our recently reported organolithium cross coupling reactions,^{5d,f-g,i-m} we envisioned the direct carbolithation-cross coupling to be a very valuable alternative. The carbolithiation of (diphenyl)acetylenes has been well-studied and has led to several useful applications in the field of synthetic organic chemistry.⁶⁻¹⁰ The quenching of the formed nucleophilic sp² vinyllithium reagent with an electrophile provides a direct approach to substituted diarylalkenes (stilbenes). Transmetallation of such anions to magnesium, boron, zinc or even aluminum yields an active cross coupling partner, but drastically lowers the atom economy and E-factor.^{11,12} The direct cross coupling of the formed organolithium reagent is therefore a highly desired synthetic shortcut, but remains unreported to the best of our knowledge. Tetrasubstituted alkenes and triphenylethylenes in particular, i.e. Tamoxifen, make up a class of highly potent and valuable drugs with (potential) application in the treatment of a variety of conditions, including (breast) cancer, dyspareunia and osteoporosis (Figure 1).13 Structural variations on the triphenylethylene scaffold are found in the alkyl-ether substituent (mostly consisting of an amine, shown in blue), para phenylene functionality (shown in red) as well as in the alkyl fragment (shown in green) on the remaining alkene position.



Figure 1: Examples of members of the triphenylethylene family of drugs.

Because of its medicinal importance, a plethoraw /orcle Online syntheses have been described for (Z)-Tamoxifen (Figure^{B02977F}

2).15-37 McMurry coupling of two ketones is a wellestablished method for the synthesis of (hindered) alkenes, and as such has proven capable of constructing the alkene fragment in Tamoxifen with reagents 1 and 2.²¹ Alternatively, 1,2-addition to ketone **3** with Grignard reagent 4 followed by elimination yields the alkene is a valuable option, however it is common that both isomers (E/Z) are isolated via this approach.^{19,24} The transmetallation of the lithium intermediate that is the product of carbolithation of the corresponding acetylene, yields the alkenyl-boronic acid/ester, or organozinc reagent 5.^{20,22} The cross coupling of these reagents with bromide 6 provides a viable route towards the final drug. The transmetallation, however, generates extra synthetic steps and/or stoichiometric waste. We therefore reasoned that the direct coupling of the alkenyllithium reagent 7, that is obtained upon carbolithiation of diphenylacetylene, would be an important atom efficient alternative to these methods.



Figure 2: Synthetic approaches to (Z)-Tamoxifen.

In order to optimize the sequential synthetic steps, the carbolithiation of acetylene 8 was optimized separately, and the product 10 resulting from a MeI quench was subjected to GC-MS analysis (Table 1). With high selectivity for the (Z)-alkene for several solvents and solvent mixtures investigated, we were trying to avoid the use of THF (Table 1, Entry 1) due to expected difficulties in the cross coupling step arising from unwanted side reactions, such as lithium-halogen exchange.5b-g,i-n However, toluene/TMEDA mixtures (Entry 2) or other ethereal solvents (Entry 3 to 5) did not prove equally efficient as reaction medium compared to THF due to a lower extent of lithiation and an increased amount of the (E)-alkene. Attempts to minimize waste production by neat carbolithiation (except for the solvent of the n-BuLi solution) resulted in mere recovery of the starting material (Entry 6). Reducing the amount of THF by using a THF-toluene mixture resulted in incomplete conversion to the carbolithiated intermediate (Entry 7). Despite the attempts to omit THF as the solvent, we found significantly better results for the carbolithiation in its presence, and therefore decided to use it as the solvent for further optimization.

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Entry	Solvent	1 h	2 h	Selectivity ^{a/b}
		Conv. ^a	Conv. ^a	
1	THF	91%	91%	96%
2	Toluene/	32%	32%	75%
	TMEDA ^c			
3	2-Me-THF	52%	70%	99%
4	MTBE	0%	6%	-
5	Ether	0%	4%	-
6	Neat	0%	0%	-
7	Toluene/	48%	65%	96%
	THF 3:1			

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Table 1: Optimization of carbolithiation of 8

Reaction conditions: 1.1 eq. of *n*-BuLi was added dropwise to a stirred 0.9 M solution of **8** in THF at 0°C. At the end of the addition the reaction mixture was quickly allowed to warm to room temperature and left reacting for 2 h before 1 eq of MeI was added. a) As determined by GC-MS analysis after MeI quench; b) (Z/E) selectivity determined by GC-MS analysis; c) 1 eq of TMEDA.

Having established the optimized conditions for the carbolithiation, the cross coupling with 1-bromonaphthalene provided the test reaction in the pursuit for the best catalyst. Our oxygen activated palladium nanoparticle catalytic system^{5m} proved to be highly active in the coupling of alkenyllithium **9** and arylbromides (Table 2, Entry 1), being only slightly outperformed by the commercial Pd-PEPPSI-Ipent complex (Entry 4).

 Table 2: Optimization of cross coupling of 9 with 1-bromonaphthalene.



Lifting	Cut. (570)	
1	$Pd(P^tBu_3)_2 + O_2$	82% (68% yield)
2	Pd-dppf	-
3	Ni-dppp	-
4	PEPPSI-IPent	88%
5	C1	51%

Reaction conditions: 2 eq. of alkenyllithium reagent was added over 20 min to a stirred solution of arylbromide and (preoxidized) catalyst in toluene at 35°C. a) As determined by GCMS analysis. (Z/E) > 9:1.

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Nickel and palladium bisphosphine complexes (Pd-dppf and Ni-dppp) did not show conversion to the desired product (Entry 2 and 3), but the nickel carbene complex $C1^{51}$ did provide the triarylethylene target 11 (Entry 5), albeit in reduced yield (for further attempts to use different electrophiles, see Supporting Information). In order to see if this cross-coupling methodology could be applicable for the cross coupling of other arylbromides, we decided to test a few further substrates (Table 3). The cross coupling methodology proceeds smoothly with both electron rich arylbromides (R = Me, OMe, Entry 1 and 2), as well as electron poor substrates (R = CF₃, Entry 3).

 Table 3: Reaction scope of cross coupling of 9 with different aryl bromides.



Entry	R	Product	Yield of 12 ^a
1	Me	12a	56%
2	OMe	12b	51%
3	CF ₃	12c	68%

Reaction conditions: 2 eq. of alkenyllithium reagent was added over 20 min to a stirred solution of arylbromide and (preoxidized) catalyst in toluene at 35°C. a) Isolated yield after column chromatography

Having tested a small variety of catalysts for the cross coupling with different substrates, the optimized conditions were employed to synthesize the desired pharmaceutical (Z)-Tamoxifen via our new methodology. Changing the nucleophile for the acetvlene carbolithiation from *n*-butyllithium to ethyllithium gave identical results albeit with a slightly longer reaction time. We were pleased to see that the oxygenated Pd(P'Bu₃)₂ catalyst gave (Z)-Tamoxifen in only slightly lower yield than with the naphthalene test substrate, but with very good (Z/E) selectivity (Table 4, Entry 1, (Z/E) > 9:1.). Pursuing a cheaper catalyst, with a more abundant metal, the attempted nickel complex gave only small amounts of the desired product (Entry 2).

Table 4: Synthesis of Tamoxifen: catalyst screening



Entry	Cat. (5%)	NMR Yield ^a
1	$Pd(P^tBu_3)_2 + O_2$	50-65% ^b
2	C1	17%

3

3	PEPPSI-IPent	0%
4	Pd ₂ dba ₃ /Xphos	36%
5	C2 ^c	60%
6	C3 ^c	59%

Reaction conditions: 2 eq. of alkenyllithium reagent was added over 20 min to a stirred solution of arylbromide and (preoxidized) catalyst in toluene at 35°C. a) Yield determined by ¹H-NMR with 1,1,2,2-tetrachloroethane as internal standard, accompanied by <10% of (*E*)-Tamoxifen relative to (*Z*)-Tamoxifen; b) Isolated yield up to 57 %; c) 2.5 mol% of the Pd dimer was used.

Much to our surprise, our "working horse" catalyst Pd-PEPPSI Ipent5g,i was completely inactive in the cross coupling with the bromophenyl-aminoether electrophile 6 (Table 4, Entry 3), whereas it showed to be the most active catalyst with the previously tested 1bromonaphthalene electrophile (Table 2, Entry 4). The chelating effect of the amino-ether moiety onto the metal center, overcrowding the palladium, might play a role making the catalyst inactive. Other dimeric palladium phosphine complexes which have recently shown to be active in related cross coupling reactions were also tested,^{5h,m} and were found to have very similar reactivity compared to the catalyst used in Entry 1. Being the cheapest of the three related structures (Entry 1, 5 and 6), we decided to proceed our investigation with the bis(tritert-butylphosphine)palladium complex. The results of further optimization are shown in Table 5. Varying the temperature did not lead to increased yield (Entry 1 and 2) providing the temperature was kept above 30 °C, below which no conversion was observed. In an attempt to dissociate potential aggregates, and activate the organolithium reagent, TMEDA was added, but this resulted in a sharp decline in yield (Entry 3). The excess of organolithium reagent could be lowered to 1.3 equivalents without significant loss in yield (Entry 4). Further lowering of the catalyst loading (2.5 mol%) led to an inactive system, with no product formed (Entry 6 and 7). This complete deactivation of the catalyst at 2.5 mol% has not been observed before, and it is potentially attributed to the chelating effect of the aminoether moiety that is present in the substrate. An attempt to prevent the chelating effect of the aminoether side chain by means of the addition of Lewis acids such as BF3 or MgCl2 did not prove beneficial for the reaction (Entry 8 and 9). To minimize waste caused by solvent, the reaction was performed in a minimal amount of solvent, with a 1 M concentration, which only led to a slight decrease in yield (Entry 10). Lower loadings (1.25 mol%) of complexes C2 and C3 provided better conversion than our catalyst of choice at those concentrations (Entry 6, 11 and 12), but still providing lower overall yields (14% and 28%, respectively).

 Table 5: Optimization of carbolithiation-cross coupling sequence.¹⁴



1	Temp 50°C	60 DOI: 10.1	View Article Online 039/C8OB02977F
2	Temp 35°C	68	
3	TMEDA (1 eq.)	25	
4	1.3 eq of 7	65	
5	10 % cat., 1.3 eq of 7	65	
6	2.5 % cat.	-	
7	2.5 % cat.°	-	
8	BF ₃	-	
9	MgCl ₂	58	
10	Concentrated (1 M) ^d	54	
11	C2 ^e 1.25 % cat.	14	
12	C3 ^e 1.25 % cat.	28	

a) Reaction conditions: 2 eq. of alkenyllithium reagent was added over 20 min to a stirred solution of arylbromide (2 mmol) and pre-oxidized catalyst in toluene (2 ml) at room temperature. b) Yield determined by ¹H-NMR with 1,1,2,2-tetrachloroethane as internal standard; c) Different batch of catalyst; d) Initial concentration of arylbromide; e) the complexes **C2** and **C3** were used with the same Pd concentration as entries 6 and 7.

Having a setup that produces this pharmaceutical compound in good yield and with minimal waste (LiBr being the only stoichiometric waste in the last step), we compared our procedure with other (recent) reported syntheses of Tamoxifen^{6,15-37} focusing on atom economy and Reaction Mass Efficiency (RME).^{12b} Figure 3 shows a large range in atom economy (shown in blue) between different reported syntheses of Tamoxifen. The method described by Larock in 2005³⁷ is the closest to the reported route in this work in terms of atom economy (48 *vs.* 67%), but due to a large excess of some reagents it scores much lower on RME (shown in red).



Figure 3: Atom economy and RME comparison for each reported Tamoxifen synthesis.

With our current setup, employing commercially available starting materials, a total atom economy of 0.67 is achieved, and the resulting RME (22%) is almost twice as high as that of the runner-up (Knochel 1997, 11%).²⁰ We believe that the currently reported methodology presents additional relevant advantages, since LiBr, NaCl and HCl are the only stoichiometrically produced waste sources, and the reaction can be performed at slightly elevated temperature in a minimal amount of solvent.

To establish the optimal isolation method, the synthesized (Z)-Tamoxifen was purified by means of crystallization,

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extraction, column chromatography and distillation. The excess organolithium reagent (protonated after reaction quenching, **12-H**) and the formed lithium bromide pose no difficulty in the separation from the product (Figure 4). Acid-base extraction or column chromatography were both suitable means to achieve purification.



The remaining impurity of dehalogenated starting material **13** exhibits near identical behavior compared to the product, but flash chromatography was able to yield the pure (E/Z)-Tamoxifen mixture. If desired, RP-preparative HPLC in water/ acetonitrile/TFA separates effectively the (E) from the (Z) isomer of the product.

In conclusion, the carbolithiation of diphenylacetylene and the consecutive cross coupling with the appropriate 4-bromo-dimethylamine-ethylether (6) yields (Z)-Tamoxifen with good (Z/E) selectivity (10:1) and with yields up to 65%. The reaction mixture was purified by flash chromatography to obtain the pure (E/Z)-Tamoxifen mixture. Further optimization could lead to a lowering of the catalyst loading and suppressing the lithium halogen exchange or E-Z isomerisation that lead to the undesired side products which have proven to be a challenge in the purification of this pharmaceutical. The method distinguishes itself from previously reported syntheses by its high atom economy, reaction mass efficiency, nontoxic waste production, step count and ease of reaction setup. The organolithium cross coupling is also an attractive strategy for the coupling of less reactive electrophiles (chlorides, fluorides and ethers)⁵¹ and future studies might further enhance the efficiency towards triarylethylenes and related products.

Conflict of Interest

There are no conflicts of interest to declare.

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Highly Selective and Atom Efficient Synthesis of Triarylethylenes

