(Z)-Tamoxifen and Tetrasubstituted Alkenes and Dienes via a Regio- and Stereospecific Three-Component Magnesium Carbometalation Palladium(0) Cross-Coupling Strategy
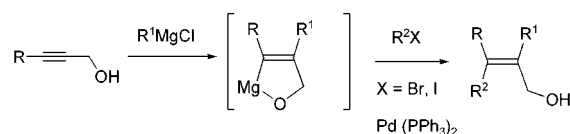
Pierre E. Tessier, Andrea J. Penwell,[†] Fabio E. S. Souza, and Alex G. Fallis*

Centre for Research in Biopharmaceuticals, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

*afallis@science.uottawa.ca*

ABSTRACT

The synthesis of various tetrasubstituted alkenes and dienes in a regio- and stereocontrolled manner is described. This three-component coupling strategy involves the addition of Grignard reagents to propargyl alcohols followed by palladium(0)-mediated cross-coupling with aryl or vinyl halides. This protocol has been applied to the synthesis of (Z)-Tamoxifen and related mimics.

We have previously described the versatility of the magnesium-mediated carbometalation of propargyl alcohols to assemble several diverse compounds generated in a single reaction, for a variety of objectives.[1]

These reactions have included the regio- and stereoselective generation of diene-halides, diene-diols, enediynes, furans, furanones, and taxoid intermediates.[2] The synthesis of differentially substituted furans in which five bonds are assembled in a one-pot, four-component coupling is representative and illustrates the common theme for this protocol via the magnesium chelate illustrated in Scheme 1.

Scheme 1. Furans by Carbometalation of Propargyl Alcohols
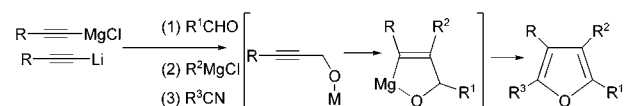
Multicomponent couplings of this type are of interest in their own right and also hold potential for diversity-oriented syntheses,[3] especially if the vinyl furans were subjected to subsequent cycloaddition reactions (R[1] or R[2] = vinyl). We wish to report the extension of these methods to a new, versatile procedure for the regio- and stereospecific one-pot palladium(0) cross-coupling of aryl and alkenyl halides from

† Present address: AstraZeneca R & D Montreal, AstraZeneca Canada Inc., 7171 Frederick-Banting, St. Laurent (Montreal), Quebec, H4S 1Z9.

(1) For a review see: (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 589. For earlier studies see (b) Eisch, J. J.; Merkley, J. H. *J. Organomet. Chem.* **1969**, *20*, 27. (c) Richey, H. G., Jr.; Von Rein, F. W. *J. Organomet. Chem.* **1969**, *20*, 32. (d) Von Rein, F. W.; Richey, H. G., Jr. *Tetrahedron Lett.* **1971**, *6*, 3777. (e) Jousseaume, B.; Duboudin, J. G. *J. Organomet. Chem.* **1975**, C1. (f) Jousseaume, B.; Duboudin, J. G. *J. Organomet. Chem.* **1979**, *91*, 6903. (g) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1. (h) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227. (i) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080. (j) Labaundinière, L.; Hanaizi, J.; Normant, J.-F. *J. Org. Chem.* **1992**, *57*, 6903.

(2) (a) Wong, T.; Tjepkema, M. W.; Audrain, H.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **1996**, *37*, 755. (b) Forgione P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11. (c) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17. (d) Forgione, P.; Wilson, P. D.; Yap, G. P. A.; Fallis, A. G. *Synthesis* **2000**, 921.

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the intermediate chelate **2** to give a variety of tetrasubstituted alkenes and dienes (Scheme 2). This protocol has also been

Scheme 2. General Synthesis of Tetrasubstituted Alkenes

R = alkyl, aryl, allyl, TMS

R^1 = alkyl, aryl, vinyl, allyl

R^2 = aryl, vinyl, allyl
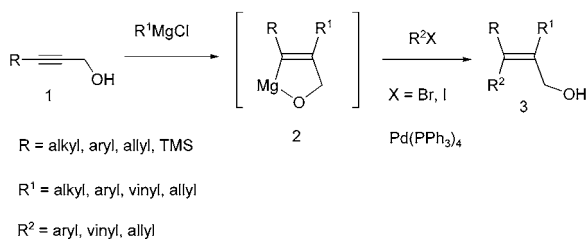
extended to a direct synthesis of (*Z*)-Tamoxifen.

An additional motivation for this study is our interest in developing an efficient route to compounds that will be recognized by the estrogen receptors such as Tamoxifen itself and related mimics. These compounds have proven utility for adjuvant therapy in women who have suffered from breast cancer.[4] In addition, recent studies suggest Tamoxifen may have cancer preventative properties[5] and effectiveness in the preservation of bone mineral density related to osteoporosis.[6] The related unsaturated acid **4** and raloxifene show similar promise[7] and thus these tetrasubstituted olefins have potential for broader medicinal applications.[8]

Previous investigations in our laboratory have demonstrated that the solvent plays an important role in these carbometalation reactions. Nonpolar solvents such as cyclohexane were essential for the direct condensation of the magnesium chelate intermediate with aldehydes and nitriles.[2b,c] However, toluene/THF mixtures (1:1) provided a significant improvement. This is a consequence of the improved solubility of the magnesium salts which afforded higher yields especially when vinyl Grignard reagents were employed.
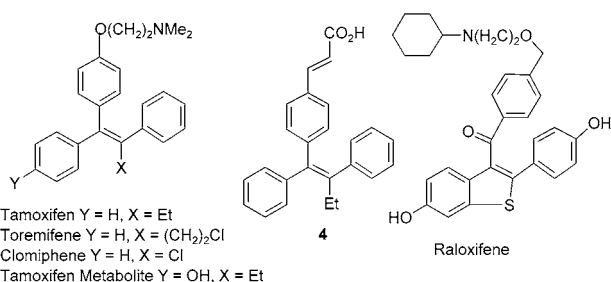

Figure 1. Tamoxifen and related drugs that recognize the estrogen receptors.

The application of this carbometalation−palladium coupling protocol is outlined in Scheme 2 and summarized in

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Table 1. Three-Component Coupling for Alkenes and Dienes[a]

entry	R^1MgCl	R^2X	product		yield (%)
1a	PhMgCl	PhI		**7**	73
1b	PhMgCl	PhBr			72
2	PhMgCl	*p*-MeOC$_6$H$_4$I		**8**	71
3	PhMgCl	CH$_2$=CHCH$_2$I		**9**	64
4	CH$_2$=CHCH$_2$MgBr	PhI		**10**	60
5	PhMgCl	Me$_2$C=CMeBr		**11**	71
6	CH=CH$_2$MgCl	PhI		**12**	61
7	CH$_2$=CHMgCl	PhI		**13**	41
8	MeMgCl	PhI		**14**	10

[a] Reagents and conditions: (a) R^{1}MgX (3.2 equiv), toluene/THF, 1:1, reflux, 14 h; (b) [Pd(PPh$_3$)$_4$], (0.05 equiv), R^{2}X (3 equiv), reflux, 24 h.

Table 1 with a variety of combinations. These include alkyl-, aryl-, allyl-, and trimethylsilyl-substituted propargyl alcohols. The aryl, vinyl, and allyl Grignard reagents were exposed to iodo or bromo coupling partners in the presence of palladium(0).

The fully substituted alkenes in entries 1a and 1b displayed no significant difference in yield upon variation of the halide. Skipped dienes were generated with allyl substituents (entries 3 and 4). In these cases the allyl functionality may be introduced as either the magnesium or palladium component. Dienes were prepared efficiently as demonstrated by entries 5, 6, and 7. In theses examples also, depending upon the synthetic objective, the second vinyl component can be introduced at the coupling stage, the Grignard addition step, or via an oxidation of the primary alcohol followed by a Wittig reaction (Scheme 3). Unfortunately, alkyl Grignard reagents such as methylmagnesium chloride are problematic. This is partly attributed to the beneficial influence of

(7) Willison, T. M.; Henke, B. R.; Momtahen, T. M.; Charifson, P. S.; Batchelor, K. W.; Lubahn, D. B.; Moore, L. B.; Oliver, B. B.; Sauls, H. R.; Baer, P. G. *J. Med. Chem.* **1994**, *37*, 1550.
(8) Grese, T. A.; Dodge, J. A. Estrogen Recptor Modulators: Effects In Non-Tradition Target Tissues. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A. Ed., Academic Press: San Diego, CA, 1996; Vol. 31, pp 181−90.

Scheme 3. Synthesis of Tamoxifen and Related Olefins[a]
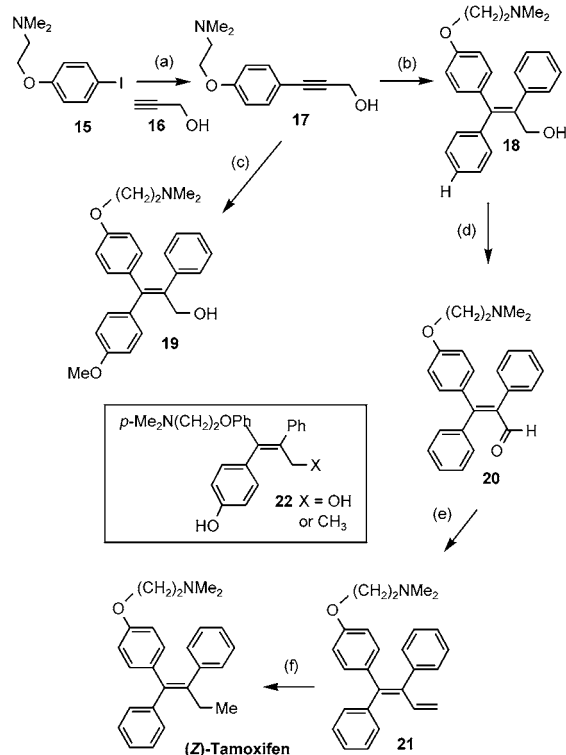
[a] Reagents and conditions: (a) PdCl$_2$(PPh$_3$)$_2$ (0.1 equiv), CuI (0.1 equiv), Et$_3$N, THF, rt, (22 °C), 18 h, 83%. (b) (1) PhMgCl (3.2 equiv), MePh, reflux, 16 h; (2) Pd(PPh$_3$)$_4$ (0.05 equiv), PhI, 72%. (c) (1) PhMgCl (3.2 equiv), MePh, reflux, 16 h; (2) Pd(PPh$_3$)$_4$ (0.05 equiv), *p*-MeOPhI (3 equiv), reflux, 24 h, 60%. (d) DMP (3 equiv), CH$_2$Cl$_2$, 22 °C, 12 h, 96%. (e) KOt-Bu (1.2 equiv), PPh$_3$CH$_2$Br (1.1 equiv), THF, reflux, 16 h, 81%. (f) H$_2$/Pd/C, EtOAc, 22 °C, 2 h. 85%.

π-orbitals in the addition component. Thus the poor result with the methylmagnesium chloride (entry 8) is due to the inefficiency of the carbometalation and not to the subsequent cross-coupling. The yield of the Grignard additions to propargyl alcohols can be enhanced, in some cases, by the addition of copper iodide.[1g] In our experience this frequently reduces the yield in condensations with carbonyl electrophiles. However, a reviewer recommended we examine the potential influence of catalytic copper iodide on one of these combined reactions due to its established beneficial influence in palladium couplings as well as conjugate additions. The effect was significant as the yield of **7** in entry 1a increased to 82% in the presence of 7.5 mol % of cuprous iodide, a yield improvement of 12%. The parallel reaction of methylmagnesium chloride in entry 8 was even more dramatic. The yield of **14** increased to 30%. Clearly, the best procedure for synthetic applications is to include catalytic CuI (7−10 mol %) for improved yields. We intend to investigate this beneficial effect in more detail.

In view of Tamoxifen's beneficial medicinal properties discussed above, we are interested in developing a short route to Tamoxifen mimics, as well as Tamoxifen itself. We desired a family of related mimics with alcohol substitution

to attach a cleavable tether tied to a breast cancer drug. Therefore the mimic should act as a site recognition agent, bind to an estrogen receptor, and subsequently release the drug by hydrolysis.

Tamoxifen's anti-estrogen biological activity resides entirely in the (*Z*) isomer. There are a limited number of stereoselective syntheses of (*Z*)-Tamoxifen,[9] although the nickel-catalyzed carbozincation sequence employing the addition of diphenylzinc to 1-phenyl-1-butyne followed by an iodine quench and palladium coupling is very direct (Figure 2).[10]
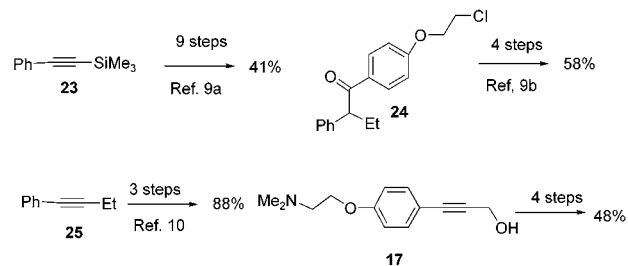

Figure 2. Comparison of (*Z*)-Tamoxifen syntheses.

Our synthesis commenced with a Sonogashira cross-coupling of the aryl halide **15** with propargyl alcohol **16** to give **17** (83%). This substituted alkynol was then subjected to the standard carbometalation protocol with phenylmagnesium chloride followed by the addition of Pd(PPh$_3$)$_4$ and phenyl iodide as the cross-coupling partner to give the Tamoxifen mimic **18** in 72% yield (Scheme 3). In a parallel carbometalation−palladium cross-coupling sequence, the methoxy ether **19** was prepared and may be converted, after demethylation, to the Tamoxifen metabolite **22** (X = Me) or provide a second hydroxyl group for substituent attachment.

Alkenol **18** was oxidized with Dess−Martin periodinane in CH$_2$Cl$_2$ to give the corresponding unsaturated aldehyde **20** (96%), which was transformed directly with methyl triphenylphosphonium bromide to give diene **21**. Selective hydrogenation of the less hindered double bond (10% Pd/C, H$_2$) afforded (*Z*)-Tamoxifen in 69% yield for the combined steps.

A comparison of the various (*Z*)-Tamoxifen syntheses is summarized in Figure 2, although a Friedel−Crafts reaction is required to generate the starting material **24**. However, only the syntheses commencing with **25** and **17** afford the pure *Z* isomer directly, although variation of the substitution pattern in **17** or the aryl Grignard allows greater versatility for analogue synthesis.

The net effect of these carbometalations is the regiocontrolled anti addition of the Grignard component relative to

(9) (a) Millar, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121. (b) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6187.
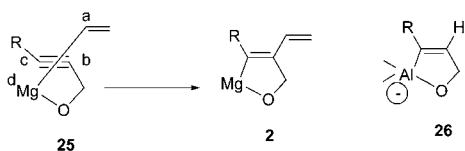(10) Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93.

Figure 3. Rational for trans addition of vinyl Grignard.

the second carbon−carbon bond. We have discussed previously the preference for sp^2 and sp centers for these Grignard additions.[2b] We believe the preferred pathway involves an intramolecular delivery of the vinyl group in which the $\pi-\pi$ interactions are beneficial and the bonding between a−b and c−d occurs in a synchronous manner as illustrated by **25**. A close analogy is provided by the anti-hydroalumination of propargyl alcohols with $LiAlH_4$ or Red-Al,[11] which are considered to involve intermediates of type **26**. Thus the initial addition of the vinylmagnesium chloride to the complexed species related to **25** is followed by collapse to **2**. No evidence was detected in earlier investigations[12] for

the involvement of a unimolecular one-electron-transfer mechanism, although a concerted $[\pi 2_s + \sigma 2_a]$ process has also been suggested.[13] The increased yield observed with methylmagnesium chloride in the presence of CuI suggests additional mechanisms involving metal complexation must also be operative.

In summary, we have developed a versatile direct synthesis of tetrasubstituted alkenes by a one-pot magnesium-mediated carbometalation of propargyl alcohols followed by palladium(0) cross-coupling with vinyl or aryl halides. This method has been applied to the regio- and stereoselective synthesis of (Z)-Tamoxifen and potential estrogen mimics with therapeutic potential.

Supporting Information Available: Experimental details and characterization for compounds **7**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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