Challenges associated with the synthesis of unusual *o*-carboxamido stilbenes by the Heck protocol : Intriguing substituent effects, their toxicological and chemopreventive implications

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Spectroscopic Features

The 2-furanocarboxamido stilbenes **15a-e** are interesting from several standpoints one of which is spectroscopic. The amide NH's are significantly deshielded (8.16-8.25d). In the case of **15b** and **15e** (Table A, entries 2 and 5) possessing 3-methoxy and 3,5-dimethoxy substituents respectively, the C(8)-H is noticeably more deshielded than the C(7)-H (see Table A). The C(8)-H is also more deshielded in **15c** and **15d** (Table A, entries 3 and 4) but in this case the chemical shift difference between C(7)-H and C(8)-H is smaller. C(8)-H has moved upfield given the mesomeric delocalization of the paramethoxy lone pair, in the case of **15c** and **15d**. In the case of **15a** possessing a solitary *ortho* methoxy substituent, the chemical shift position is reversed with C(7)-H being now more deshielded than C(8)-H in contrast to the previously described molecules (Table A, entries 1). This could be explained by taking into account the projection in space of the *ortho*-methoxy lone pairs (paramagnetic effect or deshielding). The greatest NH deshielding is also seen in **15a**, a remarkable demonstration of paramagnetic deshielding of a group at some distance from the 2-methoxy group in **15a**.

For the series of stilbenes incorporating 3,4-dimethoxy moieties where the furan carboxamides have been substituted by other groups, NH-deshielding is maximum for the benzamide analogue **11e** and the naphthylamide **11f** (see Table B). In general C(8)-H is more deshielded than C(7)-H although for the cyclohexylamido stilbene **11d** the C(7)-H and C(8)-H chemical shifts are much closer. It is noteworthy that for the 3,4-dimethoxy furancarboxamide **15c**, the olefinic chemical shifts are very similar to those of **11e** and **11f** but the amide NH chemical shift is 8.19, slightly more than the latter stilbenes (see Table B).

The carboxamidostilbenes that incorporate the biphenyl moiety represent another interesting set of compounds. In the three members of the set **13a-c** the NH protons for **13a** and **13b** but not **13c** are strongly deshielded. The C(8)-H protons are more deshielded than the C(7)-H (see Table C).

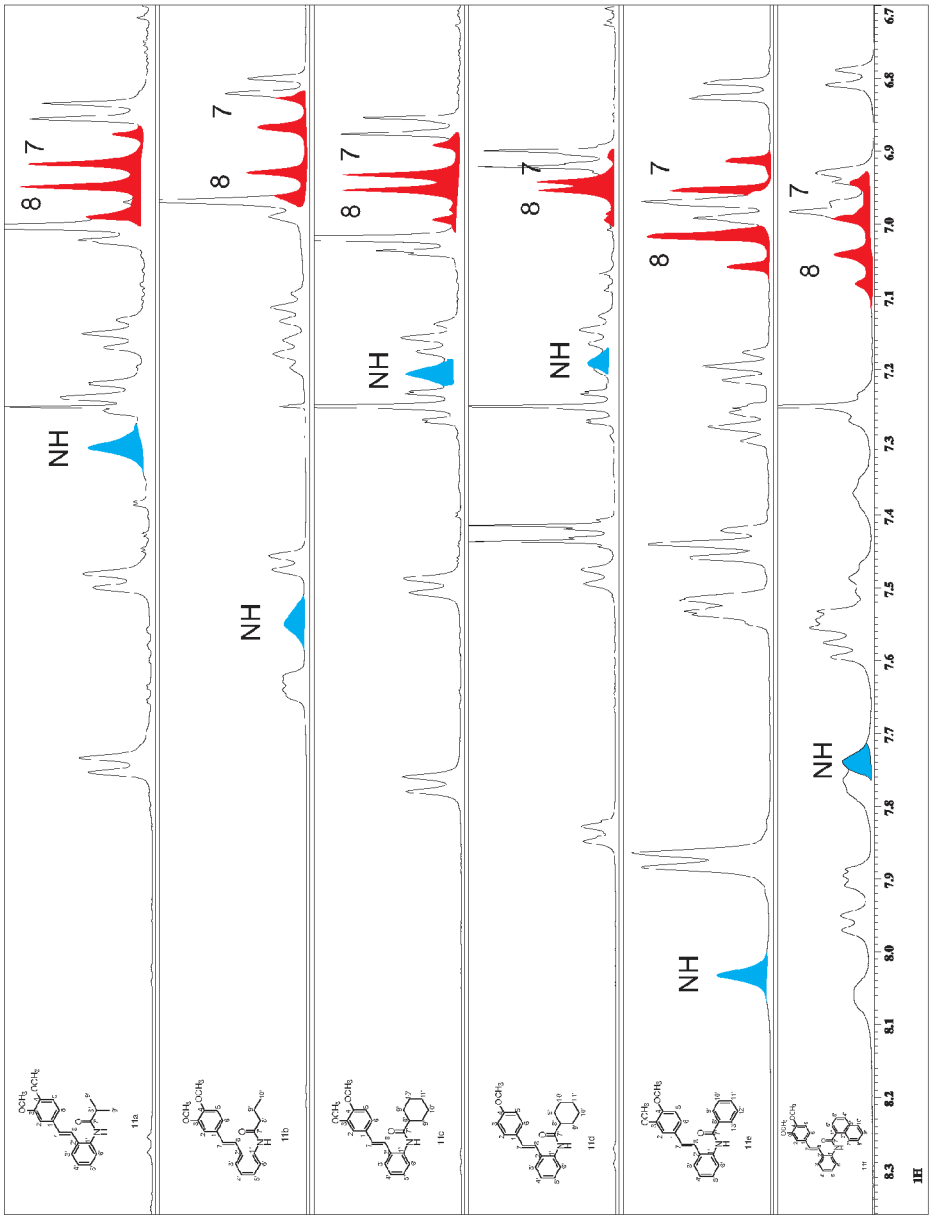


Figure A 1H NMR spectra of **11a-f**.

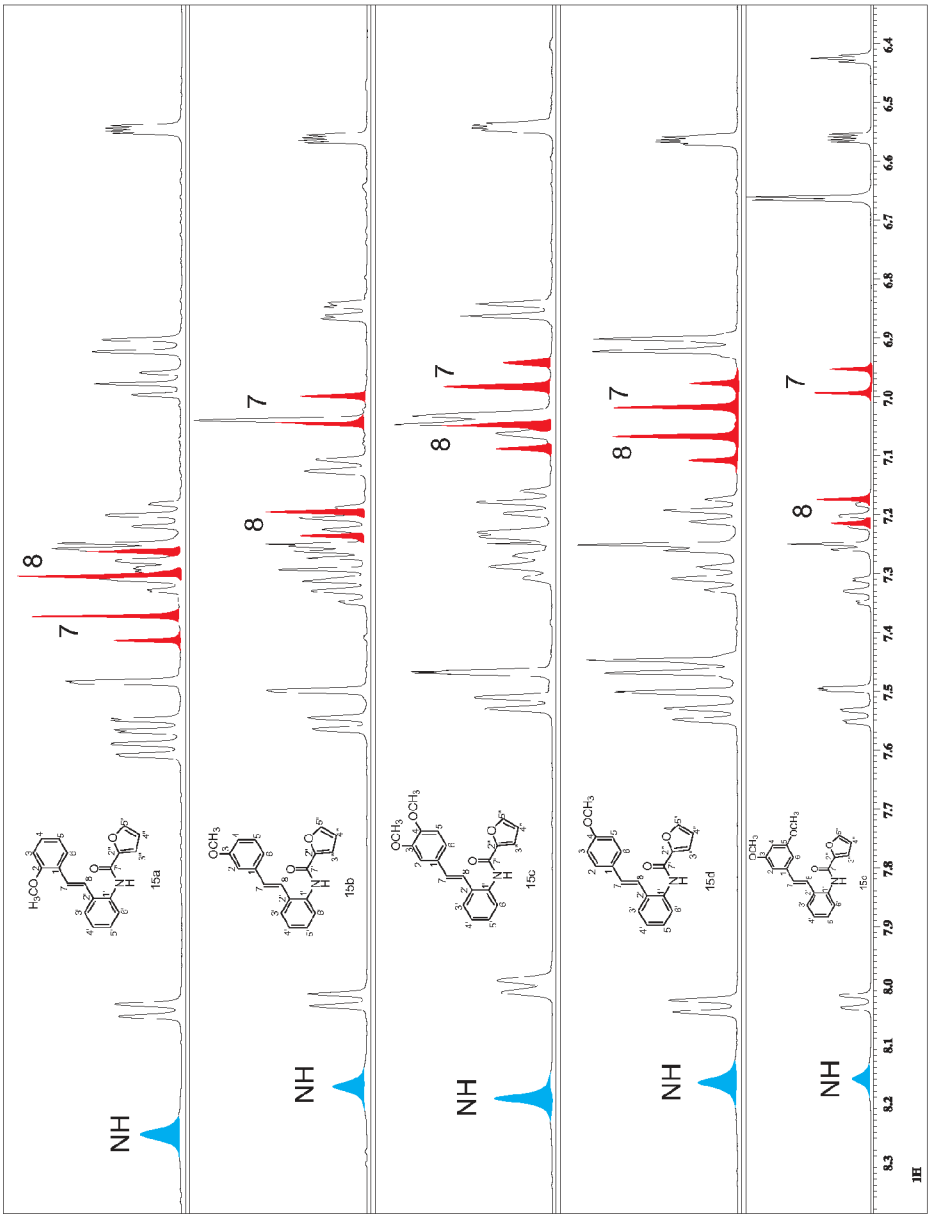


Figure B 1H NMR spectra of **15a-e**.

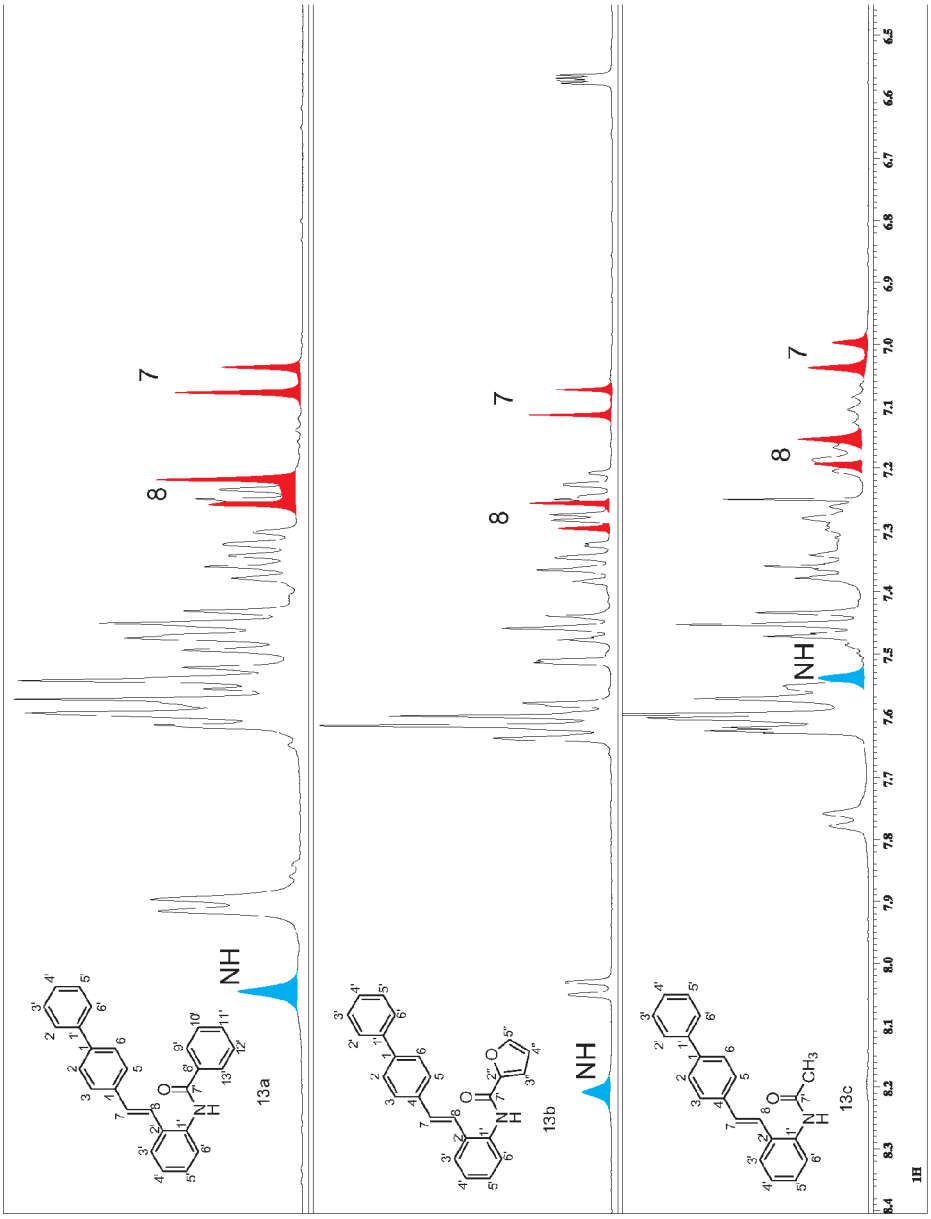


Figure C 1H NMR spectra of **13a-b**.

Table A ^{1}H NMR [400MHz, $^{\delta}$H(*J*, Hz)] of stilbene **15a-e** in $CDCl_3$

Entry	Product	C(7)-H(J,Hz)	C(8)-H(J,Hz)	NH
1	**15a**	7.40(d, 16.5)	7.29(d, 16.8)	8.25
2	**15b**	7.02(d, 16.5)	7.22(d, 16.0)	8.17
3	**15c**	7.00(d, 16.5)	7.09(d, 16.5)	8.19
4	**15d**	6.96(d, 16.5)	7.07(d, 16.5)	8.17
5	**15e**	6.99(d, 16.0)	7.21(d, 16.0)	8.16

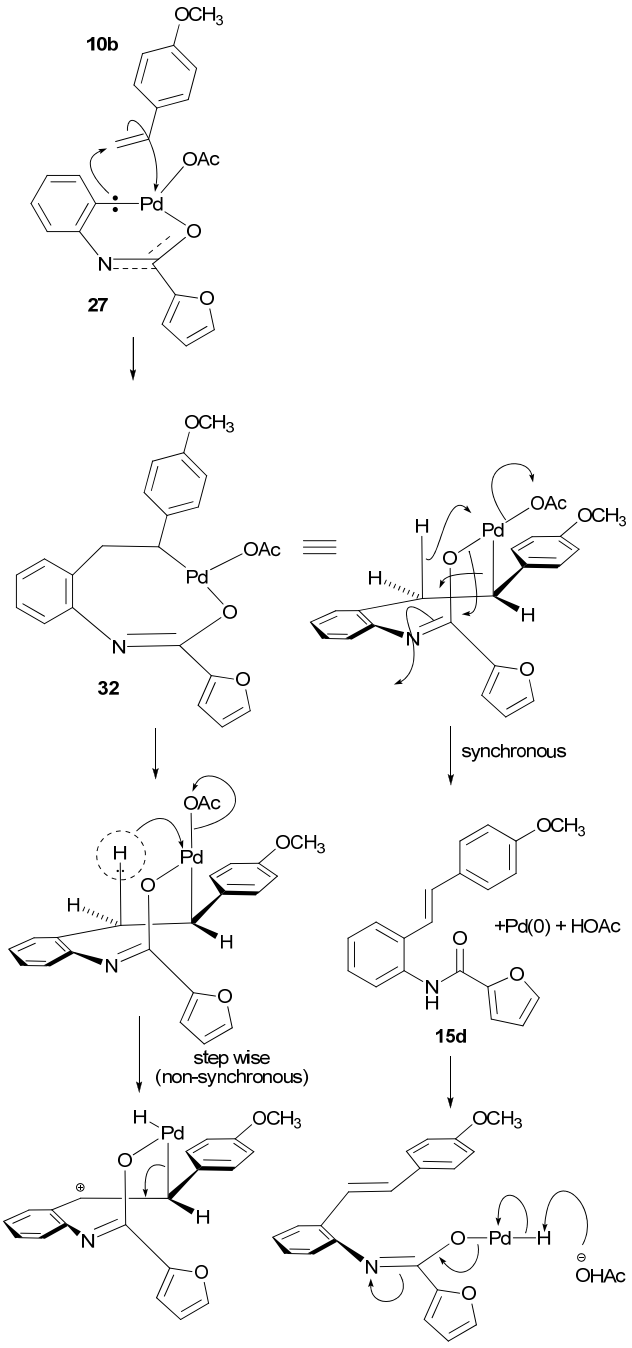
Table B ^{1}H NMR [400MHz, $^{\delta}$H(*J*, Hz)] of stilbene **11a-f** in $CDCl_3$

Entry	Product	C(7)-H(J,Hz)	C(8)-H(J,Hz)	NH
1	**11a**	6.90(d, 16.5)	6.97(d, 16.4)	7.31
2	**11b**	6.85(d, 16.2)	6.95(d, 15.6)	7.56
3	**11c**	6.91(d, 16.5)	6.97(d, 16.5)	7.21
4	**11d**	6.93(d, 16.5)	6.99(d, 16.4)	7.17
5	**11e**	6.93(d, 16.0)	7.04(d, 16.0)	8.03
6	**11f**	Overlapping	7.06(d, 16.5)	7.78

Table C ^{1}H NMR [400MHz, $^{\delta}$H(*J*, Hz)] of stilbene **13a-c** in $CDCl_3$

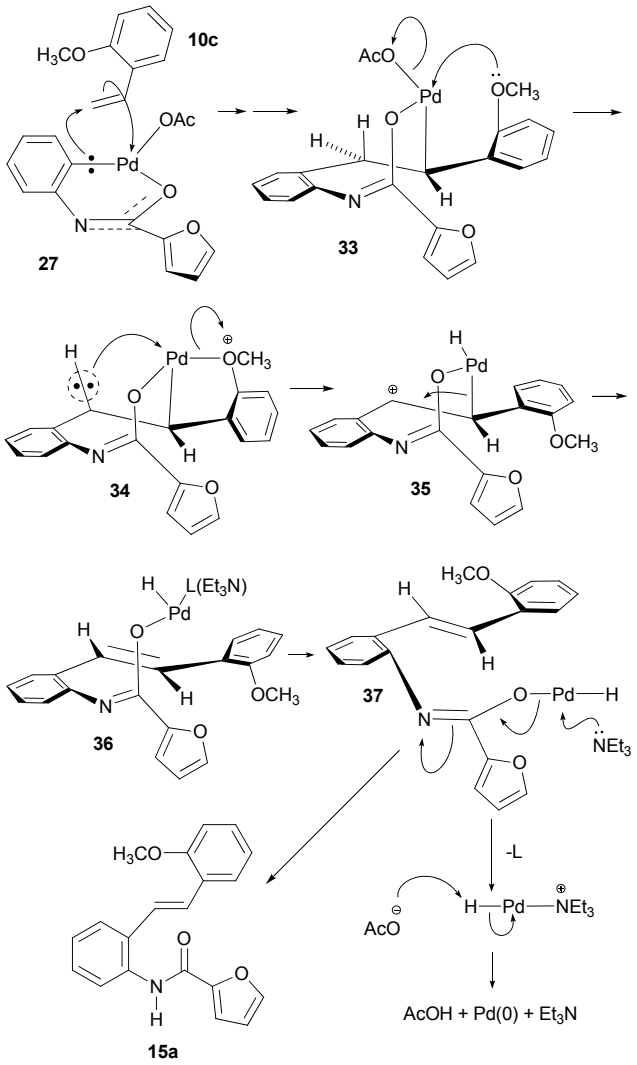
Entry	Product	C(7)-H(J,Hz)	C(8)-H(J,Hz)	NH
1	**13a**	7.06(d, 16.5)	7.24(d, 16.0)	8.05
2	**13b**	7.10(d, 16.5)	7.28(d, 16.5)	8.19
3	**13c**	7.01(d, 16.5)	7.17(d, 16.0)	7.54

An Alternative Proposal : Carbopalladation, *syn*-β-hydride Elimination



Scheme 9 The *syn*-β-hydride elimination within an eight membered palladacycle.

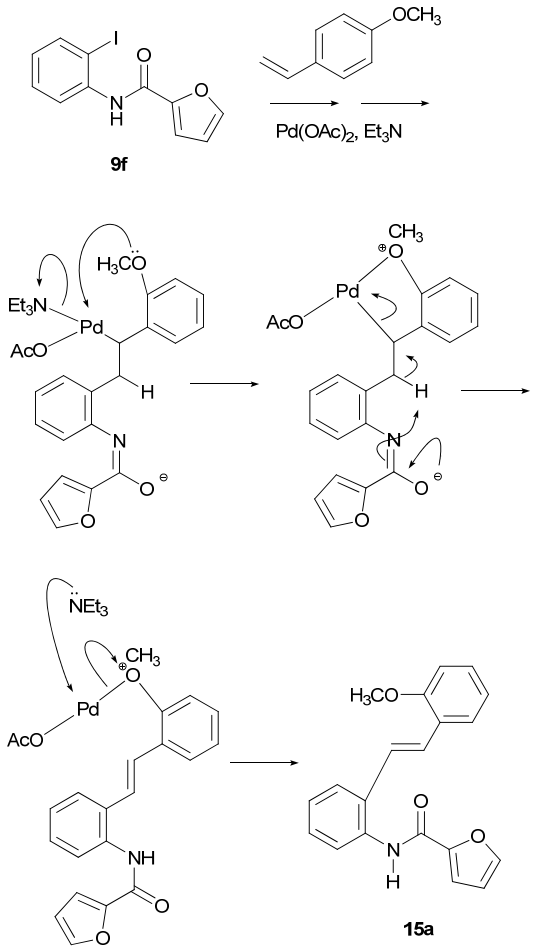
An alternative depiction of the mechanism of formation of **15d** is shown (see Scheme 9). **32** is obtained by "*exo*" carbopalladation of the styrene **10b**. In this alternative the complex adopts a conformation consistent with *syn*-β-hydride elimination[1] via synchronous and non-synchronous pathways. The relatively higher yields (49%) for the Heck reaction culminating in the furancarboxamido stilbene **15a** are presented in Table 3 (manuscript). In this case the relatively greater efficiency of Heck construction of **15a** (with the *ortho* methoxy group) may be rationalized by examining the effect of this group **33** on our eight membered ring furan carboxamide palladacycle (as proposed in Scheme 9, **32**, see also Scheme 10). This palladacycle collapses via OAc displacement **33→34**, rapid hydride transfer **34** and non-synchronous depalladation of the resulting benzylic carbenium ion (**35→15a**) via **36** and **37**. The "internal base" pathway (compare with Scheme 8 in manuscript) could also be employed, to explain a more facile E-2 eliminating leading to **15a**.



Scheme 10 Proposed pathway for the 2-methoxy styrene insertion (carbopalladation) into palladacycle **27** followed by *syn*-dihydropalladation.

A certain caution is advisable in suggesting mechanistic hypothesis regarding the Heck construction of the stilbenes in for example Table 3 (manuscript). Thus, although it would be tempting to speculate on the unfavourable repulsive dipoles for *meta* methoxy groups (for the case of **15c** and **15e**) and the resulting relative instability of the complexes analogous to **31** (Scheme 7, manuscript) or **32** (Scheme 9), the stilbenes **15c** and **15e** posed more severe purification (chromatographic) difficulties than all other stilbenes in Table 3 (manuscript) and this may well explain at least in part of the lower yields. These difficulties multiply considerably in the biphenyl series (Table 2, manuscript) with **13a** incorporating the

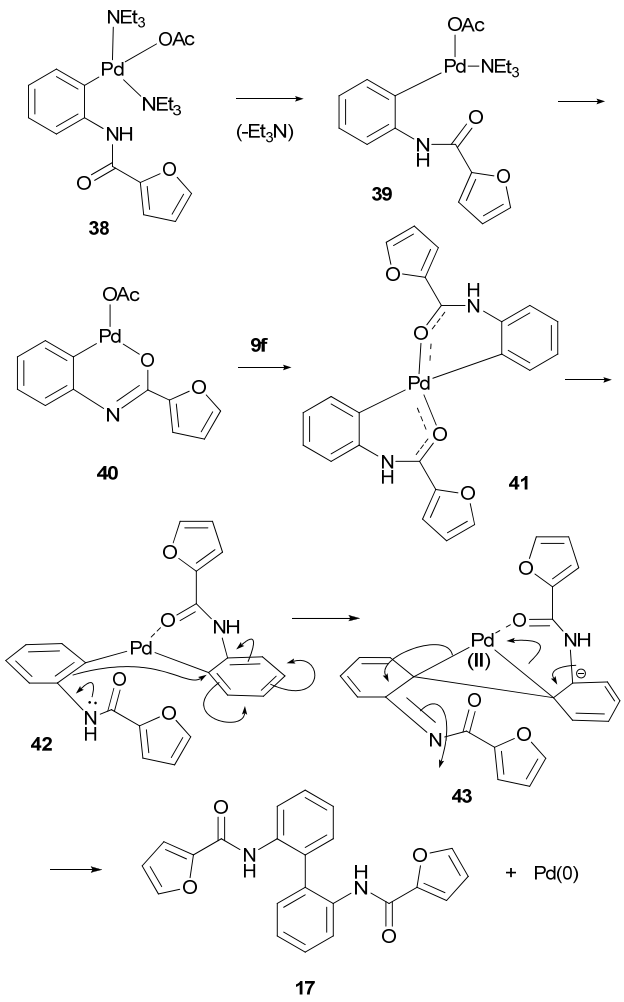
phenylcarboxamide presenting fewer chromatographic problems. The stilbene cyclohexylcarboxamides **11d**, in contrast to others in the series, crystallized out beautifully to yield pure compounds without the need for chromatographic purification - sadly an all too rare phenomenon!



Scheme 11 Mechanistic interpretation (open-chain) E-2 pathway leading to **15a**.

Formation of the Biaryl Side Product

In this case the organopalladium complex is envisaged to undergo a second oxidative addition to the iodophenyl furancarboxamide **9f** to yield the palladated dimer **41** via **40**. The complex then fragments via three membered ring Pd metallacycle to produce the bisbiaryl furan carboxamide **17** (see Scheme 12). A Scifinder search revelaed compound **17** is known and the compound has been assigned a CAS number but no synthetic, spectroscopic or crystallographic data were provided.



Scheme 12 Formation of bisbiaryl furan carboxamide – a mechanistic proposal.

1. A. Whiting and J. P. Knowles, *Org. Biomol. Chem.*, 2007, **5**, 31-44.