

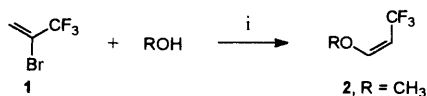
Palladium-catalysed arylation and alkenylation of *cis*-trifluoroprop-1-enyl methyl ether. A novel entry into trifluoromethylated compounds

Guo-qiang Shi,* Xian-hai Huang and Feng Hong

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, 200032 Shanghai, P. R. China

The palladium-catalysed reaction of *cis*-3,3,3-trifluoroprop-1-enyl methyl ether **2** with a variety of aryl and alkenyl halides or triflates occurred regioselectively to afford the α -arylated and alkenylated products in good yield.

Considerable efforts have been made to develop effective routes to trifluoromethyl substituted organic compounds because of their importance as new and effective medicines, agrochemicals and materials.¹ Trifluoromethylation,² fluorination³ and halogen exchange⁴ reactions are possible means for introducing the CF₃ group into an organic molecule. However, most of these methods suffer from low selectivity and harsh reaction conditions, and are generally only suitable for the synthesis of trifluoromethylated aromatic compounds. An attractive alternative approach is to make use of CF₃-containing intermediates as building-blocks for the construction of the target molecules. As a result, the development of readily available and synthetically versatile CF₃-containing building blocks has been the subject of intensive investigation.^{5,6} We have recently developed a convenient one-step synthesis of several *cis*-3,3,3-trifluoropropenyl ethers from the readily available 2-bromo-3,3,3-trifluoropropane **1** (Scheme 1).⁷ As



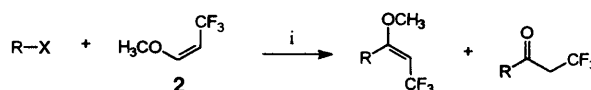
Scheme 1 Reagents and conditions: i, KOH, 86–96%

part of our effort to explore the utility of these CF₃-substituted vinyl ethers as building blocks for the synthesis of selectively trifluoromethylated compounds, we were interested in exploring the feasibility of using these fluorinated vinyl ethers as olefin substrates in palladium-catalysed Heck reactions. In this paper we report the results of our investigation.

The palladium-catalysed arylation and alkenylation of olefins (the Heck reaction) is known to be one of the most useful synthetic methods for making a carbon–carbon bond.⁸ As a particular type of olefin, simple cyclic and acyclic vinyl ethers have been employed in the Heck reaction.⁹ However, reactions with acyclic vinyl ethers do not appear to be of great synthetic importance since early investigations into their intermolecular arylation often revealed poor regioselectivity.⁹ With the presence of a synthetically valuable CF₃ group in the vinyl ethers, we have now found that our CF₃-substituted vinyl ethers are reasonably well behaved olefin substrates for the palladium-catalysed Heck reaction.

Because of its structural simplicity, the methyl ether **2** has been selected as a standard vinyl ether in experiments to assess the feasibility of the Heck reaction. After initial screening of catalysts and bases using iodobenzene as the reaction partner, it was found that the desired arylation reaction could take place under several different conditions affording the product with high selectivity towards α -arylation. The best yields

and regioselectivities were achieved when the reaction was performed in DMF using Ag₂CO₃ as the base¹⁰ and Pd(OAc)₂–PPh₃ as the catalyst. These conditions were then used for the reaction of **2** with other halides (Scheme 2).



Scheme 2 Reagents and conditions: i, Pd(OAc)₂ (3 mol%), PPh₃ (6 mol%), base (1.0 equiv.), DMF


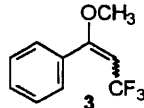
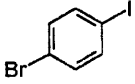
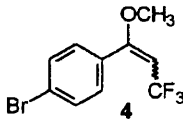
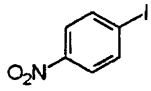
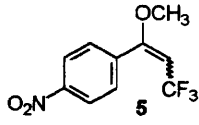

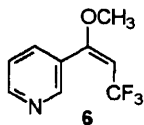
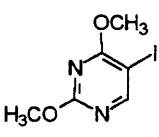
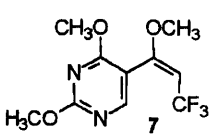

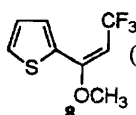
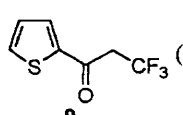
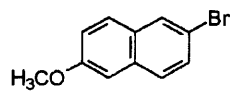
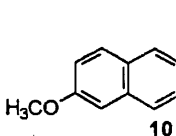
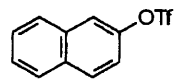
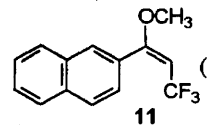
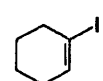
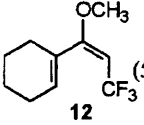
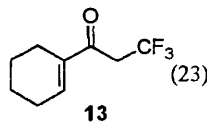
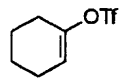
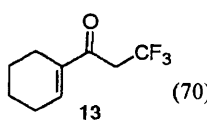
However, with the triflate substrates the reaction was found to proceed equally well when Ag₂CO₃ was replaced with triethylamine.

The results obtained with a number of aryl and alkenyl halides and triflates are summarised in Table 1. It can be seen that both aryl iodides and triflates appear to be useful substrates for the coupling reaction. The reaction with bromides was somewhat sluggish and moderate yields were obtained only after prolonged heating. In some cases, a ketone resulting from the hydrolysis of the primary product was also obtained. The tendency towards hydrolysis appeared to be more pronounced in the case of alkenylation products (entries 9 and 10).

An interesting feature of the reaction described above is the regioselectivity for α -substitution, *i.e.*, addition of the organic group of the alkenyl or aryl palladium intermediate to the oxygen-bearing carbon of the double bond, regardless of the type of substrate employed. In the palladium-catalysed arylation of simple acyclic vinyl ethers, the regioselectivity was found to be dependent on the reaction conditions and the type of substrates. In reactions with aryl halides under standard conditions, *e.g.* the use of Pd(OAc)₂ and PPh₃ as the catalyst and triethylamine as the base, steric and electronic factors are influential, giving rise to the formation of both α - and β -arylated products.⁸ However, the use of a bidentate ligand, silver(I) or thallium(I) salt, or a triflate substrate has been recently found to favour a reaction pathway *via* a cationic palladium complex that favours the formation of α -arylated products.^{8b} The complete control of the regioselectivity of the present reactions can be attributed to the use of the silver(I) salt or triflate substrates as well as the highly polarised nature of the enolic double bond in **2** induced by the push–pull interaction between the trifluoromethyl and methoxy groups.

The stereochemistry of the coupling product has been examined. As shown in Table 1, most of the coupling products were found to contain a single *E* isomer. In some reactions, a small amount of the *Z* isomer could be detected. The percentage of this minor isomer was found to be dependent on the reaction time and varied from batch to batch within a given reaction, ranging from 10% to less than 3%, indicating that isomerisation of the primary product had occurred to some extent. The assignment of the configuration was based on a strong

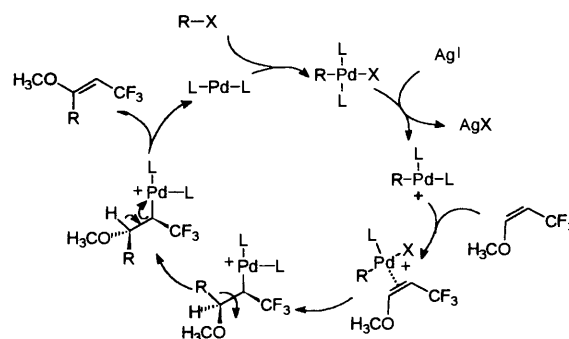
Table 1 Palladium-catalysed arylation and alkenylation of *cis*-3,3,3-trifluoroprop-1-enyl methyl ether 2^a

Entry	R-X	Base	T/°C, t/h	Product (yield, %; Z/E) ^b
1		Ag ₂ CO ₃	80,48	 (90; 2 : 98)
2		Ag ₂ CO ₃	80,24	 (85; 10 : 90)
3		Ag ₂ CO ₃	80,24	 (80; 3 : 97)
4		Ag ₂ CO ₃	80,48	 (65; >2 : 98)
5		Ag ₂ CO ₃	80,36	 (85; >2 : 98)
6		Ag ₂ CO ₃	80,36	 (24; 2 : 98)  (40)
7		Ag ₂ CO ₃	80,72	 (58)
8		Et ₃ N	80,24	 (60; 10 : 90)
9		Ag ₂ CO ₃	80,48	 (55; >2 : 98)  (23)
10		Et ₃ N	50,12	 (70)

^a All reactions were performed in DMF under nitrogen on a 2 mmol scale for 2 equivalents of the vinyl ether 2 using 3 mol% of Pd(OAc)₂, 6 mol% of PPh₃ and 1.0 equivalents of the indicated base. ^b Yield of isolated product.

correlation between the vinylic proton and the methoxy group in the NOESY spectra of the *E* isomers.

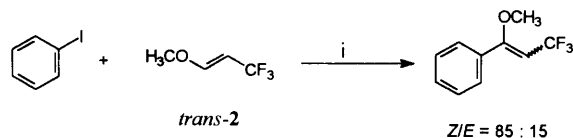
Although we have made no detailed studies that permit the evaluation of the exact reaction mechanism for the arylation and alkenylation of 2, the observed stereoselectivities imply that the reaction has followed a commonly accepted pathway involving *cis* addition of the arylpalladium intermediate to the *cis* double bond of 2 followed by *syn* β-hydride elimination after internal rotation to give the *E*-product (Scheme 3). Thus, the present reaction provides one more example in which the *syn* requirement has to be complied with even at the expense of the significant eclipsing interaction between the R and the CF₃ groups. Since isomerisation by readdition of the palladium hydride to the initially formed product is known to be inhibited



Scheme 3 Mechanism of the Heck reaction

by the use of silver salt,¹⁰ the formation of some *Z*-isomer was most probably caused by proton or silver ion catalysed isomerisation of the primary product. This notion was supported by the observation of the hydrolysed product in some reactions since both the isomerisation and hydrolysis processes were believed to proceed through a common carbocationic intermediate.

According to the proposed mechanism, the arylation of the *trans* isomer of **2** should afford the arylated product with *Z* configuration. Indeed, when the *trans* isomer of **2** was treated with iodobenzene under the same catalytic conditions, the *Z* isomer of the coupling product was formed predominantly (Scheme 4). Again, some isomerisation of the primary product occurred in this reaction.



Scheme 4 Reagents and conditions: i, Pd(AcO)₂ (3 mol%), PPh₃ (6 mol%), Ag₂CO₃ (1.0 equiv.), DMF, 70%

In conclusion, we have established a convenient method for the α -arylation and α -alkenylation of the readily prepared *cis*-3,3,3-trifluoroprop-1-enyl ethers *via* the palladium-catalysed Heck reaction. While the α -arylation provides the arylated enol ethers as the readily isolable products, the alkenylation reaction appears to be more suitable for the direct synthesis of α,β -unsaturated ketones due to the susceptibility of the primary product, *i.e.* a dienyl ether, towards hydrolysis under the reaction conditions. Overall, the present method provides a novel entry into trifluoromethylated compounds which can be further functionalised by virtue of the capability of the enol ether or the derived keto functionality to undergo a variety of other synthetic transformations.

Experimental

(*Z*)-1-Methoxy-3,3,3-trifluoroprop-1-ene **2**⁷ Bp 82–84 °C (lit.,¹¹ 83–84 °C).

General procedure for the Heck reactions exemplified by the reaction of the enol ether **2** with iodobenzene

A mixture of iodobenzene (0.41 g, 2.0 mmol), the enol ether **2** (0.50 g, 4.0 mmol), silver carbonate (0.55 g, 2.0 mmol), palladium acetate (0.014 g, 0.060 mmol) and triphenylphosphine (0.30 g, 0.12 mmol) in DMF (2.0 cm³) was heated under nitrogen at 80 °C for 48 h. The reaction mixture was diluted with diethyl ether and filtered. The filtrate was washed with water (2 × 20 cm³) and dried over sodium sulfate. After evaporation of the filtrate, the residue was subjected to chromatography on silica gel eluting with a 9:1 mixture of light

petroleum and ethyl acetate to afford 1-methoxy-1-phenyl-3,3,3-trifluoropropene **3** (0.36 g, 90%) as a 2:98 *Z/E* mixture; *E*-isomer: δ_{H} (300 MHz; CD₃COCD₃) 7.63 (m, 1 H), 7.54 (m, 2 H), 7.37 (m, 2 H), 4.96 (q, *J* 7.6 Hz, 1 H) and 3.75 (s, 3 H); δ_{F} (60 MHz; CD₃COCD₃) –26.0 (d, *J* 7.6 Hz); *Z*-isomer: δ_{H} (300 MHz; CD₃COCD₃) 7.5 (m, 5 H), 5.25 (q, *J* 8.0 Hz, 1 H) and 3.62 (s, 3 H); δ_{F} (60 MHz; CD₃COCD₃) –20.0 (d, *J* 8.0 Hz); *m/z* 202 (M⁺, 51%), 201 (100), 171 (26), 91 (36) and 77 (12) (Found: C, 59.4; H, 4.5. C₁₀H₉F₃O requires C, 59.29; H, 4.53%).

Acknowledgements

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References

- (a) *Biomedical Aspects of Fluorine Chemistry*, eds. R. Filler and Y. Kobayashi, Kodansha Ltd., Tokyo, 1982; (b) J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; (c) *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications*, eds. R. Filler and Y. Kobayashi, Elsevier, Amsterdam, 1993; (d) H. Yoshioka, C. Nakayama and N. Matsuo, *J. Syn. Org. Chem. Jpn.*, 1984, **42**, 809; (e) H. Nohira, *J. Syn. Org. Chem. Jpn.*, 1991, **49**, 467.
- (a) T. Umemoto, K. Adachi, *J. Org. Chem.*, 1994, **59**, 5692; (b) M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555.
- G. A. Boswell, Jr., T. C. Ripka, R. M. Schribner and C. W. Tillock, *Org. React. (N. Y.)*, 1974, **21**, 1.
- T. Hudlicky, *Chemistry of Organic Fluorine Compounds*, Wiley, New York, 1976, p. 96.
- For a comprehensive review on trifluoromethyl-containing building-blocks, see: K. Uneyama, *J. Syn. Org. Chem. Jpn.*, 1991, **49**, 612.
- Recent examples: (a) T. Yamazaki, K. Mizutani and T. Kitazume, *J. Org. Chem.*, 1995, **60**, 6046; (b) Y. Makino, K. Iseki, K. Fujii, S. Oishi, T. Hirano and Y. Kobayashi, *Tetrahedron Lett.*, 1995, **36**, 6527; (c) P. V. Ranachandran, B. Gong and H. C. Brown, *J. Org. Chem.*, 1995, **60**, 41; (d) J.-P. Begue, F. Benayoud and D. Bounet-Delpon, *J. Org. Chem.*, 1995, **60**, 5029; (e) T. Yamazaki, S. Hiraoka and T. Kitazume, *J. Org. Chem.*, 1994, **59**, 5100; (f) Y.-y. Xu, F.-q. Jin and W.-y. Huang, *J. Org. Chem.*, 1994, **59**, 2638; (g) Y. Kobayashi, *Tetrahedron Lett.*, 1993, **34**, 8147.
- F. Hong and C.-M. Hu, *J. Chem. Soc., Chem. Commun.*, 1996, 57.
- For recent reviews, see: (a) A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379; (b) W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2.
- A. Daves, Jr. and A. Hallberg, *Chem. Rev.*, 1989, **89**, 1433.
- R. C. Larock, W. H. Gong and E. Baker, *Tetrahedron Lett.*, 1989, **30**, 2603.
- A. L. Henne and M. Nager, *J. Am. Chem. Soc.*, 1952, **74**, 650.

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