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Ruthenium-Catalyzed Remote Electronic Activation of Aromatic C–F Bonds

Andrew J. A. Watson,[a] Benjamin N. Atkinson,[a] Aoife C. Maxwell,[b] and Jonathan M. J. Williams[a,*]

[a] Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.
E-mail: j.m.j.williams@bath.ac.uk
[b] GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.

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Abstract: The tandem isomerization and nucleophilic aromatic substitution of allylic fluoro-substituted benzylic alcohols is described for the first time. In the presence of the ruthenium complex $Ru(PPh_3)_3(CO)(H)_2$, 1-(4-fluorophenyl)prop-2-en-1-ol is converted into the corresponding *para*-amino ketone or *para*-phenolic substituted ketone.

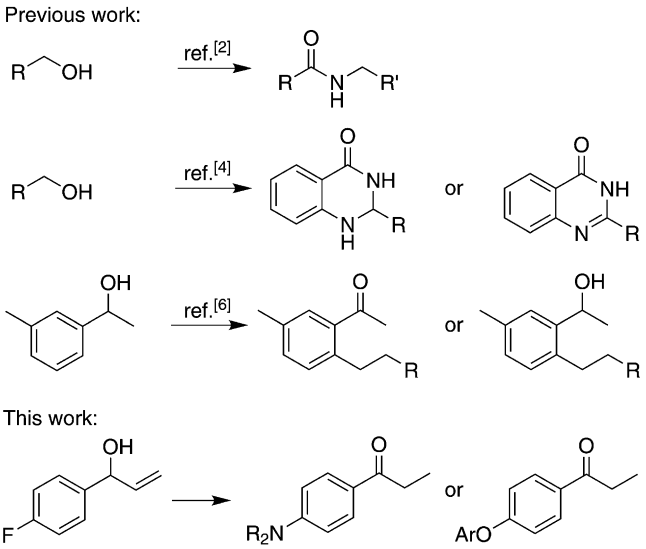
Keywords: arenes; isomerization; nucleophilic substitution; ruthenium

Introduction

Alcohols are widely accessible and more stable than their aldehyde or ketone counterparts. However, the range of chemistry applicable to alcohols is very limited when compared with the diversity offered by aldehydes and ketones. Therefore a technology capable of harnessing the reactivity and breadth of chemistry accessible to carbonyl compounds, but from the alcohol would be very powerful. Furthermore, it would avoid oxidations whilst reducing the amount of waste by-products and number of synthetic steps.

Hydrogen transfer reactions are one approach to this idea.[1] The transfer of two hydrogen atoms from the alcohol to an oxidant generates the aldehyde *in situ*, which can then react further. We have previously reported several examples of this approach (Scheme 1) to access amides,[2] activated alkenes,[3] heterocycles,[4] esters[5] and more recently substituted aromatic ketones and alcohols.[6]

Nucleophilic aromatic substitution proceeds well for electron-deficient arenes, however, it is unsuccessful for electron-rich arenes (Scheme 2). This provides an opportunity to apply hydrogen transfer methodology. By starting from the alcohol, which cannot undergo substitution, and then converting into the ketone which can undergo the nucleophilic aromatic substitution, an activation/substitution tandem process could be achieved. We chose to take two approaches to this reaction; a direct oxidation of the alcohol (Scheme 3) and an isomerization of an allylic alcohol (Scheme 4).

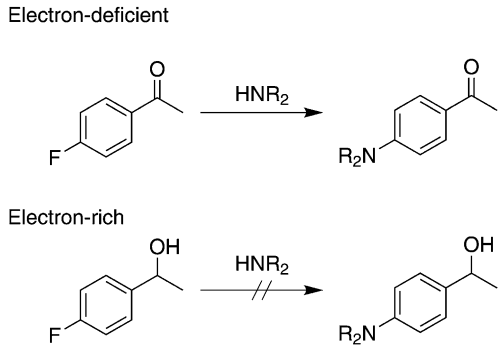


Scheme 1. Applications of hydrogen transfer chemistry.

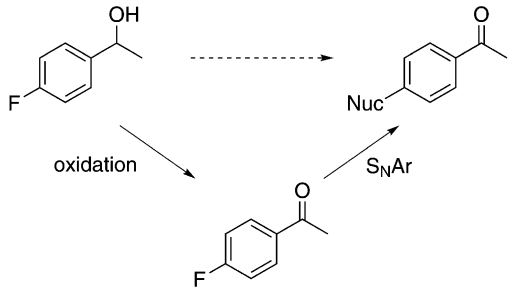
The latter can also be considered as an oxidation of the alcohol, followed by reduction of the alkene. Alternative approaches to metal-catalyzed C–F bond activation are reported in the literature.[7]

Results and Discussion

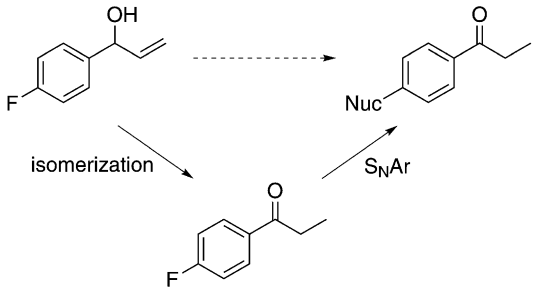
Work began by looking at the nucleophilic aromatic substitution of 4-fluoroacetophenone with morpholine (Scheme 5) as this reaction dictates the conditions to



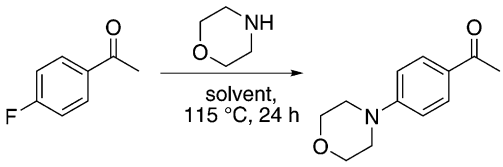
Scheme 2. S_NAr reactions of fluoro-aromatics.



Scheme 3. Tandem oxidation/aromatic substitution.



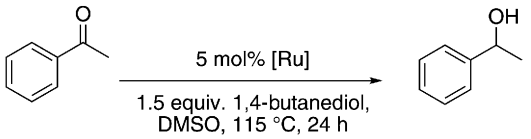
Scheme 4. Tandem isomerization/aromatic substitution.



Scheme 5. Nucleophilic aromatic substitution reaction in DMSO.

be used for the oxidation, if it is to occur *in situ* as desired. Despite many reports in the literature,[8] there is very little detail on the limitations of this reaction. A screen of solvents[9] showed that only DMSO gave 100% conversion to the product.

Having previously avoided DMSO as a solvent due to its high boiling point, a screen of several widely used ruthenium precursors was conducted to establish which were active for hydrogen transfer in DMSO (Scheme 6 and Table 1).



Scheme 6. Hydrogen transfer reaction in DMSO.

Several likely catalysts proved to be inert in DMSO, although two catalysts were active, Shvo's catalyst **1** (Table 1, entry 4) and $Ru(PPh_3)_3(CO)(H)_2$ **2** (Table 1, entry 5) returning 23% and 93% conversion, respectively. Considering the success of **2**, the related catalyst $Ru(PPh_3)_3(CO)(H)(Cl)$ **3** (Table 1, entry 6) was also added to the screen, however, it was not as active, returning only 28% conversion.

Optimization of the tandem oxidation/substitution reaction (Scheme 3) began with an oxidant screen. This highlighted that previously successful oxidants such as crotononitrile, ketones and levulinic acid derivatives[10] were all unsuitable due to the occurrence of side reactions. The use of unfunctionalized alkenes was more successful, despite the low conversion (6–34%).[9]

Steric and electronic tuning of the catalyst by the addition of alternative ligands (Table 2) improved the conversion to 60%, however, further improvement past this point was unsuccessful. The alternative approach (Scheme 4) using an allylic alcohol was then considered, as this would not require an external oxidant. Furthermore, tandem metal-catalyzed isomerizations are well known[11] and have been used previously with other reactions such as reduction,[12] C–H activation[13] and fluorination.[14] Using the data already obtained, a ligand screen (Table 3) using **2** in DMSO was conducted for the isomerization of the model allylic alcohol (Scheme 7).

From the results, two ligands clearly generated more efficient catalysts, DPEphos (Table 3, entry 9)

Table 1. Catalyst screen.

Entry[a]	Catalyst	Conversion [%][b]
1	$[Ru(p\text{-cymene})Cl_2]_2$	0
2	$RuCl_2(PPh_3)_3$	0
3	$Ru_3(CO)_{12}$[c]	0
4	Shvo's catalyst **1**	23
5	$Ru(PPh_3)_3(CO)(H)_2$ **2**	93
6	$Ru(PPh_3)_3(CO)(H)(Cl)$ **3**	28

[a] *Conditions:* acetophenone (1 mmol), 1,4-butanediol (1.5 mmol), [Ru] (5 mol%), DMSO (1 mL), 115 °C, 24 h.
[b] Conversion determined by ^1H NMR.
[c] 6 mol% ruthenium.

Table 2. Ligand screen for oxidation.

Entry[a]	Ligand	Conversion [%][b]
1	dppm	48
2	dppe	47
3	dppp	34
4	dppb	24
5	dpppent	15
6	dppbe	41
7	Xantphos	41
8	DPEphos	17
9	(+/−)-BINAP	33
10	Triphos	10
11	dcpe	60

[a] *Conditions:* 1-(4-fluorophenyl)ethanol (1 mmol), morpholine (2.2 mmol), 1-octene (1.5 mmol), **2** (5 mol%), DMSO (1 mL), 115 °C, 24 h.
[b] Conversion determined by ^{1}H NMR.

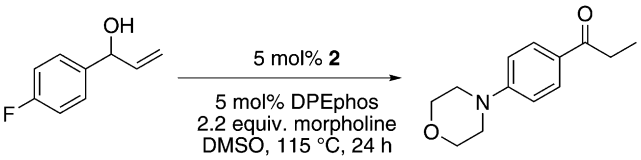
Table 3. Isomerization ligand screen.

Entry[a]	Ligand	Conv. [%][b]
1	no ligand	13
2	dppm	16
3	dppe	19
4	dppp	35
5	dppb	20
6	dpppent	13
7	dppbe	16
8	(+/−)-BINAP	12
9	DPEphos	50
10	Xantphos	27
11	1,2-bis(dicyclohexylphosphino)ethane	27
12	1,4-bis(dicyclohexylphosphino)butane	58
13	Triphos	15
14	*cis*-1,2-bis(diphenylphosphino)ethylene	17
15[c]	DPEphos	71
16[d]	DPEphos	81
17[e]	DPEphos	>99

[a] *Conditions:* 1-(4-fluorophenyl)prop-2-en-1-ol (1 mmol), **2** (5 mol%), DMSO (1 mL), 115 °C, 90 min.
[b] Conversion determined by ^{1}H NMR.
[c] Reaction run for 3 h.
[d] Reaction run for 5 h.
[e] Reaction run for 24 h.

and 1,4-bis(dicyclohexylphosphino)butane (Table 3, entry 12) returning 50% and 58% conversion, respectively. Despite being less active, DPEphos was chosen

Scheme 7. Model allylic alcohol isomerization.



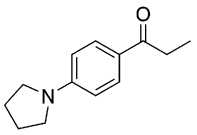
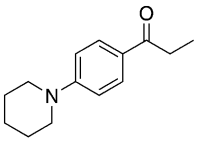
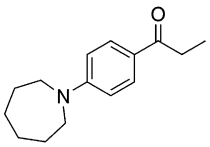
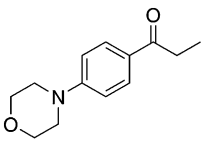
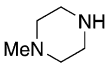
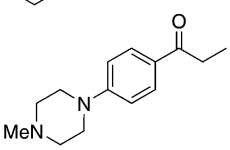
Scheme 8. Tandem isomerization/substitution test.

for further work due to its lower relative cost. With the conversion at 50%, the reaction time was doubled to 3 h, in order to drive the reaction to completion. However, the reaction only proceeded to 71% conversion (Table 3, entry 15). Further heating to 5 h (Table 3, entry 16) also resulted in incomplete conversion, but leaving the reaction for 24 h led to complete conversion (Table 3, entry 17).

The isomerization and nucleophilic substitution were then run together to test whether the combination would indeed give the desired result (Scheme 8). ^{1}H NMR analysis of the reaction showed full conversion. It was also possible to reduce the catalyst loading slightly to 4 mol% without reducing overall conversion.

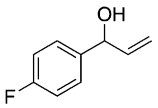
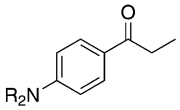
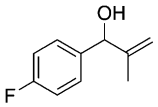
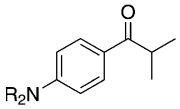
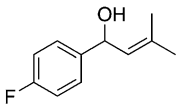
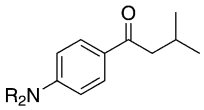
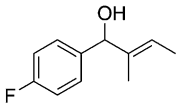
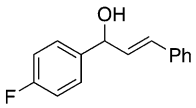
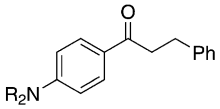
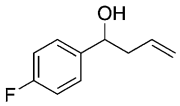
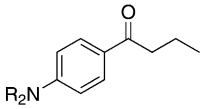
With conditions optimized, the substrate scope was evaluated. Earlier work on the aromatic substitution of 4-fluoroacetophenone had highlighted that only

Table 4. Cyclic secondary amine scope.

Entry[a]	Amine	Product	Isolated Yield [%]
1			77
2			87
3			81
4			86
5			71

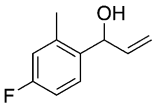
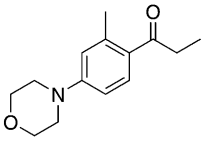
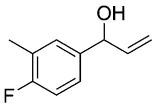
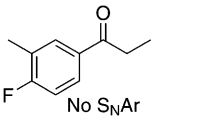
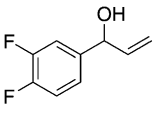
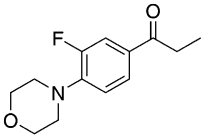
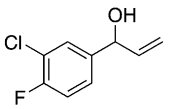
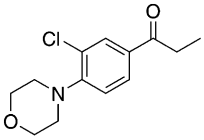
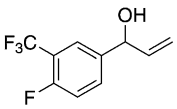
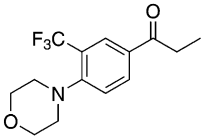
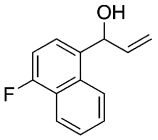
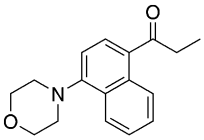
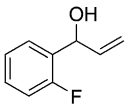
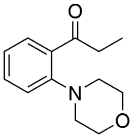
[a] *Conditions:* 1-(4-fluorophenyl)prop-2-en-1-ol (3 mmol), morpholine (6.6 mmol), **2** (4 mol%), DPEphos (4 mol%), DMSO (3 mL), 115 °C, 24 h.

Table 5. Double bond substitution scope.

Entry[a]	Starting Material	Product	Isolated Yield [%]
1			86
2[b]			52
3[b]			57
4		–	0[c]
5[b]			37
6			85

[a] *Conditions:* 1-(4-fluorophenyl)prop-2-en-1-ol (3 mmol), morpholine (6.6 mmol), **2** (4 mol%), DPEphos (4 mol%), DMSO (3 mL), 115 °C, 24 h. R_2N- is morpholino.
[b] 5 mol% catalyst and ligand used and the reaction run for 48 h.
[c] Determined by ^{1}H NMR.

Table 6. Aromatic ring substitution.

Entry[a]	Starting Material	Product	Isolated Yield [%]
1			51
2			74
3			67[b]
4			58
5			61
6			41[c]
7			35[b]

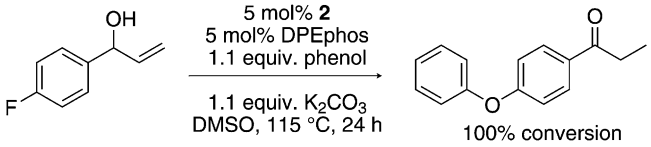
[a] *Conditions:* 1-(4-fluorophenyl)prop-2-en-1-ol (3 mmol), morpholine (6.6 mmol), **2** (4 mol%), DPEphos (4 mol%), DMSO (3 mL), 115 °C, 24 h.
[b] 5 mol% catalyst and ligand used.
[c] 5 mol% catalyst and ligand used for 48 h.

cyclic secondary amines proceeded well, with acyclic examples returning poor conversions and primary amines showing no conversion at all. With this in mind, a range of cyclic secondary amines was screened under the reaction conditions (Table 4).

All the substrates used led to good isolated yields, with 5-, 6- and 7-membered rings being tolerated for the substitution reaction (Table 4, entries 1–3). Functionalized amines were also well tolerated including morpholine (Table 4, entry 4) and 1-methylpiperazine (Table 4, entry 5).

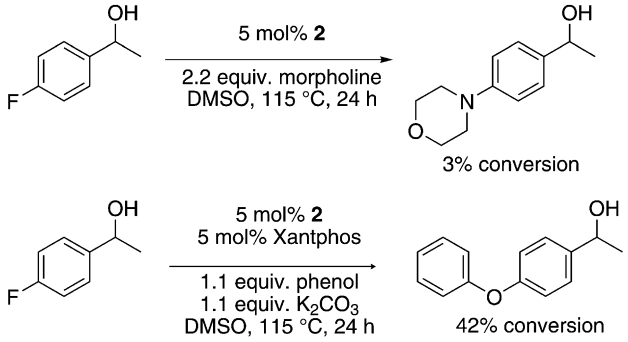
Substitution around the alkene was considered next (Table 5), as this would have an effect on the rate of isomerization. As expected, these results were less successful, with only the homoallylic alcohol (Table 5, entry 6) performing as well as the allylic examples (Table 5, entry 1). Higher catalyst loadings and longer reaction times were required for more substituted alkenes (Table 5, entries 2 and 3). However, the tetrasubstituted alkene (Table 5, entry 4) did not give the desired product, even with the higher loading and longer reaction time, instead returning the alternative isomer of the starting material. The use of a conjugated alkene (Table 5, entry 5) also required higher catalyst loading and longer reaction times to achieve similar conversions to the other substituted alkenes. The low isolated yield in this case is due to the difficulty in isolating the product from the reaction mixture.

Finally, substitution on the aromatic ring was evaluated (Table 6). Introducing methyl groups into the *ortho* and *meta* positions (Table 6, entries 1 and 2) still allowed the isomerization to occur successfully. However, the aromatic substitution was severely hampered when the methyl substituent was *ortho* to the fluorine (Table 6, entry 2). Whilst in this case the isomerization was complete, analysis of the crude reaction mixture by ^{1}H NMR showed only 6% conversion for the aromatic substitution. Interestingly, alternative substituents located *ortho* to the fluoro group did not



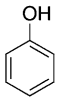
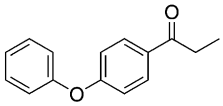
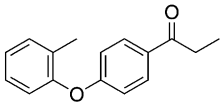
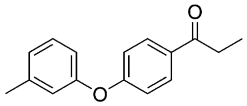
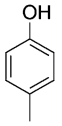
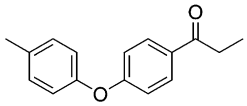
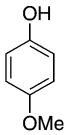
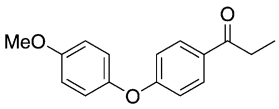
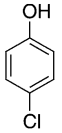
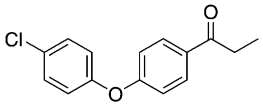
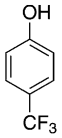
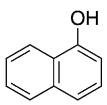
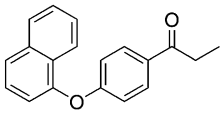
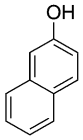
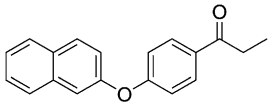
Scheme 9. Tandem isomerization/substitution phenol test.

prevent substitution (Table 6, entries 3–5). In particular, the trifluoromethyl derivative (Table 6, entry 5) isomerized well and returned a good yield on the aromatic substitution. This suggests that the substitution process is sensitive to electronic effects as well as steric effects.



Scheme 10. Borrowing hydrogen methodology.

Table 7. Isomerization ligand screen.

Entry[a]	Phenol	Product	Isolated Yield [%]
1			61
2			56
3			58
4			59
5			55
6			65
7		–	9[b]
8			55
9			63

[a] *Conditions:* 1-(4-fluorophenyl)prop-2-en-1-ol (3 mmol), phenol (3.3 mmol), K_2CO_3 (3.3 mmol), **2** (5 mol%), DPEphos (5 mol%), DMSO (3 mL), 115 °C, 24 h.
[b] Conversion determined by ^{1}H NMR.

Other nucleophiles known to participate in S_NAr reactions were examined. However, replication of the results of aromatic substitution with 4-fluoroacetophenone achieved with heterocycles[15] was unsuccessful at 115 °C. However, the use of phenols was successful with a catalyst loading of 5 mol% (Scheme 9).

A range of phenols was then screened with the higher catalyst loading. Except for 4-(trifluoromethyl)phenol (Table 7, entry 7), the yields were consistent (55–65%). In this case only 9% conversion of the aromatic substitution was observed. The same result was obtained with aromatic substitution with 4-fluoroacetophenone, indicating that this phenol is not a good nucleophile, presumably due to the electron-withdrawing trifluoromethyl group. The introduction of methyl groups in the *meta*, *para* or even the *ortho* position had little effect on the amount of substitution (Table 7, entries 2-4). Whilst the inclusion of other substituents (Table 7, entries 5 and 6) also had little effect. Both 1- and 2-substituted naphthols (Table 7, entries 8 and 9) were also well tolerated.

Having applied nucleophilic aromatic substitution to a tandem hydrogen transfer system, it was hoped that it would also work under borrowing hydrogen[16] conditions (Scheme 10). However, whilst the reaction did work in both cases, it still requires a significant amount of further work in order to achieve good conversions into product. We believe that reduction of the intermediate substituted ketones is disfavoured due to their stability arising from the electron-donating *para*-substituent.

Conclusions

In summary, this report describes the application of a ruthenium-catalyzed isomerization and tandem nucleophilic aromatic substitution. The reaction proceeds well with a variety of substrates and with both cyclic secondary amines and phenols. The effects of

substitution on both the alkene and aromatic ring were investigated.

Experimental Section

General Information

The ^{1}H and ^{13}C NMR were recorded on a Bruker Avance 300 MHz spectrometer. The chemical shifts (δ) are reported in ppm and the coupling constants (*J*) in Hz. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltronics micrOTOF (ESI-TOF). Column chromatography was performed on 60 Å silica gel and TLC was performed using polythene-backed plates pre-coated with Macherey–Nagel Sil G/UV_{254nm} neutral silica gel.

All reactions were carried out under nitrogen in dried glassware. All chemicals were used as received unless otherwise stated and the solvents were all purchased as anhydrous and used as such.

General Procedure I: Synthesis of Allyl Alcohol Starting Materials

Under a nitrogen atmosphere 4-fluoro aldehyde (30 mmol) was added to THF (100 mL). This was then cooled with an ice bath before the corresponding Grignard reagent (33 mmol, 1.1 equiv.) was added dropwise. Once the addition was complete, the reaction was left for 2 h before quenching with NH_4Cl (saturated solution, 50 mL) and H_2O (50 mL). The organic layer was then separated and the aqueous layer extracted with EtOAc (2×100 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated under vacuum before purifying by silica column chromatography (eluent: petroleum ether bp 40–60 °C/diethyl ether).

General Procedure II: Tandem Isomerization/Substitution of 4-Fluorophenylalkenyl Alcohols with Amines

$Ru(PPh_3)_3(CO)(H)_2$ (**2**) (110 mg, 4 mol%) and DPEphos (65 mg, 4 mol%) were added to an oven-dried, nitrogen-purged ampule. The alcohol (3 mmol) in anhydrous DMSO (3 mL) was then added followed by the amine (6.6 mmol, 2.2 equiv.) before the vessel was sealed with a Young's tap. The reaction mixture was then agitated and heated to 115 °C for 24 h. After 24 h, the mixture was allowed to cool to room temperature before transferring it to a separating funnel and washing with DMSO. H_2O (20 mL) and brine (5 mL) were added before the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were then concentrated under vacuum before purifying by silica column chromatography (eluent: hexane/EtOAc).

General Procedure III: Tandem Isomerization/Substitution of 4-Fluorophenylalkenyl Alcohols with Phenols

Phenol (3.3 mmol, 1.1 equiv.), $Ru(PPh_3)_3(CO)(H)_2$ (**2**) (138 mg, 5 mol%), DPEphos (81 mg, 5 mol%) and K_2CO_3 (3.3 mmol, 1.1 equiv.) were added to an oven-dried, nitrogen-purged ampule. The alcohol (3 mmol) in anhydrous DMSO (3 mL) was then added before the vessel was sealed with a Young's tap. The reaction mixture was then agitated and heated to 115 °C for 24 h. After 24 h, the mixture was allowed to cool to room temperature before transferring it to a separating funnel and washing with DMSO. H_2O (20 mL) and brine (5 mL) were added before the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were then concentrated under vacuum before purifying by silica column chromatography (eluent: hexane/EtOAc).

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