Pergamon

Tetrahedron Letters 42 (2001) 4275–4278

TETRAHEDRON LETTERS

A general method to fluorous ponytail-substituted aromatics

Weiping Chen, Lijin Xu and Jianliang Xiao*

Leverhulme Centre for Innovative Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK

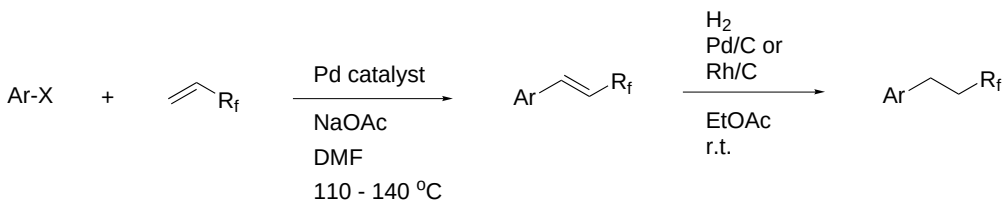
Received 19 March 2001; revised 19 April 2001; accepted 27 April 2001

Abstract—Palladium-catalyzed olefination of aryl halides led to a variety of fluorous ponytail-substituted, functionalized aryl compounds with good to excellent yields. The same chemistry was also applied to the synthesis of binaphthols bearing fluorinated ponytails. © 2001 Elsevier Science Ltd. All rights reserved.

Aryl compounds bearing long fluoroalkyl chains have been used in a number of instances as building blocks for the construction of soluble ligands applicable to catalysis in supercritical CO_2 ($scCO_2$) and fluorous phases.[1–6] However, only a few approaches have been developed for the preparation of fluoroalkylated aromatics.[7–15] The most frequently used method is based on the copper-mediated cross coupling of a perfluoroalkyl iodide with an aryl halide to give a perfluoroalkylated aromatic species.[7,9,10,13] This method does not allow one to introduce an ethylene spacer between the aromatic ring and the perfluoroalkyl unit, and this spacer is often necessary to reduce the strong electron-withdrawing effect of the latter. Spacer groups can be introduced by the copper-catalyzed coupling of arylmetal reagents, such as arylmagnesium bromides, with 1*H*,1*H*,2*H*,2*H*-perfluoroalkyl iodides, which leads to aromatics having ethylene-spaced perfluoroalkyls.[8,11] In this case, however, the purification procedure is tedious because of the formation of fluorous by-products, such as the homo-coupling product of 1*H*,1*H*,2*H*,2*H*-perfluoroalkyl iodides, which is difficult to remove. In addition, functional groups, such as CN, C=O, CO_2R, NH_2 and OH, which are sensitive to organometallic reagents, are not tolerated.

We recently developed two simple, efficient routes to fluoroalkylated arylphosphines.[16,17] The key step of one method is the copper-mediated coupling of bromoarylphosphine oxides with perfluoroalkyl iodides. The other method involves the Heck reaction of the same oxides with 1*H*,1*H*,2*H*-perfluoro-1-alkenes. With these two methods, arylphosphines with fluorous ponytails with or without ethylene spacers can easily and economically be accessed. In continuing our study in this area, we present herein a simple, general method for the synthesis of various aromatics bearing ethylene-spaced perfluoroalkyl chains. The method simply involves the Heck coupling of aryl halides with commercially available fluoroalkyl-substituted ethylenes followed by the reduction of the resultant double bonds (Scheme 1). While the preparation of β-trifluoromethylstyrene via the palladium-catalyzed arylation of trifluoropropene was reported two decades ago, we are not aware of any reports that have extended the chemistry to terminal olefins with long fluoroalkyl chains.[18,19]

The olefination of aryl halides proceeded smoothly to give the expected *trans* product. In a typical reaction, an aryl halide was mixed with 1.1 equiv. of a



Scheme 1.

Keywords: fluorinated aromatics; Heck reaction; fluorous ponytails; palladium catalysts.

* Corresponding author. Tel.: 44-(0)151-7942937; fax: 44-(0)151-7943589; e-mail: j.xiao@liv.ac.uk

PII: S0040-4039(01)00714-6

fluoroolefin, ca. 1.3 equiv. of NaOAc, and 0.5–1 mol% of the Herrmann–Beller palladacycle catalyst in DMF and, after heating for a certain time, the *trans* olefin was obtained in more than 90% isolated yields in most cases without optimization (Table 1).[20,21] As with normal Heck reactions, a variety of functionalities are tolerated, making further functionalization of the products feasible. The coupling reaction works equally well with both long and short fluoroolefins and so aromatics with fluorous ponytails of different sizes can easily be obtained. Thus, the olefination of 4-bromobezaldehyde with 1*H*,1*H*,2*H*-perfluoro-1-hexene, 1*H*,1*H*,2*H*-perfluoro-1-octene, and 1*H*,1*H*,2*H*-perfluoro-1-decene all proceeded to give the corresponding *trans* olefins in over 90% yields (Table 1, entries 1–3). A longer reaction time was employed for 1*H*,1*H*,2*H*-perfluoro-1-hexene, considering its higher volatility. Aryl bromides and iodides can both be used as substrates. In the case of the latter, however, the presence of phospine ligands inhibits the coupling reactions, as is known for other Heck reactions involving iodides.[22] Thus, while the reaction of methyl 4-bromobenzoate with 1*H*,1*H*,2*H*-perfluoro-1-octene, when catalyzed by the Herrmann–Beller catalyst, afforded *trans* methyl 4-(1*H*,2*H*-perfluoro-1-octenyl)benzoate in 97% yield at 125°C in 10 h reaction time, the reaction with the corresponding iodide yielded the benzoate in less than 20% yield when performed at 100°C for 16 h (entries 5, 6). The coupling reaction involving the iodide is better performed under the Jeffery conditions, that is, in a polar solvent such as DMF in the presence of a quaternary ammonium salt as promoter without using a phosphine.[23] Under such conditions, high yields of the coupling product were obtained with methyl 4-iodobenzoate as well as 4-iodoacetanilide (entries 7, 8). With the deactivated 4-bromotoluene and 4-bromoanisole, higher temperatures and longer reaction time were necessary, as is true of Heck reactions involving other olefins (entries 11, 12).[22] Because of the difference in reactivity between aryl bromides and iodides, the Heck reaction of the three bromoiodobenzenes with 1*H*,1*H*,2*H*-perfluoro-1-octene each selectively gave the mono-substituted bromides in high yields (entries 13–15).

To use these ponytail-attached aromatics as building blocks for ligands, the C=C double bonds would normally need to be reduced. Hydrogenation of the double bonds by Pd/C did not proceed with the crude Heck reaction products, probably due to poisoning of the catalyst by the phosphine ligand in the mixture. Consistent with this, purification of the perfluoroalkenyl-substituted aromatics by flash chromatography allowed easy reduction of the C=C double bonds under standard Pd/C catalyzed hydrogenation conditions. However, reduction of the perfluoroalkenyl-substituted aryl bromides was accompanied with debromination under the hydrogenation conditions. Fortunately, on replacement of Pd/C with Rh/C, the olefinic double bonds of the bromides were selectively reduced to give 1*H*,1*H*,2*H*,2*H*-perfluoroalkyl-substituted aryl bromides. Similar observations were also made in Ref. 19

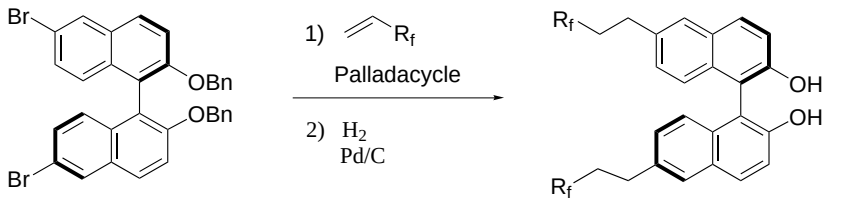
Using the protocol developed, 3- or 4-(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)bromobenzene, one of the key building blocks for $scCO_2$ and fluorous-soluble phosphines, can now be accessed more conveniently and in a far higher yield. Thus, following hydrogenation by Rh/C of the coupling product 4-(1*H*,2*H*-perfluorooctenyl)-bromobenzene, the saturated compound was obtained in 92% yield, corresponding to an overall isolated yield of 84%. With the previously reported Grignard route, starting with dibromobenzene, these compounds were produced in yields less than 50%, and isolation of the pure compound from the crude product, which contains a dimerized fluoroalkyl iodide, proved to be laborious.[11]

We also applied the same chemistry to the fluoroalkylation of a BINOL derivative. The reactivity of the benzyl protected 6,6′-dibromo-1,1′-bi-2-naphthol appears to be

Table 1. Preparation of fluoroponytail-attached aromatics by arylation of CH_2=CHR_f with ArX

Entry	Ar	X	R_f	Catal.[a]	Temp. (°C)/Time (h)	Yield (%)[b]
1	4-HOC-C_6H_4	Br	*n*-C_4F_9	A	125/12	93
2	4-HOC-C_6H_4	Br	*n*-C_6F_{13}	A	125/5	94
3	4-HOC-C_6H_4	Br	*n*-C_8F_{17}	A	125/8	94
4	4-Ac-C_6H_4	Br	*n*-C_6F_{13}	A	125/6	96
5	4-MeOCO-C_6H_4	Br	*n*-C_6F_{13}	A	125/10	97
6	4-MeOCO-C_6H_4	I	*n*-C_6F_{13}	A	100/16	<20
7	4-MeOCO-C_6H_4	I	*n*-C_6F_{13}	B	110/24	93
8	4-AcHN-C_6H_4	I	*n*-C_6F_{13}	B	120/24	95
9	4-NC-C_6H_4	Br	*n*-C_6F_{13}	A	125/10	93
10	4-F-C_6H_4	Br	*n*-C_6F_{13}	A	140/72	87
11	4-Me-C_6H_4	Br	*n*-C_6F_{13}	A	140/72	75[c]
12	4-MeO-C_6H_4	Br	*n*-C_6F_{13}	A	140/72	70[c]
13	2-Br-C_6H_4	I	*n*-C_6F_{13}	B	110/24	86
14	3-Br-C_6H_4	I	*n*-C_6F_{13}	B	110/24	82
15	4-Br-C_6H_4	I	*n*-C_6F_{13}	B	110/24	91

[a] Catalyst, A = Herrmann–Beller palladacycle catalyst; B = $Pd(OAc)_2$+*n*-Bu_4NBr (20 mol%).
[b] Isolated yield.
[c] Determined by ^1H NMR.



$R_f = C_6F_{13}$, 86% overall yield.
$R_f = C_8F_{17}$, 82% overall yield.

Scheme 2.

similar to activated aryl bromides, such as 4-acetylphenyl bromide and 4-bromobenzaldehyde. Thus, the coupling of the benzyl protected (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol with 1*H*,1*H*,2*H*-perfluoro-1-octene was complete in 24 h reaction time at 125°C to give the expected *trans* substituted product in 95% isolated yield.[20] Following hydrogenation by Pd/C to reduce the double bonds and debenzylate at the same time, the fluoroalkylated (*R*)-1,1′-bi-2-naphthol was obtained in 86% overall yield (Scheme 2).[21] The coupling with 1*H*,1*H*,2*H*-perfluoro-1-decene worked equally well, affording the substituted binaphthol in 82% overall yield. Binaphthols are extensively used as ligands or building blocks for ligands in asymmetric catalysis. Our methodology offers an easy and versatile route for adapting such ligands for catalysis in $scCO_2$ or perfluorocarbons. A multi-fluoroalkylated BINOL has recently been prepared via the organolithium mediated reaction of a 6,6′-dibromo-1,1′-bi-2-naphthol derivative with a fluoroalkylated bromosilane.[15]

In conclusion, the results presented here demonstrate that fluorous ponytail-substituted aromatics are readily accessible by the Heck reaction. The approach overcomes problems encountered with currently used methods, allows easy access to fluorous and $scCO_2$-soluble ligands, and should encourage the wider use of these novel solvents in catalysis.

Acknowledgements

We are grateful to the EPSRC, the Leverhulme Centre for Innovative Catalysis and its Industrial Partners (Synetix, Johnson Matthey, Catalytica, Air Products, and Syntroleum) for financial support.

References

1. Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475.
2. Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641.
3. Barthel-Rosa, L. P.; Gladysz, J. A. *Cood. Chem. Rev.* **1999**, *192*, 587.
4. Hope, E. G.; Stuart, A. M. *J. Fluor. Chem.* **1999**, *100*, 75.
5. Fish, R. H. *Chem. Eur. J.* **1999**, *5*, 1677.
6. De Wolf, E.; Van Koten, G.; Deelman, B. J. *Chem. Soc. Rev.* **1999**, *28*, 37.
7. Bhattacharyya, P.; Gudmunsen, D.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Stuart, A. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3609.
8. Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1628.
9. Betzemeier, B.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2623.
10. Pozzi, G.; Montanari, F.; Quici, S. *Chem. Commun.* **1997**, 69.
11. Kainz, S.; Luo, Z.; Curran, D. P.; Leitner, W. *Synthesis* **1998**, 1425.
12. Sinou, D.; Pozzi, G.; Hope, E. G.; Stuart, A. M. *Tetrahedron Lett.* **1999**, *40*, 849.
13. Mathivet, T.; Monflier, E.; Castanet, Y.; Mortreux, A.; Couturier, J.-L. *Tetrahedron Lett.* **1999**, *40*, 3885.
14. Richter, B.; Deelman, B.-J.; Van Koten, G. *J. Mol. Catal.* **1999**, *145*, 317.
15. Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57.
16. Chen, W.; Xiao, J. *Tetrahedron Lett.* **2000**, *41*, 3697.
17. Chen, W.; Xu, L.; Xiao, J. *Org. Lett.* **2000**, *2*, 2675.
18. Fuchikami, T.; Yatabe, M.; Ojima, I. *Synthesis* **1981**, 365.
19. While this manuscript was in preparation, a paper appeared on the Heck reaction of perfluoroalkenes with arenediazonium salts: Darses, S.; Pucheault, M.; Genêt, J.-P. *Eur. J. Org. Chem.* **2001**, 1121.
20. A typical procedure is given for (*R*)-6,6′-bis(1*H*,2*H*-perfluoro-1-octenyl)-2,2′-dibenzyloxy-1,1′-binaphthyl: A solution of (*R*)-6,6′-dibromo-2,2′-dibenzyloxy-1,1′-binaphthyl (1.24 g, 2 mmol), 1*H*,1*H*,2*H*-perfluoro-1-octene (1.73 g, 5 mmol), Hermman's palladacycle catalyst (19 mg, 0.02 mmol) and NaOAc (410 mg, 5 mmol) in DMF (10 ml) was stirred for 24 h at 125°C. After cooling to ambient temperature, the solvent was removed under reduced pressure, and the residue was partitioned between EtOAc (50 ml) and water (50 ml). The organic layer was separated, washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane:EtOAc = 8:1) to give the title compound as pale-yellow oil (2.19 g, 95%). ^{1}H NMR ($CDCl_3$): δ 7.96 (2H, d, J = 9.06 Hz), 7.92 (2H, s), 7.45 (2H, d, J = 9.06), 7.36 (2H, dd, J = 8.80 and 1.64 Hz), 6.96 ~ 7.18 (14H, m), 6.19 (2H, dt, $J_{H\text{-}H}$ = 16.20 and $J_{F\text{-}H}$ = 12.10 Hz), 5.09 (4H, s). Anal. calcd for $C_{50}H_{28}F_{26}O_2$: C, 52.02; H, 2.44. Found: C, 52.41; 2.18; $[\alpha]_D^{10}$ −60.76 (*c* 1.5, $CHCl_3$).

21. A typical procedure for reduction is given for (*R*)-6,6′-bis(1*H*,1*H*,2*H*,2*H*-perfluoro-1-octyl)-2,2′-dihydroxy-1,1′-binaphthyl: A mixture of (*R*)-6,6′-bis(1*H*,2*H*-perfluoro-1-octenyl)-2,2′-dibenzyloxy-1,1′-binaphthyl (1.73 g, 1.5 mmol), 10% Pd/C (400 mg) and EtOAc (10 ml) was stirred overnight at room temperature under 30 bar of hydrogen. After carefully releasing the hydrogen, the mixture was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, hexane:EtOAc = 2:1) to give the title compound as pale-yellow oil, which crystallized on standing (1.34 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.94 (2H, d, J = 8.80 Hz), 7.73 (2H, s), 7.39 (2H, d, J = 8.80 Hz), 7.17 (2H, dd, J = 8.52 and 1.92 Hz), 7.10 (2H, d, J = 8.52 Hz), 5.01 (2H, s), 3.04 (4H, m), 2.43 (4H, m). Anal. calcd for $C_{36}H_{20}F_{26}O_2$: C, 44.19; H, 2.06. Found: C, 44.58; 1.85; $[\alpha]_D^{10}$ −33.33 (*c* 1.1, $CHCl_3$).
22. Tsuji, J. *Palladium Reagents and Catalysts—Innovations in Organic Synthesis*; Wiley: Chichester, 1995.
23. Jeffery, T. *Tetrahedron Lett*. **1985**, *26*, 2667.