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Trifluoroacetic Acid-Mediated Hydroarylation: Synthesis of Dihydrocoumarins and Dihydroquinolones

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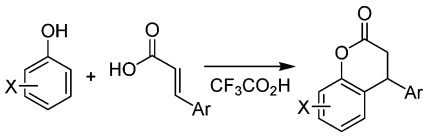
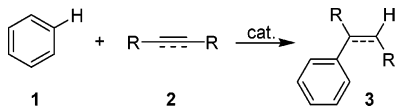


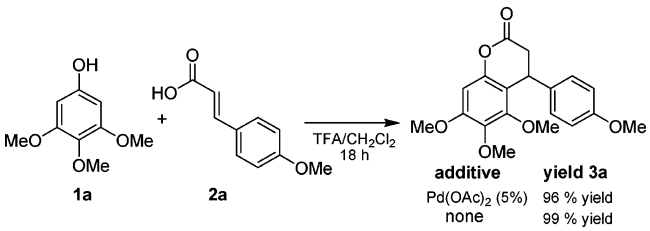
Trifluoroacetic acid mediates the hydroarylation of alkenes to afford dihydrocoumarins and dihydroquinolones in good yield. Intermolecular hydroarylation of cinnamic acids by phenols is particularly facile, which leads to the conclusion that previous reports of palladium-catalyzed hydroarylation of cinnamic acids in trifluoroacetic acid are erroneous.

Development of catalysts for the hydroarylation of alkynes and olefins by the addition of a C−H bond across a π-bond has received significant recent attention.[1,2] These reactions are particularly interesting from the standpoint of green chemistry because hydroarylation exhibits perfect atom economy and relies on the use of simple arene reactants (Scheme 1).[3] Furthermore, the ability to synthesize coumarins[4] and chromenes[5] through hydroarylation of alkynes establishes the synthetic utility of these C−H bond functionalization reactions.

SCHEME 1



SCHEME 2



In comparison to the hydroarylation of alkynes, the catalytic addition of arenes to alkenes has received much less attention. Thus, we were intrigued by reports that $Pd(OAc)_2$ in trifluoroacetic acid (TFA) effected the room temperature hydroarylation of alkenes.[1,4] With the goal of investigating possible mechanistic differences between alkyne and olefin hydroarylation, we began examining the intra- and intermolecular hydroarylation of alkenes. In the course of these studies we discovered that, in contrast to literature reports, the hydroarylation of cinnamic acids in trifluoroacetic acid is not palladium catalyzed.

We began our study by repeating the reported procedure for the hydroarylation of *p*-methoxycinnamic acid **2a** with 3,4,5-trimethoxyphenol **1a** in the presence of 1 mol % of $Pd(OAc)_2$ in 4:1 TFA:CH_2Cl_2 (Scheme 2).[1a,4a] Consistent with the literature report, a 96% yield of the dihydrocoumarin derivative **3a** was isolated. To determine the background rate of uncatalyzed hydroarylation, we repeated this experiment in the absence of $Pd(OAc)_2$. Much to our surprise, a 99% yield of **3a** was isolated after 16 h at ambient temperature. To confirm that there was no difference in the qualitative rates of product formation with or without $Pd(OAc)_2$, the two reactions were monitored by ^{1}H NMR spectroscopy.[6] Indeed product **3a** was observed in 30% and 29% conversion after a 3.5 h reaction period in CF_3CO_2D with and without 5 mol % of $Pd(OAc)_2$, respectively. Thus, hydroarylation of cinnamic acids is not palladium catalyzed in this case or any other we have investigated.[7]

Having failed to validate the catalytic role of palladium, we turned our attention to the investigation of TFA-mediated hydroarylation. We began by comparing intermolecular and intramolecular procedures for hydroarylation of cinnamic acids with phenols. Coupling the acid (**1a**) and phenol (**2a**) to form an ester (**4a**) prior to

(1) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992−1995. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252−7263. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633−639.

(2) (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859−8868. (b) Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752−3755. (c) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc*. **2003**, *125*, 4518−4526. (d) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc*. **2002**, *124*, 1586−1587. (e) Song, C. E.; Jung, D.-u.; Choung, S. Y.; Roh, E. J.; Lee, S.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 6183−6185. (f) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem*. **2003**, *18*, 3485−3496. (g) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414−7415. (h) Shi, Z.; He, C. *J. Org. Chem*. **2004**, *69*, 3669−3671.

(3) Aresta, M.; Armor, J. N.; Barteau, M. A.; Beckman, E. J.; Bell, A. T.; Bercaw, J. E.; Creutz, C.; Dinjus, E.; Dixon, D. A.; Domen, K.; Dubois, D. L.; Eckert, J.; Fujita, E.; Gibson, D. H.; Goddard, W. A.; Goodman, D. W.; Keller, J.; Kubas, G. J.; Kung, H. H.; Lyons, J. E.; Manzer, L. E.; Marks, T. J.; Morokuma, K.; Nicholas, K. M.; Periana, R.; Que, L.; Rostrup-Nielson, J.; Sachtler, W. M. H.; Schmidt, L. D.; Sen, A.; Somorjai, G. A.; Stair, P. C.; Stults, B. R.; Tumas, W. *Chem. Rev.* **2001**, *101*, 953−996.

(4) (a) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516−7522. (b) Kitamura, T.; Yamamoto, K.; Kotani, M.; Oyamada, J.; Jia, C.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1889−1895.

(5) (a) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053−4055. (b) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856−11857.

(6) The palladium-free reaction was conducted in a brand new NMR tube and care was taken to avoid any exposure to palladium.

(7) We routinely treat slowly reacting substrates with $Pd(OAc)_2$ and have yet to observe any rate acceleration. Specific examples include **3b**, **3c**, **3d**, **6a**, **6c**, and **6i**.

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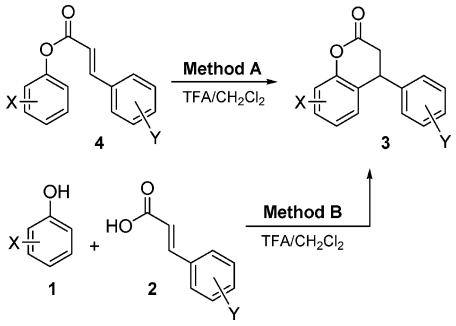
SCHEME 3

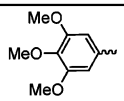
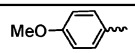
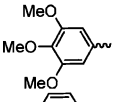
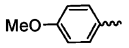
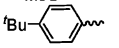
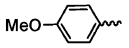
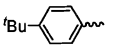
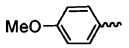
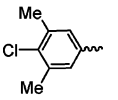
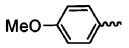
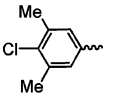
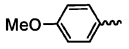
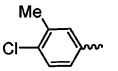
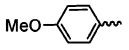
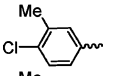
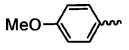
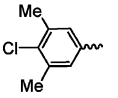
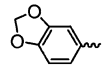
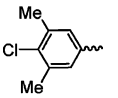
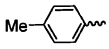
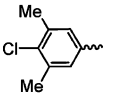
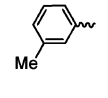
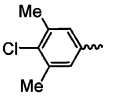
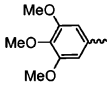
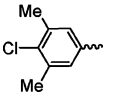


hydroarylation was not beneficial; however, product **3a** was obtained in high yield after 18 h at room temperature (Method A, Scheme 3). The ^{1}H NMR spectrum of this reaction mixture after 3.5 h shows somewhat lower conversion (22%) to **3a** as compared to the intermolecular reaction (30%, Method B). In addition to product **3a**, new resonances corresponding to **1a** (6%) and **2a** were apparent, indicating that the aryl ester (**4a**) had been partially hydrolyzed under the reaction conditions. Hydroarylation of other substrates confirmed that intermolecular hydroarylation is more facile than the analogous intramolecular hydroarylation. For example, intramolecular hydroarylation (Method A) with substrate **4b** (X = *p*-CMe$_3$, Y = *p*-OMe) proceeded sluggishly to provide a 54% yield of hydrocoumarin **3b** after 2 days (Scheme 3). In contrast, the intermolecular hydroarylation (Method B) of *p*-methoxycinnamic acid **2a** with phenol **1b** provides **3b** in 95% yield after 18 h.

A survey of a small subset of phenol reaction partners shows that there is no obvious electronic requirement for facile hydroarylation (Table 1). In contrast, cinnamic acids that are less electron rich than *p*-methoxycinnamic acid required elevated reaction temperatures to achieve reasonable reaction rates. Furthermore, the potential for regioselective hydroarylation was demonstrated by using unsymmetrical 3-methyl-4-chlorophenol, which underwent cyclohydroarylation to afford the product of addition by the least substituted ortho-carbon (Scheme 4). Interestingly, the regioselectivity is identical in the intramolecular cyclization of the aryl cinnamate **4d**.

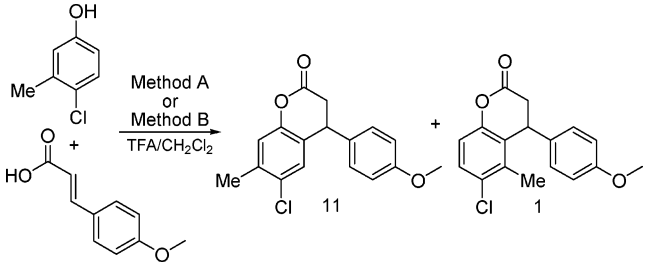
The trifluoroacetic acid-catalyzed hydroarylation reaction is not limited to the synthesis of dihydrocoumarins; the analogous dihydroquinolones are readily prepared in good yield by coupling anilines with cinnamic acids prior to hydroarylation. For example, cinnamanilide **5a** reacts smoothly in TFA to provide dihydroquinolone **6a** in 82% yield after 23 h at ambient temperature (Scheme 5). In contrast to the activity of phenols for the intermolecular hydroarylation of alkenes, unprotected anilines do not hydroarylate alkenes under our conditions. This is expected based on the favorable protonation of anilines by trifluoroacetic acid, which will greatly decrease the nucleophilicity of the arene. The electronics of the cinnamic acid derivative are important in predicting the conditions required for intramolecular hydroarylation. While the electron-rich *p*-OMe ($\sigma_p = -0.268$) substrate provides dihydroquinolone **6a** in good yield (82%) after 23 h at room temperature, the electron-deficient *m*-OMe ($\sigma_m = +0.115$) substituted **5c** fails to react even at 50 °C. The deactivating effect of the meta withdrawing substituent can be overcome by incorporation of a sufficiently electron donating para substituent (entry **6e**). Furthermore, the electron-deficient *p*-chlorocinnamanilide ($\sigma_p = +0.232$) substrate **5i** undergoes the cycloisomerization only at elevated temperature (100 °C) and requires extended reaction times (5 d). However, the same reaction

TABLE 1. Hydroarylation of Cinnamic Acids HO$_2$CCH=CHAr$_2$ with Phenols HOAr$_1$

Product	Ar$_1$	Ar$_2$	Method[a]	Time (h)	Yield %[b]
3a			A	18	99
3a			B	23	99
3b			B	18	95
3b			A	48	54
3c			A	16	93
3c			B	16	95
3d			A	72	43[c]
3d			B	16	72[c]
3e			B	23	99
3f			B	23[d]	99
3g			B	40[d]	90
3h			B	16[d]	99
3i			B	16[d]	99

[a] A = intramolecular, B = intermolecular. [b] Isolated yields. [c] 11:1 mixture of regioisomers. [d] Reaction was run at 100 °C.

SCHEME 4



SCHEME 5

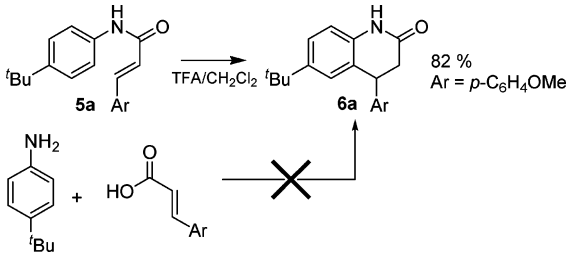
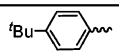
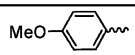
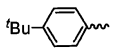
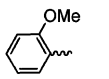
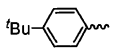
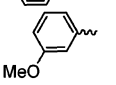
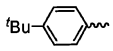
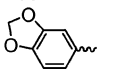
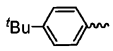
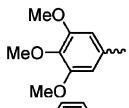
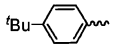
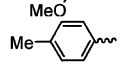
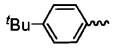
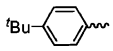
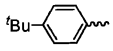
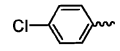
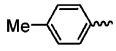
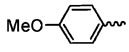
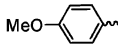
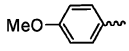
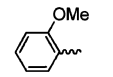
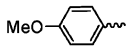
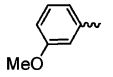
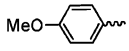


TABLE 2. Hydroarylation of Aryl Cinnamides $Ar_1NCOCH{=}CHAr_2$ (5)

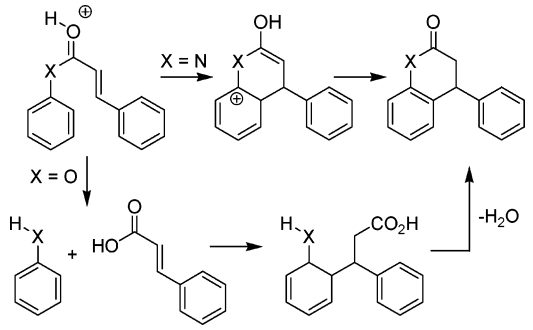
Product	Ar_1	Ar_2	Time	Temp. (°C)	Yield %[a]
6a			40 h	rt	84
6b			16 h	50	66
6c			40 h	50	NR
6d			40 h	rt	94
6e			72 h	50	87
6f			7 h	50	84
6g			40 h	100	92
6h			16 h	100	92
6i			5 d	100	70
6j			23 h	rt	91
6k			23 h	rt	90
6l			40 h	rt	99
6m			16 h	rt	40[b]

[a] Isolated yields. [b] 3.4:1 ratio of regioisomers.

can be performed conveniently in a microwave reactor at 180 °C, resulting in 50% conversion to product **6i** in 15 min.

The success of the intramolecular hydroarylation is not as dependent on the electronics of the aniline fragment, with the *p*-methoxyanilide and *m*-methoxyanilide both providing product within 24 h at room temperature. While the electronics of the aniline fragment are not crucial to the success of the hydroarylation, ultimately the most facile hydroarylation occurs when both aniline and cinnamic acid precursors contain electron-rich aromatic rings. In these cases, hydroarylation generally occurs within 24−40 h at 24 °C and provides high yields of dihydroquinolones. Prior to this work, the acid-catalyzed cyclization of aryl cinnamates was largely limited to catalysis by polyphosphoric acid (PPA), which

SCHEME 6



generally proceeds in moderate yield (22−90%; 51% average);[8] dihydrocoumarin byproducts have also been observed in Fries rearrangements of aryl 3-methylbut-2-enoates catalyzed by methane sulfonic acid.[9] Similarly, the thermal (120−190 °C) cyclizations of cinnamanilides have been reported in the presence of PPA.[10] The results of our investigation suggest that TFA may be a superior acid for the Friedel−Crafts cyclization since both dihydrocoumarins and dihydroquinolones are formed in good to excellent yield. Furthermore, TFA-catalyzed hydroarylation occurs, in most cases, at room temperature. These relatively mild reaction conditions preclude dearylation of the product dihydroquinolones which can occur under the conditions of PPA-catalyzed hydroarylation.[10]

The mechanism of catalysis likely involves protonation of the carbonyl, which activates the olefin toward nucleophilic attack (Scheme 6).[11] Thus, the more facile intermolecular hydroarylation of phenols, as compared to the intramolecular hydroarylation of aryl cinnamates, is simply a result of the higher nucleophilicity of phenols. Furthermore, the observation of ester cleavage under the conditions of "intramolecular" cyclization suggests that the reaction of aryl cinnamates may proceed intermolecularly as well. The fact that the intra- and intermolecular hydroarylation procedures afford product with identical regioselectivity supports this hypothesis.

In conclusion, we have developed a highly atom economical route to dihydrocoumarins and dihydroquinolones based on acid-mediated hydroarylation of alkenes. The simplicity of this approach makes it particularly attractive for use in combinatorial synthesis.

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Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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