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Acid-Catalyzed ortho-Alkylation of Anilines with Styrenes: An Improved Route to Chiral Anilines with Bulky **Substituents**

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ABSTRACT



Reaction of para-substituted anilines with styrene derivatives at elevated temperatures, when catalyzed by CF₃SO₃H, results in highly chemoselective ortho-alkylation of the aniline. When R = H, dialkylation can be achieved by varying the ratio of styrene to aniline. Several different substituted anilines and styrenes were examined, and good yields (42-87%) were obtained, except in the case where electronwithdrawing substituents are present on the styrene.

Advances in the field of homogeneous catalysis have led to the synthesis of well-defined transition metal complexes capable of catalyzing a wide range of organic transformations.¹ The commercial availability of chiral ligands such as bisoxazolines and binaphthyl derivatives provides a facile route to stereoselective catalysts.² Controlling the stereochemistry of polymerizations has also been the focus of a significant amount of research,³ as it leads to polymers with highly regular structures, often giving improved physical and mechanical properties. Many catalyst structures based on N–N and N–O chelating ligands derived from bulky anilines such as 2,6-diisopropylaniline have been shown to exhibit excellent catalytic behavior.⁴ However, examples of stereocontrol are generally limited to those with chain-end control mechanisms,⁵ while site-controlled stereoselectivity remains a challenging problem. We therefore hypothesized that anilines with ortho-substituents containing stereogenic centers could be universal chiral building blocks for the genesis of a wide array of stereoselective catalysts.

The Lewis acid catalyzed Friedel-Crafts alkylation of substituted aromatic rings is a highly versatile C-C bondforming method. Reactions are typically enhanced by electron-donating substituents, such as amine groups. However, alkylation of aniline is difficult, as the Lewis acid typically binds to the amine substituent, thereby deactivating the aromatic ring toward substitution.⁶ Initial efforts in our laboratory to synthesize anilines with bulky chiral substituents relied on the zeolite-catalyzed reaction of phenylacetylene and *p*-toluidine,⁷ followed by subsequent hydrogenation of the 2,6-bis(1-phenylvinyl)anilines catalyzed by

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Pd/C. This method provided a route to C_2 -symmetric chiral anilines with *sec*-phenethyl substituents, which were incorporated into an α -diimine Ni(II) catalyst (Figure 1) for the



Figure 1. Enantiomerically pure α -diimine Ni(II) catalyst with chiral aniline groups for isospecific alkene polymerization.

isospecific polymerization of *trans*-2-butene.⁸ However, the scope of anilines that could be synthesized with this method was limited, so we sought a general one-step method for the *ortho*-alkylation of anilines.

Several methods have been reported for the orthoalkylation of anilines with styrenes. Hart and Kosak found aniline could be ortho-alkylated to 2-(sec-phenethyl)aniline at 220 °C in 82% yield in the presence of aniline hydrochloride and an excess of styrene and aniline.⁹ Bergman and Arnold reported that $[PhNH_3][B(C_6F_5)_4]$ is a catalyst for the hydroamination and hydroarylation of several different types of alkenes with anilines.¹⁰ Several metal-mediated routes have been recently reported, using catalysts such as aluminum phenoxide,¹¹ [Rh(1,5-cyclooctadiene)]BF₄/4 PPh₃/ HBF4,12 and Ru3(CO)12.13 After screening a number of Brønsted acids and transition metal catalysts for the orthoalkylation of p-toluidine with styrene,¹⁴ we found that CF₃SO₃H,¹⁵ an inexpensive and readily available compound, was an excellent catalyst for the reaction, prompting our further study.

As shown in Table 1, the reaction of *p*-toluidine (1) with styrene in xylenes, in the presence of CF_3SO_3H catalyst (160 °C, 16 h), resulted in three different products: mono-*C*-alkylated (2), di-*C*-alkylated (3), and *N*-alkylated (4). The high reaction temperature minimized the formation of 4, possibly by its isomerization to 2. Solvent volume was kept to a minimum (1 g of *p*-toluidine per 1 mL of xylenes) to

Table 1. Alkylation of p-Toluidine with Styrene							
NH ₂ + (CF3SO3H 160 °C	NH2 			+ +		
		2	produ	ıct dist	ributior	n ^a (%)	
entry	[styrene]/[1]	[1]/[CF ₃ SO ₃ H]	1	2	3	4	
1	0.75	0.2	44	44	8	4	
2	1.0	0.2	0	81	18	1	
3	2.0	0.2	0	65	23	12	
4	5.0	0.2	0	0	88	12	
5	1.0	0.1	0	81	12	7	
6	1.0	0.5	0	75	20	5	
^a Det	termined by ¹ H	NMR spectroscopy					

deter polystyrene formation. The ratio of *p*-toluidine to styrene has a large impact on the amounts of 2 and 3 formed. Even with an excess of *p*-toluidine (1.3 equiv to styrene, entry 1), some dialkylation occurred, giving 8% of 3. In this entry alone, the reaction was incomplete, with residual *p*-toluidine observed by NMR spectroscopy. Increasing the ratio of styrene to p-toluidine to 1:1 results in a high proportion of 2 (81%, entry 2). Further increases in the amount of styrene resulted in an increase in dialkylation, giving high proportions of **3**: 88% when 5 equiv of styrene was used (entry 4). It should be noted that in all cases 3 was obtained as a \sim 55/45 mixture of the racemic/meso diastereomers. Changes in the amount of CF₃SO₃H catalyst had little effect on the product distribution, possibly increasing the formation of 4 with decreasing catalyst concentration (entry 5).

A number of commercially available aniline and styrene derivatives were studied in the synthesis of monoalkylated products (Table 2). An equimolar ratio of aniline and styrene

Table 2. Monoalkylation of Substituted Anilines with StyreneDerivatives a



entry	R	Ar	product	isolated yield $(\%)$
1^a	Н	Ph	2	53
2^b	н	$4 - MeC_6H_4$	5	63
3^a	Н	4-t-BuC ₆ H ₄	6	42
4^a	Н	2-naphthyl	7	45
5^b	Н	$2,4,6$ -Me $_3C_6H_2$	8	76
6^c	CH_3	4-t-BuC ₆ H ₄	9	43
7^b	CH_3	$2,4,6$ -Me $_3C_6H_2$	10	65
8^b	\mathbf{F}	$2,4,6$ -Me $_3C_6H_2$	11	65
9^a	Н	C_6F_5	12	0

^{*a*} Aniline/styrene/CF₃SO₃H = 1:1:0.2. ^{*b*} Aniline/styrene/CF₃SO₃H = 1.5: 1:0.2. ^{*c*} Aniline/styrene/CF₃SO₃H = 1:2:0.2. ^{*d*} Based on the limiting reagent.

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was used successfully in most cases. However, in the case of more expensive styrenes, the aniline was used in excess. Good yields were obtained in all cases, with the exception of pentafluorostyrene (entry 9).

When the ratio of styrene to *p*-toluidine was increased, dialkylation of *p*-toluidine occurred preferrentially (Table 3).

NH2 +	← CF ₃ SO ₃ H Ar 160 °C	Ar Ar	Ar + Ar	
entry	Ar	product	isolated yield (%) ^c	
1^a	Ph	3	77	
2^b	4- t -BuC ₆ H ₄	13	75	
3^b	2-naphthyl	14	87	
0	- •			

 Table 3. Dialkylation of p-Toluidine with Styrene Derivatives^a

^{*a*} Aniline/styrene/CF₃SO₃H = 1:10:0.2. ^{*b*} Aniline/styrene/CF₃SO₃H = 1:5:0.2. ^{*c*} Based on *p*-toluidine.

Four different styrenes were used, and high yields were obtained in all cases. Diastereomeric products were obtained in all cases, and rac- and meso-13-15 could be efficiently separated by flash chromatography. rac-3 and meso-3 eluted too closely to be separated by this method. However, rac-3 and meso-3 could be separated by successive recrystallization from EtOH, and the meso diastereomer was assigned by X-ray crystallography (Figure 2). (R,R)-3, (S,S)-3, and meso-3 could be separated by semipreparative HPLC equipped with a chiral column (RegisTech, (S,S) Whelk-01). A crystal structure of one enantiomer of rac-3 (later determined to be (R,R)-3) was also obtained (Figure 2). The absolute configuration of (S,S)-3 was assigned on the basis of the absolute structure (Flack) parameter of the X-ray crystal structure of a ligated Ni complex containing the aniline.^{8,16} Enantiomers of 3 and 5-11 and 13-15 were separated by semipreparative chiral HPLC, and only rac-15 exhibited incomplete resolution with this method.

In summary, we report the CF₃SO₃H-catalyzed alkylation of substituted anilines with styrene derivatives. Combined with chiral chromatography separation techniques, this method provides a facile route to anilines with chiral *ortho*substituents. Use of these anilines in stereoselective homogeneous catalysts in our group has already proven promis-



Figure 2. Molecular structures of *meso-***3** and (*R*,*R*)-**3** with thermal ellipsoids at the 40% probability level.

ing,^{8,17} and we will continue to explore the use of these new chiral ligand components.

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Supporting Information Available: Compound synthesis, characterization, and X-ray crystal structures of (R,R)-3 and *meso*-3. This material is available free of charge via the Internet at http://pubs.acs.org.

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