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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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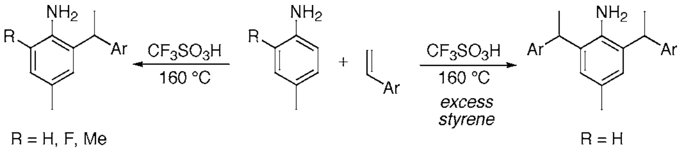
ABSTRACT



Reaction of *para*-substituted anilines with styrene derivatives at elevated temperatures, when catalyzed by CF_3SO_3H, 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 electron-withdrawing 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 bond-forming 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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(1) (a) Herrmann, W. A.; Cornils, B. *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley-VCH: Weinheim, 2002. (b) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis: The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*, 2nd ed.; Wiley & Sons: New York, 1992.

(2) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693.

(3) Coates, G. W. *Chem. Rev.* **2000**, *100*, 1223−1252.

(4) Gibson, V. C.; Spitzmesser, S. K. *Chem. Rev.* **2003**, *103*, 283−315.

(5) (a) Pellechia, C.; Zambelli, A.; Oliva, L.; Pappalardo, D. *Macromolecules* **1996**, *29*, 6990−6993. (b) McClain, S. J.; Feldman, J.; McCord, E. F.; Gardner, K. H.; Teasley, M. F.; Coughlin, E. B.; Sweetman, K. J.; Johnson, L. K.; Brookhart, M. *Macromolecules* **1998**, *31*, 6705−6707. (c) Nozaki, K.; Hiyama, T. *J. Organomet. Chem.* **1999**, *576*, 248−253. (d) Small, B. L.; Brookhart, M. *Macromolecules* **1999**, *32*, 2120−2130.

(6) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; John Wiley & Sons: New York, 1992; p 536.

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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 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.

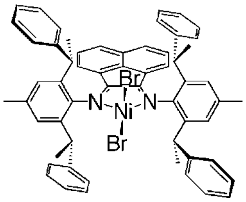
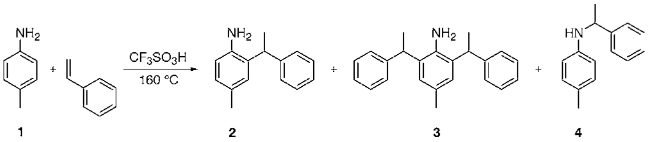


Figure 1. Enantiomerically pure α-diimine Ni(II) catalyst with chiral aniline groups for isospecific alkene polymerization.

Several methods have been reported for the *ortho*-alkylation 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] $[Rh(1,5\text{-cyclooctadiene})]BF_4/4\ PPh_3/HBF_4$,[12] and $Ru_3(CO)_{12}$.[13] After screening a number of Brønsted acids and transition metal catalysts for the *ortho*-alkylation of *p*-toluidine with styrene,[14] we found that CF_3SO_3H,[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 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 ∼55/45 mixture of the racemic/meso diastereomers. Changes in the amount of CF_3SO_3H catalyst had little effect on the product distribution, possibly increasing the formation of **4** with decreasing catalyst concentration (entry 5).

Table 1. Alkylation of *p*-Toluidine with Styrene

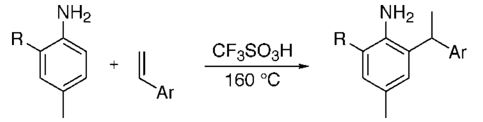


entry	[styrene]/[**1**]	[**1**]/[CF_3SO_3H]	product distribution[a] (%) **1**	**2**	**3**	**4**
1	0.75	0.2	44	44	8	4
2	1.0	0.2	0	81	18	1
3	2.0	0.2	0	65	23	12
4	5.0	0.2	0	0	88	12
5	1.0	0.1	0	81	12	7
6	1.0	0.5	0	75	20	5

[a] Determined by ^1H NMR spectroscopy.

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 Styrene Derivatives[a]



entry	R	Ar	product	isolated yield[d] (%)
1[a]	H	Ph	**2**	53
2[b]	H	4-MeC_6H_4	**5**	63
3[a]	H	4-*t*-BuC_6H_4	**6**	42
4[a]	H	2-naphthyl	**7**	45
5[b]	H	2,4,6-$Me_3C_6H_2$	**8**	76
6[c]	CH_3	4-*t*-BuC_6H_4	**9**	43
7[b]	CH_3	2,4,6-$Me_3C_6H_2$	**10**	65
8[b]	F	2,4,6-$Me_3C_6H_2$	**11**	65
9[a]	H	C_6F_5	**12**	0

[a] Aniline/styrene/CF_3SO_3H = 1:1:0.2. [b] Aniline/styrene/CF_3SO_3H = 1.5:1:0.2. [c] Aniline/styrene/CF_3SO_3H = 1:2:0.2. [d] Based on the limiting reagent.

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(7) Arienti, A.; Bigi, F.; Maggi, R.; Marzi, E.; Moggi, P.; Rastelli, M.; Sartori, R.; Tarantola, F. *Tetrahedron* **1997**, *53*, 3795−3804.

(8) Cherian, A. E.; Lobkovsky, E. B.; Coates, G. W. *Chem. Commun.* **2003**, *20*, 2566−2567.

(9) Hart, H.; Kosak, J. R. *J. Org. Chem.* **1962**, *27*, 116−121.

(10) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, ASAP.

(11) Olifirov, D. I.; Koschii, V. A.; Kozlikovskii, Y. B. *Zh. Org. Khim.* **1992**, *28*, 1206−1212.

(12) Beller, M.; Thiel, O. R.; Trauthwein, H. *Synlett.* **1999**, *2*, 243−245. This paper also reports the metal-free, HBF_4-catalyzed alkylation of an activated aniline (*p*-anisidine) with styrene.

(13) Uchimaru, Y. *Chem. Commun.* **1999**, 1133−1134.

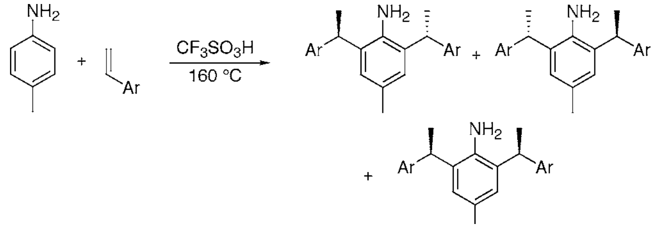
(14) Other attractive routes to 2-(1-arylethyl)anilines include thermal rearrangements of *N*-(1-arylethyl)anilines in the presence of Brønsted and Lewis acids,[9] and reduction of 2,1-benzothiazines. Harmata, M.; Kahraman, M. *Synthesis* **1994**, 142−144.

(15) For the alkylation of aniline with propylene using CF_3SO_3H, see: Burgoyne, W. F.; Dixon, D. D. *Appl. Catal.* **1990**, *63*, 117−127.

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).

Table 3. Dialkylation of *p*-Toluidine with Styrene Derivatives[a]



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
4[b]	2,4,6-(CH$_3$)$_3$C$_6$H$_2$	**15**	84

[a] Aniline/styrene/CF$_3$SO$_3$H = 1:10:0.2. [b] Aniline/styrene/CF$_3$SO$_3$H = 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 CF$_3$SO$_3$H-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 promising,[8,17] and we will continue to explore the use of these new chiral ligand components.

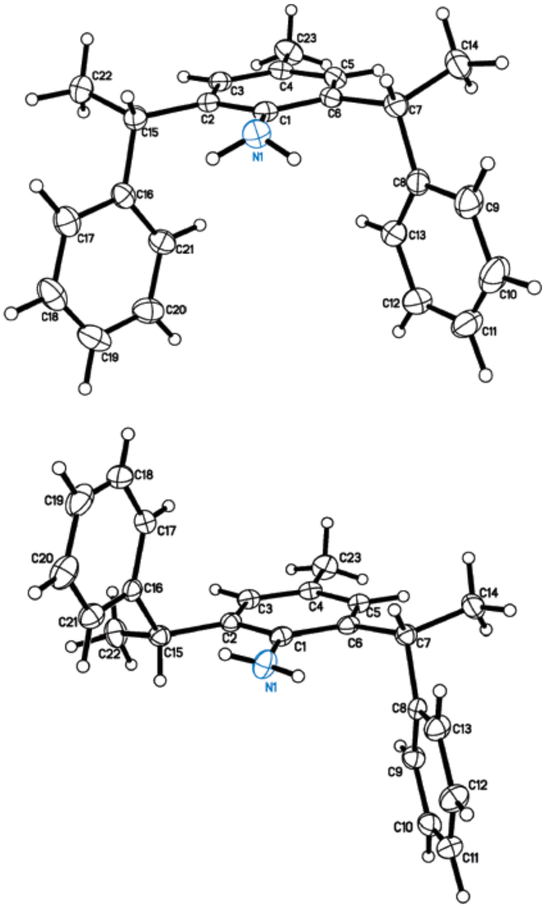


Figure 2. Molecular structures of *meso*-**3** and (*R*,*R*)-**3** with thermal ellipsoids at the 40% probability level.

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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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(16) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143−1148.

(17) Cherian, A. E., Rose, J. M., Lobkovsky, E. B., Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 13770−13771.