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Lanthanide-Promoted Ethylation of Schiff Bases by Triethylaluminum

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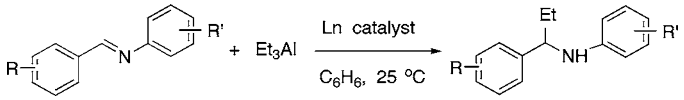
ABSTRACT



Schiff bases of aromatic aldehydes and anilines that fail to react with triethylaluminum are smoothly alkylated at room temperature in the presence of lanthanide catalysts. The alkylation takes place selectively at the vinylic carbon atom.

Recently, we reported[1] that the inefficient and nonselective palladium-catalyzed cross-ethylation of bromoarenes with Et$_3$Al can be transformed into an efficient and highly selective process upon addition of a stoichiometric amount of CeCl$_3$. We now report on another alkylation process in which lanthanide derivatives have an even more pronounced stimulating effect. Schiff bases of aromatic aldehydes and anilines proved to be completely refractory toward Et$_3$Al.[2] In the presence of *catalytic* quantities of europium, praseodymium, or ytterbium complexes, however, smooth and selective C-alkylation takes place at room temperature. When, for example, a solution of *N*-(phenylmethylene)aniline (C$_6$H$_5$CH═NC$_6$H$_5$, 33.5 mmol) and the NMR shift reagent, (*O*,*C*-6-11)-tris(2,2,6,6-tetramethyl-3,5-heptanedionato-*O*,*O′*)-europium [europium tris-(dipivaloylmethane, Eu(dpm)$_3$, 1.7 mmol], in 30 mL of dry benzene is treated for 24 h under an Ar atmosphere at 25 °C with Et$_3$Al (33.5 mmol), followed by quenching of the reaction mixture with MeOH and NaOH, 73% of C$_6$H$_5$CH(C$_2$H$_5$)NHC$_6$H$_5$ and 25% of unreacted starting material are isolated.[3] Under similar reaction conditions, C$_6$H$_5$CH═NC$_6$H$_4$-4-CH$_3$, 4-CH$_3$C$_6$H$_5$CH═NC$_6$H$_5$, 4-ClC$_6$H$_4$CH═NC$_6$H$_5$, 4-NCC$_6$H$_4$CH═NC$_6$H$_5$, and (2-C$_5$H$_4$N)CH═NC$_6$H$_5$ have been ethylated.[4] The results are summarized in Table 1.

All the Schiff bases listed in Table 1 proved to undergo alkylation exclusively at the vinylic carbon atoms, and no detectable amounts of side products were formed. Despite

Table 1. Lanthanide-Catalyzed Alkylation of Schiff Bases by Trialkylaluminum Reagents under Comparable Conditions[a]

$$\mathrm{ArCH{=}NAr^1 + R_3Al} \xrightarrow[\text{2) MeOH, NaOH}]{\text{1) Ln catalyst}} \mathrm{ArCH(R)NHAr^1}$$

entry	Schiff base	R	catalyst	yield, %[b]
1	C$_6$H$_5$CH═NC$_6$H$_5$[c]	CH$_3$	Eu(dpm)$_3$	53
2	C$_6$H$_5$CH═NC$_6$H$_5$	C$_2$H$_5$	Eu(dpm)$_3$	73
3	C$_6$H$_5$CH═NC$_6$H$_5$	C$_2$H$_5$	Eu(tfc)$_3$	55
4	C$_6$H$_5$CH═NC$_6$H$_5$	C$_2$H$_5$	Yb(OTf)$_3$	29
5	C$_6$H$_5$CH═NC$_6$H$_5$	C$_2$H$_5$	Pr(tfc)$_3$	11
6	C$_6$H$_5$CH═NC$_6$H$_4$-4-CH$_3$	C$_2$H$_5$	Eu(dpm)$_3$	33
7	4-CH$_3$C$_6$H$_4$CH═NC$_6$H$_5$	C$_2$H$_5$	Eu(dpm)$_3$	41
8	4-ClC$_6$H$_4$CH═NC$_6$H$_5$	C$_2$H$_5$	Eu(dpm)$_3$	82
9	4-NCC$_6$H$_4$CH═NC$_6$H$_5$	C$_2$H$_5$	Eu(dpm)$_3$	70
10	(2-C$_5$H$_4$N)CH═NC$_6$H$_5$	C$_2$H$_5$	Eu(dpm)$_3$	99

[a] Reaction conditions: 33.5 mmol of Schiff base, 33.5 mmol of R$_3$Al in 30 mL of hexane, 1.7 mmol of lanthanide catalyst, 30 mL of dry benzene; Ar atmosphere; 25 °C; 24 h. [b] Unreacted Schiff base makes up the remainder of the material. [c] Performed with 67.0 mmol of Me$_3$Al.

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(3) A detailed general procedure for the alkylation of the Schiff bases is given in Supporting Information.

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the fact that triethylaluminum disproportionates in the presence of various metals into ethylene and the highly reactive diethylaluminum hydride,[5] no reduction products of the amines (i.e., nonalkylated saturated amines) could be detected. The experiment listed as entry 1 indicates that the lanthanide-promoted alkylation is applicable also to Schiff base methylations. The application of a chiral catalyst [(+)-Eu(tfc)$_3$] in this experiment led to the formation of the optically active (*R*)-(+)-$C_6H_5CH(CH_3)NHC_6H_5$ of 82% optical purity.[6]

Both the nature of the lanthanide metal and the ligands on the catalysts were found to affect the reaction rate. Among the four catalysts studied, Eu(dpm)$_3$, (*O*,*C*-6-22)-tris[1,7,7-trimethyl-3-(trifluoroacetyl)bicyclo[2.2.1]heptan-2-onato-*O*,*O*′]europium [Eu(tfc)$_3$], (*O*,*C*-6-22)-tris-[1,7,7-trimethyl-3-(trifluoroacetyl)bicyclo[2.2.1]heptan-2-onato-*O*,*O*′]praseodymium [Pr(tfc)$_3$], and ytterbium(+3) trifluoromethanesulfonate [Yb(OTf)$_3$] (see entries 2−5), the Eu(dpm)$_3$ was found to be the most efficient. The alkylation proved to depend on the electronic nature of the unsaturated substrate. While electron-withdrawing groups (Cl, CN) seem to enhance the rate, the electron-donating methyl group located on either the benzylidene or the benzeneamine moiety causes the ethylation to slow as compared with the reaction rate of the unsubstituted *N*-(1-phenylmethylene)aniline. This dependence is opposite to that observed in the ethylation of Schiff bases by Et_2Zn and by Et_2Cd.[7] *N*-(2-Pyridylmethylene)aniline (entry 10) is the only Schiff base studied that, at room-temperature, undergoes slow alkylation in the absence of the lanthanide catalyst. However, under such conditions, a variety of undesired side products are formed. In the presence of Eu(dpm)$_3$, pure *N*-[(1-pyridin-2-yl)propyl]aniline is obtained in quantitative yield. It is notable that, under the conditions of Table 1, optimum results are obtained when a 1:1 molar ratio of the substrate and Et_3Al is employed. Additional reagent has no effect on the yield. The *methylation* of the Schiff bases requires, however, the presence of excess Me_3Al.[8] The rate dependence of the ethylation of *N*-(1-phenylmethylene)aniline by Eu(dpm)$_3$ on the nature of the solvent was shown to decrease in the order benzene > benzene−hexane > hexane > dichloromethane > dimethylformamide. No reaction takes place in THF, which strongly coordinates with the aluminum reagent.[9] The temperature effect on the process was studied between 2 and 78 °C and was found to give the best results at 22−28 °C.

The clean ethylation of 4-[(phenylimino)methyl]benzonitrile, $4\text{-}NCC_6H_4CH{=}NC_6H_5$ to give solely 4-(1-anilinopropyl)benzonitrile is rather surprising, because Eu(dpm)$_3$ also catalyzes the slow ethylation of aromatic nitriles to form ethylimines that are hydrolyzed during the workup to the corresponding ketones. For example, benzo- and 1-naphthonitrile are converted under the conditions of Table 1 within 24 h into 47 and 4% of 1-phenylpropanone and 1-(1-naphthyl)propanone, respectively.[10] The selective alkylation of $4\text{-}NCC_6H_4CH{=}NC_6H_5$ at the double bond may thus be rationalized by the significant difference between the rate of ethylation of the imine and the nitrile functions.

Two possible mechanisms for the lanthanide-assisted alkylation of Schiff bases by Et_3Al are considered. The fact that the catalytic activity of various lanthanide compounds is often assigned to their Lewis acidity,[11] and the observation that the addition of some metal alkyls to imines is promoted by acids[12] could suggest Lewis acid alkylation for our process. However, experiments to replace the lanthanide catalysts in the ethylation of $C_6H_5CH{=}NC_6H_5$ by Me_3SiCl, BF_3, $InCl_3$, or $ZnCl_2$ (which enhance the ethylation of the Schiff base by Et_2Zn[12]) gave negative results. Only a large molar excess of either the silicon or the zinc compound afforded traces of $C_6H_5CH(C_6H_5)NHC_6H_5$ at room temperature. Thus, we assume that it is more likely that our ethylation proceeds via the intermediacy of an alkyl lanthanide formed from Et_3Al by transmetalation. The ability of such lanthanide compounds to alkylate unsaturated substrates,[13] including carbon−nitrogen multiple bonds, has already been demonstrated.[11]

In summary, Et_3Al, which fails to alkylate aromatic Schiff bases, is activated by several lanthanide catalysts. The imines undergo selective C-alkylation, which is assumed to take place via an alkyllanthanide intermediate. The application of a chiral europium catalyst induces asymmetry during the alkylation process.

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(4) Known products $C_6H_5CH(CH_3)NHC_6H_5$,[14] $C_6H_5CH(C_2H_5)NHC_6H_5$,[15] $C_6H_5CH(C_2H_5)NHC_6H_r\text{-}4\text{-}CH_3$,[7,16] $4\text{-}CH_3\text{-}C_6H_4CH(C_2H_5)NHC_6H_5$,[7] and 4-Cl $C_6H_4CH(C_2H_5)NHC_6H_5$[7,17] were compared with authentic samples prepared according to the procedures reported in the literature. Physical data (bp/mp; ^1H and ^{13}C NMR; EI-mass spectra) and elemental analyses of all new compounds, as well as the relevant data for known compounds that are not documented in the literature, are presented in Supporting Information.

(5) See, Gelman, D.; Höhne, G.; Schumann, H.; Blum, J. *Synthesis* **2001**, 591 and references therein.

(6) Calculation of the optical purity is based on the value of $[\alpha]^{25}_D = 26.1°$ reported by: Ogata, Y.; Takeuch, K. *J. Org. Chem*. **1970**, *35*, 1642. For examples of the enantioselective addition of organoaluminums to aldehydes, see: (a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (b) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593. (c) Lu, J.-F.; You, J.-S.; Gau, H.-M. **2000**, *11*, 2531.

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(10) Ethylation of the nitrile was performed in the same manner as the alkylation of the Schiff bases (see Supporting Information) except that the quenching of the reaction mixture was carried out with 60 mL of 10% hydrochloric acid instead of with NaOH.

(11) For typical examples, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

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Supporting Information Available: Experimental procedures for the alkylation of the Schiff bases and the nitriles and characterization data (mp/bp, ^{1}H and ^{13}C NMR, mass spectra, and elemental analyses) are presented for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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