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Stereoselective Barbier-Type Allylation Reaction of Trifluoromethyl Aldimines

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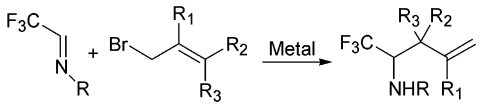
Abstract: Trifluoromethyl aldimines could react, under Barbier conditions in the presence of activated zinc, in DMF at room temperature or in THF at reflux, with various allyl bromides to provide the corresponding homoallylamines. Secondary homoallyl trifluoromethylamines were stereoselectively obtained from the optically active aldimine **12** with an excellent diastereoisomeric excess (98%).

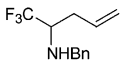
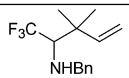
The allylation of imines, providing the corresponding homoallylamines, is an important synthetic transformation.[1] Important classes of compounds such as 1,3-amino acids, 1,3-amino alcohols, and 1-amino-3,4-epoxides[2] and even pyrrolidines and piperidines[3] are accessible by this approach.

Despite the possible interest in fluorinated analogues of these synthons,[4] the preparation of homoallyl trifluoromethylamines has not been intensively studied so far. One synthesis has been reported from the *N*-(*p*-toluenesulfonyl)trifluoromethyl aldimine by an ene reaction.[5] More recently, a Lewis acid-mediated addition of an allylsilane to aldimines or hemiaminals, derived from fluoral, has been described in racemic[6] and in chiral versions.[6,7] Concerning the organometallic approach, to our knowledge few examples were reported: reactions involve the addition of allylmagnesium on a trifluoromethyl sulfenimine generated by electrooxidation of CF_3-CH_2NR_2[8] and on *N*-acyl-1-chloro-2,2,2-trifluoro ethylamine,[9] and more recently, the addition of allyllithium, generated from tetraallyltin with phenyllithium, on trifluoromethylated hydrazones.[10] Nevertheless, it was previously reported that the *N*-(*R*)-phenethyltrifluoromethyl aldimine was unreactive toward the allyl bromoester in the Barbier-type conditions with zinc powder in THF.[11] These surprising results prompted us to explore more deeply this organometallic approach for the preparation of trifluoromethyl homoallylamines. First, we investigated the allylation reaction of the *N*-benzyltrifluoroacetaldimine **1** with the allyl bromides **2a**,**b** in the presence of two different metals, magnesium in ether, and indium in DMF[12] in the Barbier conditions. Results are summarized in Table 1.

TABLE 1. Allylation Reaction Coupling of Allyl Bromides with Imine 1 and Metal



1 **2** **3**

2	Metal	Time (h)	**3**	Yield (%)
 **2a**	Mg[a]	0.75	 **3a**	75
	In[b]	1		96
 **2b**	Mg[a]	1	 **3b**	20
	In[b]	24		Traces

[a] In ether at rt. [b] In DMF at rt.

With both magnesium and indium reagents generated from the allyl bromide **2a**, the homoallylamine **3a** was obtained in good yield. Under these conditions, the reductive homocoupling of the imine was not detected by ^{1}H NMR or ^{19}F NMR. With organometallic reagents generated from the allyl bromide **2b**, reactions were not efficient. None or very low conversion into the homoallylic amine **3b** was observed at room or at higher temperatures (50−80 °C).

We then revisited the allylation reaction involving zinc reagents with the following changes: turnings of zinc were used and they were activated in situ by TMSCl,[13] and the reaction was conducted in DMF which has been proved to be an excellent solvent in allylation reactions.[14] Zn-mediated allylation reaction was performed with the imine **1** and a range of allyl bromides (1.3 equiv) in the presence of 1.3 equiv of zinc. Results are reported in Table 2.

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(13) Zinc was activated in situ by TMSCl: Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796.

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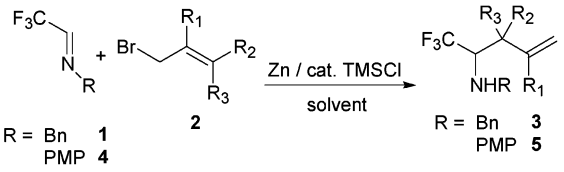
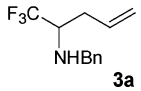
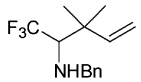
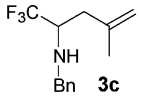
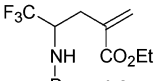
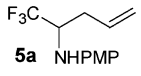
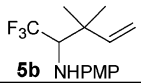
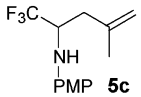
TABLE 2. Allylation Reaction with Zinc in DMF and THF

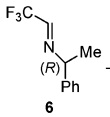
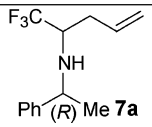
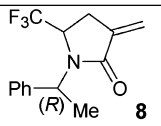


2	Time (h)	Solvent	3	Yield (%)
2a	0.75	DMF[a]	 **3a**	95
		THF[b]		85
2b	1	DMF[a]	 **3b**	97
		THF[b]		82
 **2c**	0.75	DMF[a]	 **3c**	75
 **2d**	0.75	DMF[a]	 **3d**	75
2a	0.75	DMF *a*	 **5a**	79
	4	THF[b]		92
2b	0.75	DMF[a]	 **5b**	82
2c	0.75	DMF[a]	 **5c**	83

[a] At room temperature. [b] At reflux.

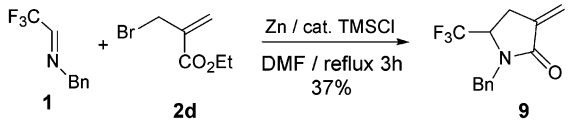
Under these new conditions, in all cases reactions were fast and clean, and yields were good to excellent (75−97%). Even hindered allyl bromides **2b**−**d** were reactive; the nonsymmetric allyl bromide **2b** reacted at the γ position (>98%). This result confirms the tendency of prenyl bromide to add to carbonyl compounds and imines at the most substituted allylic terminus[15] despite the steric hindrance of the CF_3 group.[16] The reaction was then extended to the *N*-*p*-methoxyphenyl aldimine **4**[17] with the same success. Homoallylic amines **5a**−**c** were isolated in good yields (79−83%). To define whether the success of the reaction was due to the activated metal or to the choice of solvent, reactions were also attempted in THF with aldimines **1** and **4** (Table 2). Reflux was required for the reaction to occur. Under these conditions, imine **1** could react with allyl bromides **2a**,**b** to afford the corresponding homoallylic amines **3a**,**b** in good yields (85%, 82% respectively), and similarly, imine **4** could react with allyl bromide **2a** to afford the homoallylamine **5a** in 92% yield.

TABLE 3. Zn-Mediated Barbier-Type Reaction with Allyl Bromides 2 and Imine 6

		T°C	(h)		(%)[b]
 **6**	**2a**	DMF, r.t.	0.5	 **7a**	87
		THF, reflux	1		78
	2d	THF, reflux	1	 **8**	60

[a] **2** (1.5 equiv) + Zn activated by TMSCl (1.5 equiv). [b] 20% of de determined by ^{19}F NMR of the crude product.

SCHEME 1



The allylation reaction was then investigated from chiral trifluoromethyl aldimines. First, the reaction was undertook with the (*R*)-*N*-phenethyl aldimine **6** and conducted as precedently with the allyl bromide **2a**, activated zinc in both THF and DMF solvents. The homoallylic amine **7a** was obtained in good yield, 78% in THF and 87% in DMF, respectively. The reaction was not diastereoselective (60/40). For comparison with the previously reported unsuccessful experiment,[11] the reaction was also performed with the allyl bromide **2d** in THF, and the butyrolactam **8** was obtained in 60% yield with a (60/40) ratio of diastereoisomers (Table 3).

It is worth noting that butyrolactams could also be obtained from CF_3-aldimines in DMF when reactions were conducted at reflux (Scheme 1).

We searched to induce a better diastereoselectivity using other chiral N-substituents. Oxazolidines **10** (62/38), which are prepared from fluoral and phenyl glycinol,[18] had been shown to provide a 70/30 mixture of diastereoisomers of chiral homoallylamine in $BF_3{\cdot}Et_2O$-promoted reaction with an allylsilane.[7] When placed under our Barbier conditions in THF at reflux and DMF at room temperature, with 1.5 equiv of zinc, oxazolidines **10** provided amines in very poor yield. Three to four equivalents of zinc were required to obtain the *N*-phenylglycinol allylamines **11** in 65% and 45% yields, respectively. Compared to reactions from **6**, the diastereoisomeric excess was improved in DMF (de = 61%) but very poor in THF (de = 9%) (Scheme 2). Analysis of ^1H and ^{19}F NMR data indicating that the minor isomer obtained in our experiments is the major isomer obtained from oxazolidine **10** under Lewis acid conditions, which was assumed to be (*R*,*R*).[7]

The change in ratio of diastereoisomers in starting material and products suggests the intermediate forma-

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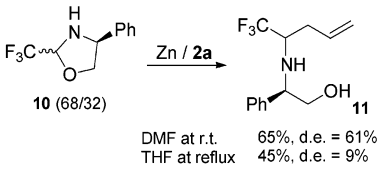
(18) Ishii, A.; Higashiyama, K.; Mikami, K. *Synlett* **1997**, 1381.

SCHEME 2

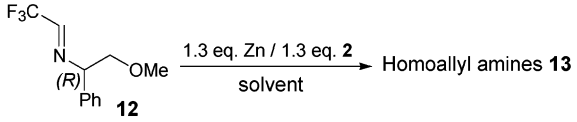


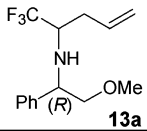
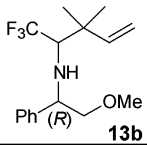
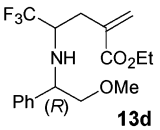
tion of an iminium ion, as already postulated in reactions using Lewis acids.[6,7] This is probably due to the excess of zinc used in these reactions, and the requirement indicates that oxazolidines are less reactive than aldimines toward allyl zinc reagents. This problem does not occur in nonfluorinated series since aldimines prepared from aldehydes and phenyl glycinol are not prone to cyclize. In this case, the organometallic agent reacts directly with the imines, and homoallylic amines are obtained with good stereoselectivities.[19] To prevent the formation of oxazolidines, we chose the methyl ether of the (*R*)-phenylglycinol[20] as chiral *N*-substituent.[21] The allylation reaction of the CF_3-aldimine **12** was performed in THF and DMF with allyl bromides **2a**,**b**,**d** (Table 4).

In all cases, the reactivity of **12** was excellent, and only 1.3 equiv of allyl bromide and zinc were required for a complete conversion. Yields of **13a**, **13b**, and **13d** were good to high, and diastereoselectivities were excellent in THF (>96%) and good in DMF (84%) for **13a**, excellent in THF (98%) for **13b**, and good in DMF (85%) for **13d**. Compared to the phenylethyl substituent, the presence of heteroatom on the N-substituent likely allows a good chelation with the metal and, hence, increases the diastereoselection. Unfortunately, great differences between NMR data of **13a**, **13b**, **13d**, and that of **11** did not allow a comparison of their configuration.

In conclusion, we have described a highly efficient and gentle method for the preparation of a new series of trifluoromethyl homoallylamines. Under Barbier-type conditions, aldimines derived from fluoral could react with allyl bromides, providing zinc was activated in situ with TMSCl. When the reaction was performed with optically active aldimines, the diastereoselectivity was dependent on the chiral N-substituent and on the solvent of reaction. Conditions were found to prepare chiral trifluoromethyl homoallylamines in good yields and in high purity (up to 98%).

TABLE 4. Allylation Reaction with the Aldimine 12



2	Solvent	Time (h)	13	yield (%)	d.e. (%)[a]
2a	THF	2	 13a	85	96
	DMF	0.5		68	84
2b	THF	0.75	 13b	65	98
2d	DMF	2	 13d	72	85

[a] Determined by ^{19}F NMR of the crude product.

Acknowledgment. We thank DSM Co. for the gift (*R*)-phenylglycine, Rhodia Co. for financial support, and Serge Ratton and Jean-Marc Paris (Rhodia) for fruitful discussions. Michèle Ourévitch is gratefully acknowledged for the fine structure determination by NMR experiments.

Supporting Information Available: Full characterization data for compounds **3a**−**d**, **5a**−**c**, **7a**, **8**, **9**, **11**, **12**, **13a**,**b**,**d**, and some experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034205C

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(21) Yanada, R.; Negoro, N.; Okaniwa, M.; Ibuka, T. *Tetrahedron* **1999**, 55, 13947.