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METHOX: A New Pyridine *N*-Oxide Organocatalyst for the Asymmetric Allylation of Aldehydes with Allyltrichlorosilanes†

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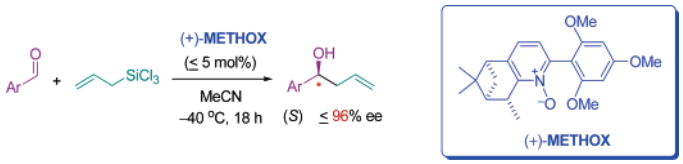
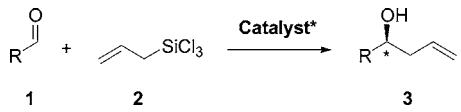
ABSTRACT



Allylation of aromatic aldehydes with allyltrichlorosilane is catalyzed by the new terpene-derived pyridine *N*-oxide (+)-METHOX (≤5 mol %) in MeCN with high enantioselectivities (≤96% ee) and conversion rates; this catalyst retains high selectivity even at room temperature.

Allyltrichlorosilane (**2**) and related reagents can be activated by chiral Lewis-basic catalysts[1] to effect asymmetric allylation of aromatic and heteroaromatic aldehydes **1** (Scheme 1).[1−7] Among the most successful catalysts reported to date[1−7] are Denmark's phosphoramides;[1] axially chiral bipyridine *N*,*N*-bisoxides, developed by Nakajima[2] and Hayashi;[3] and our pyridine-type *N*-monoxides PINDOX (**4**),[4] *iso*-PINDOX (**5**),[7] and QUINOX (**6**)[6] (Figure 1), which give ≤96% ee (Table 1, entries 1−6). For the reactions catalyzed by **4** and **5**, we proposed the silicon chelation between the oxygen of

Scheme 1



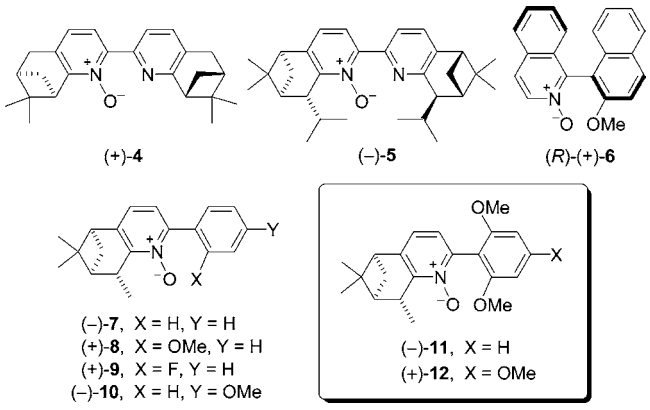


Figure 1.

† Dedicated to Dr. Jiří Závada on the occasion of his 70th birthday.

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(1) For leading reviews, see: (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

(2) Nakajima, N.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

(3) (a) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799. (b) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329.

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Table 1. Allylation of Aldehydes **1** with **2** Catalyzed by Chiral Lewis Bases (Scheme 1)[a]

entry	aldehyde	R	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c,d]
1	**1a**	Ph	(+)-**4** (10)	CH_2Cl_2	−60	24	78	90[f]
2	**1a**	Ph	(+)-**4** (10)	MeCN	−20	24	95	84[g]
3	**1a**	Ph	(−)-**5** (10)	CH_2Cl_2	−20	18	23[e]	93[g]
4	**1a**	Ph	(−)-**5** (10)	MeCN	−40	18	75	96[g]
5	**1a**	Ph	(+)-**6** (10)	CH_2Cl_2	−40	2	60	87[h,i]
6	**1a**	Ph	(+)-**6** (10)	MeCN	−40	12	60	70[h,i]
7	**1a**	Ph	(−)-**7** (10)	CH_2Cl_2	−60	18	66	41[j,k]
8	**1a**	Ph	(+)-**8** (10)	CH_2Cl_2	−60	18	55	68[j,k]
9	**1a**	Ph	(+)-**9** (10)	CH_2Cl_2	−60	18	15[e]	16[j,k]
10	**1a**	Ph	(−)-**10** (10)	CH_2Cl_2	−60	18	35[e]	58[j,k]
11	**1a**	Ph	(−)-**11** (10)	CH_2Cl_2	−60	18	44[e]	80[j]
12	**1a**	Ph	(−)-**11** (10)	MeCN	−40	18	46[e]	80[j]
13	**1a**	Ph	(−)-**11** (10)	$CHCl_3$	−60	18	52	82[j,l]
14	**1a**	Ph	(+)-**12** (10)	CH_2Cl_2	−40	18	74	96
15	**1a**	Ph	(+)-**12** (10)	CH_2Cl_2	−20	18	63	94
16	**1a**	Ph	(+)-**12** (10)	CH_2Cl_2	0	18	49	90
17	**1a**	Ph	(+)-**12** (10)	MeCN	−40	18	≥95	96
18	**1a**	Ph	(+)-**12** (5)	MeCN	−40	18	≥95	96
19	**1a**	Ph	(+)-**12** (1)	MeCN	−40	18	68	95
20	**1a**	Ph	(+)-**12** (10)	MeCN	−20	18	≥95	96
21	**1a**	Ph	(+)-**12** (5)	MeCN	−20	18	≥95	93
22	**1a**	Ph	(+)-**12** (2)	MeCN	−20	18	90	93
23	**1a**	Ph	(+)-**12** (10)	MeCN	0	18	≥95	91
24	**1a**	Ph	(+)-**12** (10)	MeCN	rt	18	≥95	87
25	**1a**	Ph	(+)-**12** (10)	$CHCl_3$	−40	18	73[m]	94
26	**1a**	Ph	(+)-**12** (10)	$CHCl_3$	−20	18	45[e]	94
27	**1a**	Ph	(+)-**12** (10)	$CHCl_3$	0	18	26[e]	89
28	**1b**	4-CF_3−C_6H_4	(+)-**12** (5)	MeCN	−40	18	86	93
29	**1c**	4-MeO−C_6H_4	(+)-**12** (5)	MeCN	−40	18	≥95	96
30	**1d**	2-MeO−C_6H_4	(+)-**12** (5)	MeCN	−40	18	≥95	89
31	**1e**	2,6-Me_2-C_6H_4	(+)-**12** (5)	MeCN	−40	18	0	

[a] Reaction was carried out at 0.4 mmol scale with 1.1 equiv of **2** in the presence of the catalyst (10 mol %, unless stated otherwise) and (*i*-Pr)$_2$NEt (1 equiv) as a base. [b] Isolated yield (product pure by ^{1}H NMR). [c] Determined by chiral HPLC or GC. [d] All products **3** were of (*S*)-(−)-configuration (unless otherwise stated), as revealed by the comparison of their optical rotations (measured in $CHCl_3$) and their GC and HPLC retention times with the literature data and with the behavior of authentic samples.[2−7] [e] Incomplete conversion. [f] Ref 4. [g] Ref 7. [h] Ref 6. [i] (*R*)-(+)-**3a** was formed. Ref 6. [j] Catalyst was of 87% ee. [k] Ref 5. [l] With the catalyst that was of 96% ee, the asymmetric induction was enhanced to 90% ee (at −40 °C). [m] Yield was 41% with 2 mol % of the catalysts; yield was 85% with 20 mol %. The catalyst loading did not alter the enantioselectivity (94−95% ee).

the pyridine *N*-oxide and the nitrogen of the remaining pyridine ring.[4,7,8] However, the monodentate catalyst **7**, lacking the second nitrogen, proved to catalyze the allylation of benzaldehyde with 41% ee (entry 7), showing that bidentate chelation is not strictly required.[5] Its *ortho*-methoxy analogue **8**, where a weak coordination of MeO to silicon might be anticipated, exhibited higher enantioselectivity (68% ee; entry 8),[5] whereas the *ortho*-fluoro derivative **9** was ineffective (entry 9).[5]

The latter results raised a question as to the role of the MeO group in **8**: does it affect the reaction via a silicon coordination or via some unidentified electronic effect (such as arene−arene interaction)? To address this issue, we have now synthesized the para isomer **10** and found it also to be fairly effective (58% ee, entry 10), which indicates that the MeO effect is likely to be of electronic origin, namely, via increasing the electron density of the phenyl moiety of the catalyst. By contrast, decreasing the electron density, as in the fluoro derivative **9**, is detrimental to the reaction (entry 9). Therefore, we set out to synthesize even more electron-rich dimethoxy and trimethoxy derivatives **11** and **12**, respectively; for the latter compound, we propose the acronym METHOX.

The synthesis of **10**−**12** relied on Kröhnke annulation[9] (Scheme 2) and commenced with the preparation of the Kröhnke salts **14a**−**c** by iodination of the corresponding acetophenones **13a**−**c** in pyridine. Pinocarvone (−)-**15**, obtained in a quantitative yield by the ene reaction of (+)-

(4) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett.* **2002**, *4*, 1047.

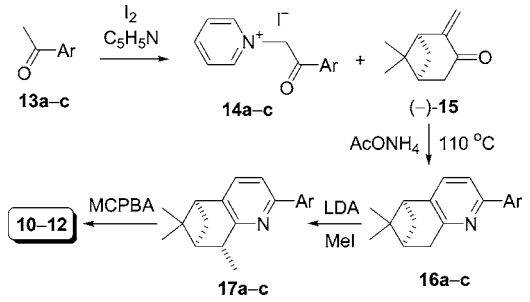
(5) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal. A* **2003**, *196*, 179.

(6) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674.

(7) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659.

(8) Similarly, both Nakajima[2] and Hayashi[3] proposed a chelation of silicon by the two oxygens of their *N*,*N*-bisoxides. For a related chelation of trifluorosilanes by phenanthroline, featuring hexacoordinate silicon, see: Nakash, M.; Gut, D.; Goldvaser, M. *Inorg. Chem.* **2005**, *44*, 1023.

Scheme 2[a]



[a] **a**, Ar = 4-MeO−C_6H_4; **b**, Ar = 2,6-$(MeO)_2C_6H_3$; **c**, Ar = 2,4,6-$(MeO)_3C_6H_2$.

α-pinene with singlet oxygen,[10,11] was then heated with the respective salts **14a**−**c** in the presence of $AcONH_4$ to produce the pyridine derivatives **16a**−**c**, whose methylation in the benzylic position, mediated by LDA,[11,12] afforded **17a**−**c**, respectively, with excellent diastereoselectivity. Oxidation of the pyridine nitrogen in **17a**−**c** provided the required *N*-oxides **10**−**12**, respectively.

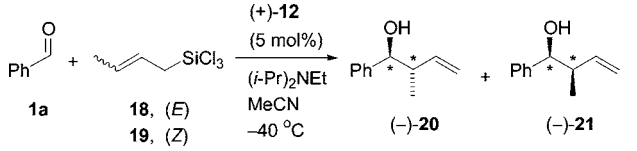
Indeed, the dimethoxy derivative (−)-**11** proved to be a more efficient catalyst than **8** or **10**, exhibiting 80% ee (compare entries 8 and 10 with 11). Switching from CH_2Cl_2 to MeCN or $CHCl_3$ had little effect (entries 12 and 13).

A real improvement was attained with the trimethoxy derivative METHOX (+)-**12** (entries 14−16), especially for the reactions run in MeCN (entries 17−19), where the conversion was essentially quantitative and the enantioselectivities were at the 96% ee level. It is notable that lowering the catalyst loading proved to have no effect on the enantioselectivity, though the reaction slowed to some extent (entries 17−19). Furthermore, increasing the temperature from the original −40 °C to room temperature resulted in only a marginal deterioration of enantioselectivity (entries 20−24 and 25−27).

The electronic effects in the aldehyde were briefly elucidated with the aid of substituted benzaldehydes **1b**−**e** and the champion catalyst METHOX (+)-**12** (entries 28−31). Both para-substituted aldehydes **1b** and **1c** proved to react with a similar level of efficiency as **1a** (entries 28 and 29), showing little dependence of the reaction on the electronics of the electrophile. High reactivity and selectivity were also observed with *ortho*-substituted aldehyde **1d** (entry 30). On the other hand, increasing the steric hindrance about the carbonyl group, as in 2,6-dimethyl-benzaldehyde (**1e**), entirely prevented the reaction (entry 31).

Finally, allylation of benzaldehyde **1a** was also carried out with crotyltrichlorosilanes **18** (*E*/*Z* 87:13)[13] and **19**[14] in MeCN (Scheme 3), in the presence of **12** as a catalyst (5 mol %). The trans isomer **18** (1.2 mol excess) reacted uneventfully, affording pure anti product (−)-**20** (anti/syn ≥99:1) of high enantiopurity (95% ee), which indicates a kinetic preference for the (*E*)-isomer. Accordingly, the reaction with pure (*Z*)-isomer **19** proved to be sluggish (26% conversion), affording a 1:6 mixture of (−)-**20** and (−)-**21** of low enantioselectivity (26% ee).

Scheme 3



In conclusion, the enantiopure, terpene-derived pyridine *N*-oxide METHOX (+)-**12** has been synthesized in three steps from the inexpensive chiral pool and shown to catalyze the asymmetric allylation of aromatic aldehydes **1** with allyltrichlorosilane **2** and crotyltrichlorosilane **18** (≤96% ee). The efficacy of **12** also demonstrates that neither the bidentate chelation of silicon to the catalyst nor the presence of a chiral axis[2−4,6,7] is a prerequisite for attaining high enantioselectivity in these reactions. METHOX **12** has been found to exhibit best activity in MeCN, and the reactions are characterized by low catalyst loading (≤5 mol %) and high tolerance to aldehyde electronics.[15] In this respect, the behavior of **12** differs dramatically from that of **6**, where a huge dependence on the aldehyde electronics has been observed.[6,16,17] Furthermore, **12** retains high enantioselectivity

(9) For a review on Kröhnke annulation, see: Kröhnke, F. *Synthesis* **1976**, 1. For recent overviews of the Kröhnke application in the synthesis of terpenoid bipyridines, see ref 7 and the following: (a) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 303. (b) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (c) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831. (d) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737.

(10) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.

(11) Malkov, A. V.; Pernazza, D.; Bell, M.; Bella, M.; Massa, A.; Teplý, F.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 4727.

(12) (a) Lötscher, D.; Rupprecht, S.; Stoeckli-Evans, H.; von Zelewsky, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4341. (b) Kolp, B.; Abeln, D.; Stoeckli-Evans, H.; von Zelewsky, A. *Eur. J. Inorg. Chem.* **2001**, 1207. (c) Lötscher, D.; Rupprecht, S.; Collomb, P.; Belser, P.; Viebrock, H.; von Zelewsky, A.; Burger, P. *Inorg. Chem.* **2001**, *40*, 5675.

(13) Prepared as an 87:13 trans/cis mixture via the CuCl-catalyzed reaction of crotyl chloride with $HSiCl_3$: Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513.

(14) Prepared as a practically pure isomer on Pd-catalyzed 1,4-addition of $HSiCl_3$ to butadiene: Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143.

(15) Note that the reactivity of METHOX **12** resembles that of the bipyridine *N*,*N*-bisoxide recently reported by Hayashi.[3]

(16) Arene−arene interactions between the electron-rich catalyst **12** and the substrate aldehyde can be proposed as a rationale for these observations. However, the latter interactions differ from those observed previously for QUINOX **6**.[6,17] High-level quantum chemical calculations are currently being used on in our laboratory to shed more light on this issue: Malkov, A. V.; Bendová, L.; Hobza, P.; Kočovský, P. Unpublished results.

(17) For recent reviews on arene−arene interactions, see: (a) Hobza, P.; Havlas, Z. *Chem. Rev.* **2000**, *100*, 4253. (b) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 651. (c) Cozzi, F.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L.; Baldridge, K. K.; Siegel, J. S. *Org. Biomol. Chem.* **2003**, *1*, 157. (d) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

at −20 and 0 °C, and even at room temperature (entries 20−24), which has industrial implications.

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Supporting Information Available: Experimental methods and ^{1}H and ^{13}C NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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