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Chiral 2,2′-Bipyridine-Type *N*-Monoxides as Organocatalysts in the Enantioselective Allylation of Aldehydes with Allyltrichlorosilane†

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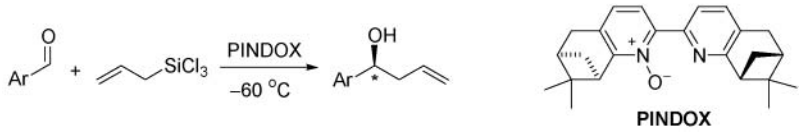
ABSTRACT



The Sakurai–Hosomi-type allylation of aromatic and heteroaromatic aldehydes can be catalyzed by the new heterobidenate bipyridine monoxide PINDOX with high enantioselectivities. The sterochemical outcome is mainly controlled by the axial chirality in PINDOX, which in turn is determined by the annulated terpene units.

In the Sakurai−Hosomi reaction of aldehydes with allyltrialkylsilanes (Scheme 1),[1] aldehyde activation with chiral Lewis acids[2,3] leads to good enantioselectivities. Complementary activation of the nucleophile by Lewis-basic oxygen donors[4,5] requires the use of allyltrichlorosilanes (**2**) and gives variable enantioselectivities for scalemic phosphoramides (21−88% ee),[6,7,8] tartrates (27−71% ee),[9] (2-pyridinyl)-oxazolines (22−74% ee),[10] formamides,[11] and ureas[12] as

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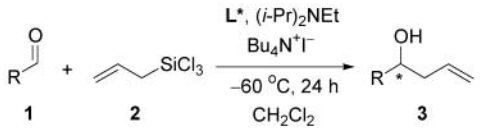
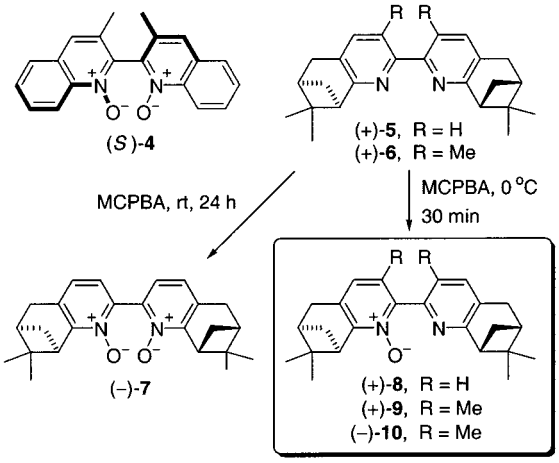
Scheme 1



catalysts. Nakajima observed ≤92% ee with the axially chiral 2,2′-bisquinoline *N*,*N*′-dioxide (*S*)-**4** (Scheme 2).[13] Herein,

Scheme 2



we report on the catalytic activity of the chiral bipyridine *N*-monoxide[14−16] PINDOX (**8**),[14] whose chirality originates from the terpene units.

Oxidation of PINDY (+)-**5**[14] (MCPBA, CH_2Cl_2, rt, 24 h) afforded *N*,*N*-dioxide (−)-**7** (62%); lower temperature (0 °C, 45 min) led exclusively to *N*-monoxide (+)-**8** (96%).[17] Addition of allyltrichlorosilane (**2**) to benzaldehyde (**1a**) (Scheme 1), carried out in the presence of (−)-**7** (7 mol %) at −90 °C, produced (*R*)-(+)-**3a** of 41% ee (Table 1, entry 2). The same enantiomer was formed with (*S*)-**4** (entry 1),

Table 1. Sakurai−Hosomi-Type Addition of **2** to **1** Catalyzed by **7**−**10** (Scheme 1)[a]

entry	catalyst	aldehyde	R	temp (°C)	time (h)	yield (%)[b]	% ee[c]	configuration of **3**[d]
1[e]	(*S*)-**4**[f]	**1a**	Ph	−78	6	85	88	(*R*)-(+)
2	(−)-**7**[f]	**1a**	Ph	−90	48	18[g]	41	(*R*)-(+)
3	(+)-**8**[f]	**1a**	Ph	−90	48	41[g]	89	(*S*)-(−)
4	(+)-**8**	**1a**	Ph	−90	24	67[g]	92	(*S*)-(−)
5	(+)-**8**	**1a**	Ph	−60	24	78[h]	90	(*S*)-(−)
6	(+)-**8**	**1a**	Ph	−40	6	65[h]	87	(*S*)-(−)
7	(+)-**8**	**1b**	*p*-Me-C_6H_4	−60	24	71[h]	87	(*S*)-(−)
8	(+)-**8**	**1c**	*p*-MeO-C_6H_4	−60	24	68[g]	87	(*S*)-(−)
9	(+)-**8**	**1d**	*p*-Cl-C_6H_4	−60	24	62[g]	89	(*S*)-(−)
10	(+)-**8**	**1e**	*p*-NO_2-C_6H_4	−60	24	58[g]	65	(*S*)-(−)
11	(+)-**8**[f]	**1f**	2-naphth	−90	48	63[g]	90	(*S*)-(−)
12	(+)-**8**	**1f**	2-naphth	−60	24	85[g]	88	(*S*)-(−)
13	(+)-**8**	**1g**	1-naphth	−60	24	51[g]	79	(*S*)-(−)
14	(+)-**8**	**1h**	$PhCH{=}CH_2$	−90	48	52[g]	83	(*S*)-(−)[i]
15	(+)-**8**[j]	**1h**	$PhCH{=}CH_2$	−60	24	56[h]	77	(*S*)-(−)[i]
16	(+)-**8**[j]	**1i**	$PhCH_2CH_2$	−40	48	44[g]	49[k]	(*R*)-(+)[l]
17	(+)-**8**[j]	**1j**	cyclohexyl	−30	48	∼10[g]	4[k]	
18	(+)-**8**	**1k**	2-furyl	−60	48	63[h]	85	(*S*)-(−)
19	(+)-**9**	**1a**	Ph	−60	12	72[h]	98	(*S*)-(−)
20	(+)-**9**	**1f**	2-naphth	−60	48	55[g]	91	(*S*)-(−)
21	(−)-**10**	**1a**	Ph	−60	24	67[g]	82	(*R*)-(+)

[a] The reaction was carried out at 1.0 mmol scale in CH_2Cl_2 with 1.1 equiv of **2**, in the presence of the catalyst (7 mol %) and Bu_4NI (1 equiv). [b] Isolated yield (note that some of the products are fairly volatile). [c] Determined by chiral HPLC or GC. [d] Established from the optical rotation (measured in $CHCl_3$) by comparison with the literature data.[13] [e] Reference 13. [f] Carried out in the absence of Bu_4NI. [g] Incomplete conversion. [h] Complete conversion. [i] **3h** is dextrorotatory in Et_2O[13] and levorotatory in $CHCl_3$. [j] With 20 mol % of the catalyst. [k] The reaction is too slow at lower temperatures. [l] The seemingly inverted configuration here is due to the change in priority of the substituents in the Cahn−Ingold−Prelog notation.

suggesting that the configuration at the chiral axis in the intermediate arising from **7** is also (*S*). A considerable improvement (∼90% ee) was observed for *N*-monoxide (+)-**8**, which gave the opposite enantiomer of **3** (entry 3). Addition of Bu_4NI[5c] resulted in a faster reaction and a slightly improved enantioselectivity (entry 4). Raising the temperature led to further acceleration, accompanied by a very minor decrease of enantioselectivity (entries 5 and 6). *p*-Substituted benzaldehydes **1b**−**e** gave similar selectivities (entries 7−10), indicating little influence of the electronic effect.[18] Naphthaldehydes **1f**,**g** and cinnamic aldehyde (**1h**) also exhibited high asymmetric induction (entries 11−15), but saturated aldehydes **1i**,**j** gave low enantioselectivities and reaction rates (entries 16 and 17), demonstrating the beneficial effect of the π-conjugation. High enantioselectivity was also observed for furfural (**1k**), showing the compatibility of this asymmetric reaction with a heteroaromatic system (entry 18).

In the transition state, the stereoelectronic control[6] requires that the N−O group of **8** be *trans*-coordinated to Si with respect to the allyl to increase its nucleophilicity. The

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(17) In contrast to (*S*)-**4**, the rotation barriers in (−)-**7** and (+)-**8** are too low to allow the separation of atropoisomers.

(18) The lower enantioselectivity observed for *p*-nitrobenzaldehyde is likely to originate from the interfering coordination by the NO_2 group rather than its electronic effect (compare entries 9 and 10).

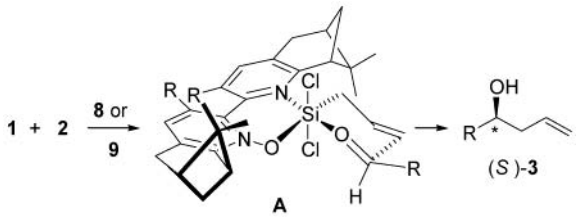
aldehyde, coordinated *cis* to the allyl[19] via a hexacoordinated silicon,[20,21] can be considered to be *trans*-disposed either to Cl or to N of the other pyridine nucleus.

Molecular modeling suggests that the preferred stereostructure of the transition state will be dictated by the twist about the 2,2′-bipy axis in **8**, which in turn must be controlled by the configuration of the terpene moieties. Since the atropoisomers of the noncoordinated (+)-**8** cannot be isolated, we envisioned that this issue could be addressed by the corresponding 3,3′-dimethyl derivative, where the rotation barrier should be higher. To this end, dimethyl-PINDY (+)-**6** was synthesized using a protocol analogous to that developed for PINDY[14] (see Supporting Information). Its oxidation with MCPBA (unoptimized) afforded a ~1:2 mixture of atropoisomeric monoxides (+)-**9** and (−)-**10** that were separated by chromatography.[22]

On the allylation reaction **1a** + **2** → **3a**, (+)-**9** induced the formation of the same enantiomer of **3a** as did (+)-**8** but with higher enantioselectivity (98% ee; entry 19); **1f** reacted similarly (entry 20). By contrast, (−)-**10** gave the opposite enantiomer with slightly lower enantioselectivity (entry 21). Hence, as expected, the asymmetric induction is mainly controlled by the configuration at the 2,2′-bipy bond, which must be identical for (+)-**8** and (+)-**9**. The configuration of (−)-**10** was found to be (*S*) by X-ray crystallography,[23] so that (+)-**9** must have (*R*) configuration. Molecular modeling shows that this architecture will favor the intermediate **A** (Scheme 3), in the case of both **9** and **8**. Interestingly, modeling and preliminary crystallographic data found (+)-**8**[24] to be (*S*)-configured at the chiral axis [rather than (*R*)]. Hence, if reproduced in the solution, the molecule would have to flip to the (*R*)-configuration upon the coordination of the reactants (prior to the reaction).

In conclusion, new bipyridine *N*-monoxide (+)-**8** has been synthesized and shown to exercise a high level of enantiocontrol in the Sakurai−Hosomi-type reaction. With the aid of the configurationally fixed pair of atropoisomers (+)-**9** and (−)-**10**, the stereochemistry of the reaction has been demonstrated to be controlled by the 2,2′-bipy chiral axis and intermediate **A** has been proposed to account for the observed sense of the asymmetric induction. The present catalyst is characterized by its heterobidentate nature (with one strong and one weak donor), which contrasts with the homobidentate and monodentate catalysts reported by other groups. The mechanistic analysis suggests that, while one ligating group (N−O) of (+)-**8** activates the allyl silane, the other N stabilizes the intermediate by chelation, thereby reducing the number of diastereoisomeric transition states, which results in high enantioselectivity. Further applications of PINDOX-type catalysts in related reactions[8,25] are being investigated.

Scheme 3



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Supporting Information Available: Experimental procedures, analytical and spectral data, crystallographic data, and copies of the NMR spectra for the key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This analysis is consistent with the Denmark model[6] but in conflict with the mechanism proposed by Nakajima for **4**,[13] where the stereoelectronic effects were not considered. Note that while **4** and **7** allow the formation of a seven-membered chelate, **8** should operate via a six-membered ring.

(22) In solution, the two atropoisomers slowly interconvert at room temperature, eventually reaching the thermodynamic equilibrium within about a week. In the solid state, (+)-**9** appears to be reasonably stable when stored in a freezer.

(23) Crystal data for (−)-**10**: white crystals, space group $P2_12_12_1$, a = 7.15070(10) Å, b = 16.83000(10) Å, c = 38.17410(10) Å, V = 4594.11(7) Å^3, Z = 8, d_{calc} = 1.123 g cm^{-3}, μ = 0.068 mm^{-1}, R_F = 0.0534. Two molecules are present in the cell, differing from each other, e.g., in the dihedral angle N(O)−C(2)−C(2′)−N (100.6° and 102.6°, respectively).

(24) Crystal data for (+)-**8**: white crystals, space group $P2_12_12_1$, a = 6.8339(2) Å, b = 11.0443(5) Å, c = 26.0682(10) Å, V = 1967.51(13) Å^3, Z = 8, d_{calcd} = 1.217 g cm^{-3}, μ = 0.074 mm^{-1}, R_F = 1.021.

(25) Thus, our preliminary experiments showed that the cleavage of cyclooctene epoxide with $SiCl_4$, catalyzed by (+)-**8**, afforded the corresponding chlorohydrin of 85% ee, which is the highest enantioselectivity reported to date. For other examples of this reaction and a recent discussion, see: (a) Denmark, S. E.; Wunn, T.; Jellerichs, B. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2255 and references cited therein. For a withdrawal of earlier claims, see: (b) Buono, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4536.