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Direct asymmetric synthesis of oxazolines from olefins using a chiral nitridomanganese complex: a novel three-component coupling leading to chiral oxazolines

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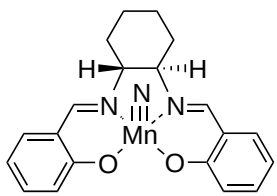
Abstract—A new synthetic method for chiral oxazolines has been developed by N1 unit transfer to olefins using a chiral nitridomanganese complex. When *trans*-disubstituted styrenes were treated with chiral complex **1** in the presence of an acid chloride, oxazolines were obtained with high enantioselectivities (up to 92% ee). Furthermore, the produced oxazolines could be easily converted into β-amino alcohols, which are ephedrine derivatives.

It is well known that optically active oxazolines are highly versatile five-membered heterocycles. The oxazolines exist in a variety of natural products and biologically active compounds,[1,2a] and they can easily be converted into optically active β-amino alcohols which are useful synthetic intermediates.[2,3] It has also been revealed in the last decade that they act as potential chiral ligands for asymmetric synthesis.[4] In general, the synthesis of chiral oxazolines from natural amino acids involves several steps.[2,5] Although natural amino acids are readily available chiral sources, their use causes limitations in the absolute configuration and the diversity of substituents on the formed oxazoline ring. Reagent-controlled synthesis of optically active oxazolines is a useful method, but only a few examples are reported to date.[6] While an alternative method for the synthesis of achiral oxazolines from olefins and *N*-acyl nitrenes has been reported, the reaction of photochemically or thermally generated *N*-acyl nitrenes with olefins suffers from the problem that a variety of by-products are also formed.[7] Recently, we reported a unique nitrogen source, a chiral nitridomanganese complex (Fig. 1), for use in the asymmetric aziridination of styrene derivatives and conjugated dienes, where *p*-toluenesulfonic anhydride (Ts_2O) played an important role as an activator of the complex to complete the reaction.[8] On the other hand, *N*-acyl aziridines are known to isomerize to oxazolines.[9,10] This situation prompted us to investigate the direct construction of oxazolines using a nitrido complex as the nitrogen source. We report here the first asymmetric synthesis of 2-oxazolines from olefins with a chiral nitrido complex in the presence of acid halides, in which 2-oxazolines are selectively produced without the formation of *N*-acyl aziridines.

As mentioned above, activating reagents of nitrido complexes often influence the structure of products in the N1 unit transfer to olefins.[8,11] Acid chlorides might be potent candidates as activators for the reaction to give *N*-acyl aziridines or 2-oxazolines.[12] While a simple olefin, styrene was employed in the reaction of the nitridomanganese complex **1** with benzoyl chloride as an initial example, only a small amount of the corresponding oxazoline was obtained, along with β-chloroamide derivative. When *trans*-β-methylstyrene was treated with the chiral nitridomanganese complex **1** in methylene chloride at room temperature for 48 h in



(*R*,*R*)-complex 1

Figure 1.

Keywords: asymmetric synthesis; chiral oxazolines; nitridomanganese complex; olefins.

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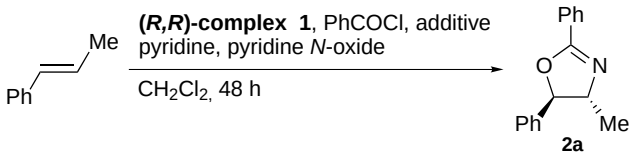
the presence of pyridine, pyridine *N*-oxide and benzoyl chloride, 4-methyl-2,5-diphenyl-2-oxazoline (**2a**) was obtained in 77% yield with 81% ee (Table 1). Although *N*-aroyl nitrenes generally added to olefins to give aziridines,[7b] oxazoline **2a** was selectively produced with no detectable formation of the corresponding *N*-benzoyl aziridine in this reaction. Moreover, the reaction gave exclusively *trans*-oxazoline with the retention of the stereochemistry of the starting olefin. Thus, the reaction conditions were optimized as follows. While the reaction proceeded with good enantioselectivity (86% ee) at 0°C, the chemical yield of **2** was moderate compared to the yield at room temperature. In order to obtain a higher chemical yield at 0°C, several additives were employed in the reaction. The addition of a silver salt such as $AgClO_4$ or $AgBF_4$ was found to dramatically improve the chemical yield with no significant loss in enantioselectivity. Furthermore, a reaction conducted in the presence of $AgBF_4$ but without pyridine gave the best result.[13,14] The use of the optimal conditions led to a better result, in terms of the formation of the oxazoline from styrene (74%, 16% ee).

Table 1. Asymmetric synthesis of oxazoline **2a** from *trans*-β-methylstyrene and complex **1**[a]



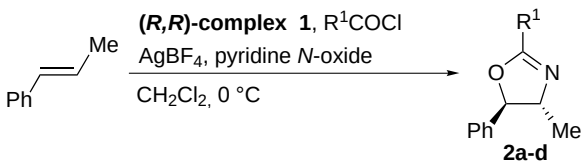
Entry	Additive	Temp. (°C)	Yield (%)	Ee (%)[b,c]
1	None	Rt	77	81
2	None	0	34	86
3	$AgClO_4$	0	65	87
4	$AgBF_4$	0	77	87
5[d]	$AgBF_4$	0	81	86

[a] Reaction conditions: (*R*,*R*)-complex **1** (1 equiv.), PhCOCl (1.2 equiv.), additive (1.2 equiv.), pyridine (0.5 equiv.), pyridine *N*-oxide (1.2 equiv.), *trans*-β-methylstyrene (10 equiv.).
[b] Enantiomeric excesses were determined by HPLC analysis using a Daicel Chiralcel OD column.
[c] Absolute configurations were determined to be (4*R*,5*R*) by comparison of the measured optical rotations with reported values.[3]
[d] Reaction was run without pyridine.

To investigate the influence of an activator of complex **1** on the synthesis of oxazolines, several acid chlorides were examined and the results are listed in Table 2. When *p*-(trifluoromethyl)benzoyl chloride was employed in the reaction, *trans*-β-methylstyrene was found to react smoothly and the corresponding oxazoline was obtained in 88% yield with 86% ee. Although it took a considerable length of time to complete the reaction in the case of *p*-methoxybenzoyl chloride, the yield and enantiomeric excess of the produced oxazoline were the same as those for the product from benzoyl chloride. These results suggest that an electron-deficient substituent on the phenyl ring of an acid chloride increases the rate of the reaction. On the other hand, pivaloyl chloride, which is an aliphatic acid chloride, was employed for the reaction to give the 2-alkylated oxazoline in good yield with excellent enantioselectivity, suggesting that the yields and enantioselectivities of oxazolines were not influenced by the nature of the acid chlorides.

The present reaction was successfully applied to the synthesis of oxazolines from styrene derivatives, as shown in Table 3. The reaction of *trans*-1-phenyl-1-pentene with **1** using benzoyl chloride afforded the desired oxazoline in good yield with high enantioselectivity. *trans*-3-Phenyl-1-methyl-2-butene and *trans*-β-cyclohexylstyrene were transformed into the corresponding oxazolines in over 90% ee, respectively. In these reactions, the *trans*-oxazolines were obtained as the sole products and *cis*-isomers were not detected. Although the present reaction permitted the conversion of cyclic olefins such as 1,2-dihydronaphthalene and 1-phenylcyclohexene into the polycyclic compounds, the yields and enantioselectivities were moderate. As shown, the complex provides a highly effective asymmetric environment for oxazoline synthesis from *trans*-substituted styrene derivatives. The tendency

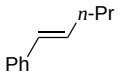
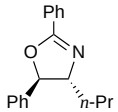
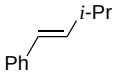
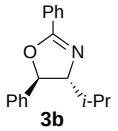
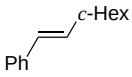
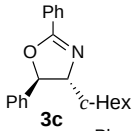
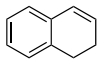
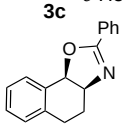
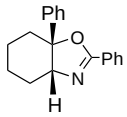
Table 2. Effect of acid chlorides on the reaction of *trans*-β-methylstyrene with complex **1**[a]



Entry	R^1	Time (h)	Oxazoline	Yield (%)	Ee (%)[b]
1	Ph	48	**2a**	81	86[c]
2	*p*-$CF_3C_6H_4$-	24	**2b**	88	86[d]
3	*p*-$MeOC_6H_4$-	168	**2c**	80	86[d]
4	*t*-Bu	48	**2d**	75	85[e]

[a] Reaction conditions: (*R*,*R*)-complex **1** (1 equiv.), PhCOCl (1.2 equiv.), $AgBF_4$ (1.2 equiv.), pyridine *N*-oxide (1.2 equiv.), *trans*-β-methylstyrene (10 equiv.).
[b] Enantiomeric excesses were determined by HPLC analysis using a Daicel Chiralcel OD column or a Chiralpak AD column.
[c] Absolute configuration was determined as (4*R*,5*R*).[3]
[d] Absolute configurations were established as (4*R*,5*R*) by comparison of the measured optical rotations with that of **2a**.
[e] Absolute configuration was determined as (4*R*,5*R*) using the corresponding amino alcohol derived from **2d**.

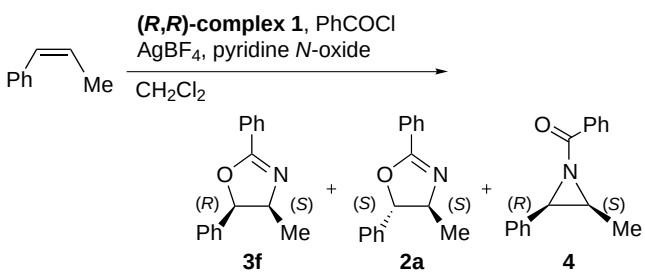
Table 3. Asymmetric synthesis of oxazolines from styrene derivatives and complex **1**[a]

Entry	Olefin	Time (h)	Oxazoline	Yield (%)	Ee (%)[b]
1		24	 **3a**	85	88[c]
2		24	 **3b**	85	90[c]
3		36	 **3c**	75	92[c]
4		72	 **3d**	55	11[d]
5		48	 **3e**	53[e]	32[d]

[a] Reaction conditions: (*R*,*R*)-complex **1** (1 equiv.), PhCOCl (1.2 equiv.), $AgBF_4$ (1.2 equiv.), pyridine *N*-oxide (1.2 equiv.), olefin (10 equiv.), CH_2Cl_2, 0°C.[b] Enantiomeric excesses were determined by HPLC analysis using Daicel Chiralcel OD column or Chiralpak AD column.[c] Absolute configurations were established as (4*R*,5*R*) by comparison of the measured optical rotations with that of **2a**.[d] Absolute configurations were not determined.[e] 1-Benzoylamino-2-phenyl-2-cyclohexene was obtained in 11% yield.

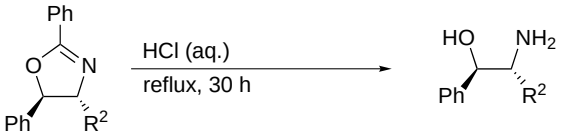
of a substituent effect on yields and enantiomeric excesses in the reactions is similar to that in the aziridination of these styrene derivatives using complex **1** and Ts_2O.[8a]

When *cis*-β-methylstyrene was treated with **1** at room temperature for 48 h, *cis*-oxazoline **3f** was obtained with *trans*-oxazoline **2a** (Eq. (1)). On the other hand, the formation of *cis*-aziridine **4** was observed at 0°C along with oxazolines **2a** and **3f**. These results suggest that the present reactions might proceed via aziridine intermediates.[10]



(1)

The produced oxazolines could be easily converted into β-amino alcohols. When oxazoline **2a** was treated with 1.2N HCl at reflux for 30 h, norpseudoephedrine (**5**) was obtained in good yield with the retention of the stereochemistry (Eq. (2)).[3] The hydrolysis of oxazoline **3c** also took place under similar conditions to give the non-natural β-amino alcohol **6** in high yield.



2a: R^2 = Me (86% ee) **5:** 93% yield (86% ee)
3c: R^2 = *c*-Hex (92% ee) **6:** 88% yield (92% ee)

(2)

In summary, we report on a reagent-controlled direct synthesis of chiral 2-oxazolines from olefins using a chiral nitridomanganese complex in the presence of acid chlorides. The study represents the first example of a [2+2+1] type asymmetric synthesis of oxazolines. The reaction of *trans*-substituted styrene derivatives gave rise to *trans*-2-oxazolines stereoselectively in good yields with high enantioselectivity. A search for applications and the mechanism of the present reaction is currently in progress.

Acknowledgements

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12. Carreira et al. reported that the use of $(CF_3CO)_2O$ as an activator for a nitrido complex leads to the formation of ring-opening products, amino alcohols, see: Ref. 11e.
13. **General procedure for asymmetric synthesis of 2-oxazolines from olefins**: Olefin (3.0 mmol) and acid chloride (0.36 mmol) were added to a mixture of **1** (0.3 mmol), $AgBF_4$ (0.36 mmol) and pyridine *N*-oxide (0.36 mmol) in CH_2Cl_2 (3 mL) under an atmosphere of nitrogen at the indicated temperature. After the mixture was stirred for the indicated time, pentane (20 mL) was added. The mixture was then passed through a 3-cm pad of silica gel using diethyl ether (125 mL) as the eluent. The filtrate was concentrated in vacuo, and the residue purified by flash column chromatography on silica gel (hexane/EtOAc). Enantiomeric excesses of the oxazolines were determined by chiral HPLC analysis (Daicel Chiralcel OD or Chiralpak AD).
14. When *trans*-β-methylstyrene was treated with (*S*,*S*)-complex **1**, (4*S*,5*S*)-**2** was obtained (82%, 85% ee).