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Ru(CO)-salen-Catalyzed Synthesis of Enantiopure Aziridinyl Ketones and Formal Asymmetric Synthesis of (+)-PD 128907

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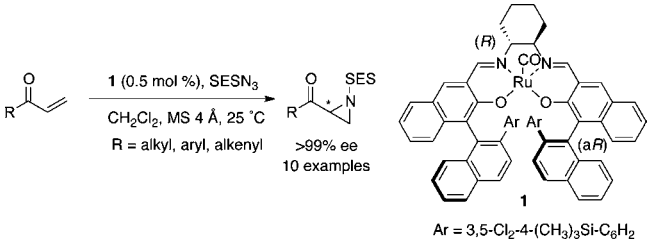
ABSTRACT



Aziridination of vinyl ketones using $SESN_3$ in the presence Ru(CO)-salen complex 1 provides the enantiopure aziridinyl ketones that can serve as useful chiral building blocks. A formal asymmetric synthesis of (+)-PD 128907 was achieved in an eight-step sequence via aziridination.

Optically active aziridinyl ketones and esters, especially ones *N*-protected with an electron-withdrawing group, are versatile building blocks because they undergo nucleophilic and reductive ring-opening to provide various chiral amine derivatives.[1,2] Thus, many methods for their enantioenriched synthesis have been developed.[1,3] Asymmetric aziridination of readily available enones and enoates is a simple and direct method for synthesis and is the method that has been explored most thoroughly.[4] Evans et al. have reported highly enantioselective copper-catalyzed aziridination using *N*-(*p*-toluenesulfonyl)iminophenyliodinane.[4a] Scott et al. also reported highly enantioselective aziridination using copper complexes of biaryl Schiff bases.[4b] Subsequently, Xu et al. reported that a particular copper-(AnBOX) complex is an excellent catalyst for asymmetric aziridination.[4c] Good substrates for these reactions are, however, largely limited to cinnamate and chalcone derivatives, and few methods can be applied to asymmetric aziridination of vinyl ketones that are polymerizable.[5] Moreover, use of arenesulfonyliminophenyliodinane

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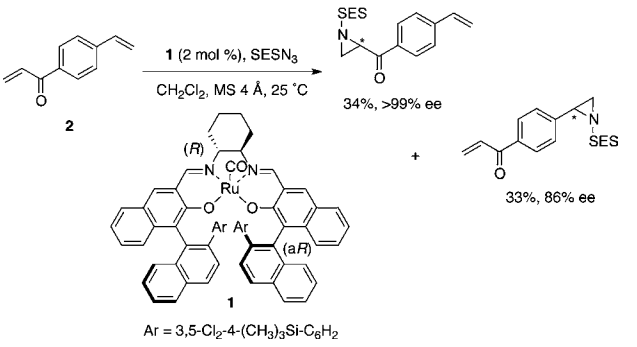
derivatives as nitrenoid precursors reduces the atom economy of the reactions[6] and causes problems with *N*-arenesulfonyl deprotection from the products.[7] Nucleophilic addition of diazo compounds or ylides to aldimines is another promising approach for obtaining optically active aziridino carbonyl compounds,[8,9] but unstable formaldimine derivatives have not yet been used as the substrate for these reactions. Recently, organocatalytic asymmetric aziridination of α,β-unsaturated carbonyl compounds using *N*-protected hydroxylamine or chloroamine derivatives via an addition−cyclization pathway has been developed.[10,11] This method has been successfully applied to the aziridination of acrolein showing high enantioselectivity of up to 94% ee.[11b] However, these reactions require high catalyst loading. Still, the enantioenriched and atom-economic synthesis of unsubstituted aziridinyl ketones, which are highly reactive to nucleophiles, remains a challenging problem.

Azide compounds,[12] in particular, the ones bearing a readily removable *N*-sulfonyl group such as *p*-nitrobenzenesulfonyl (*p*-Ns)[7a,b] and 2-(trimethylsilyl)ethanesulfonyl (SES) groups,[7c] are an ideal nitrenoid precursor in terms of atom efficiency and synthetic application. Müller et al. reported that *p*-NsN_3 serves as a nitrenoid precursor for Rh-mediated aziridination under UV-irradiation with modest enantioselectivity.[13−15] We discovered that Ru(CO)-salen complexes catalyze enantioselective aziridination of simple olefins using *N*-toluenesulfonyl azides at room temperature without irradiation.[16] Moreover, Ru(CO)-salen complex **1** bearing a robust ligand could catalyze aziridination using *p*-NsN_3 and $SESN_3$.[16b−e] Zhang et al. also reported on asymmetric aziridination using azide compounds as nitrenoid sources.[17] During our study, we observed that **1** catalyzes aziridination of benzyl acrylate with excellent enantioselectivity.[16d] Although metal nitrenoids are isoelectronic species of metal oxenoids that are an electrophilic species, they undergo aziridination of electron-deficient olefins smoothly (*vide supra*).[4] Considering the mild Lewis acidity of Ru(CO)-salen complexes,[18] we expected that complex **1** would serve as a good catalyst for aziridination of unstable vinyl ketones. Thus, we first examined the intramolecular competitive aziridination of *p*-vinylphenyl vinyl ketone **2** using $SESN_3$. Although the styrene and the acroyl moieties of **2** reacted at almost equal rates, the enantioselectivity of aziridination of the acroyl moieties was much better than that of the styrene moiety (Scheme 1). No polymerization of the vinyl ketone was observed.

Scheme 1. Intramolecular Competitive Aziridination Using **1** as Catalyst



Encouraged by these results, we investigated the asymmetric aziridination of various vinyl ketones using a complex **1**/$SESN_3$ system (Table 1). As expected, the reaction of phenyl vinyl ketone **3a** proceeded with almost complete

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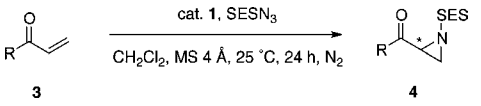
(19) CCDC 771523 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

enantioselectivity (entry 1). Furthermore, the catalyst loading could be reduced to 0.5 mol % without decreasing the enantioselectivity and the yield (entry 3). Under the conditions, the reactions of various aryl vinyl ketones **3b**–**f** gave the corresponding aziridinyl ketones also with almost complete enantioselectivity and high yields, irrespective of the location and electronic nature of the substituents (entries 4–8). The reactions of alkyl and cycloalkenyl vinyl ketones **3g** and **3h** were slower, and 1 mol % of **1** was required to ensure high yields (entries 9 and 10). The reactions of alkenyl vinyl ketones **3h** and **3i** occurred only at the vinyl moiety with almost complete enantioselectivity (entries 10 and 11).

Table 1. Asymmetric Aziridination of Vinyl Ketones with $SESN_3$ in the Presence of Ru(CO)-salen Complex **1**[a]



3 **4**

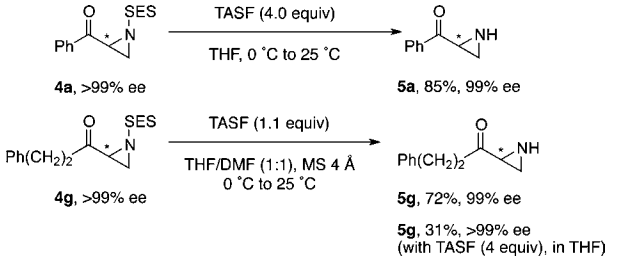
entry	vinyl ketone (R)	cat. (mol %)	yield (%)[b]	% ee[c]
1	Ph (**3a**)	2.0	99	>99
2	Ph (**3a**)	1.0	99	>99
3	Ph (**3a**)	0.5	99	>99
4	*p*-ClC_6H_4 (**3b**)	0.5	96	>99
5	*m*-ClC_6H_4 (**3c**)	0.5	96	>99
6	*o*-ClC_6H_4 (**3d**)	0.5	98	>99
7	*p*-$MeOC_6H_4$ (**3e**)	0.5	92	>99
8	*m*-$MeOC_6H_4$ (**3f**)	0.5	99	>99
9	$PhCH_2CH_2$ (**3g**)	1.0	99 (64)[d]	>99
10	1-cyclohexenyl (**3h**)	1.0	92 (67)[d]	>99 (*R*)[e]
11	(*E*)-PhCH=CH (**3i**)	0.5	95	>99

[a] The reaction was carried out on a 0.5 mmol scale at 25 °C under a N_2 atmosphere, unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis with a chiral stationary phase, as described in the Supporting Information. [d] Catalyst loading was 0.5 mol %. [e] Absolute configuration was determined to be *R* by X-ray analysis (ref 19).

The *N*-SES group of phenyl aziridinyl ketone **4a** was deprotected by exposure to tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[20] in tetrahydrofuran (THF) with little racemization to give the corresponding aziridines **5a** with good yield (Scheme 2). Treatment of 2-phenylethyl aziridinyl ketone **4g** under the same conditions also gave **5g** without racemization, but in a modest yield. However, the reaction using 1.1 equiv of TASF in 1/1 THF/dimethylformamide (DMF) gave **5g** in a better yield with little racemization.

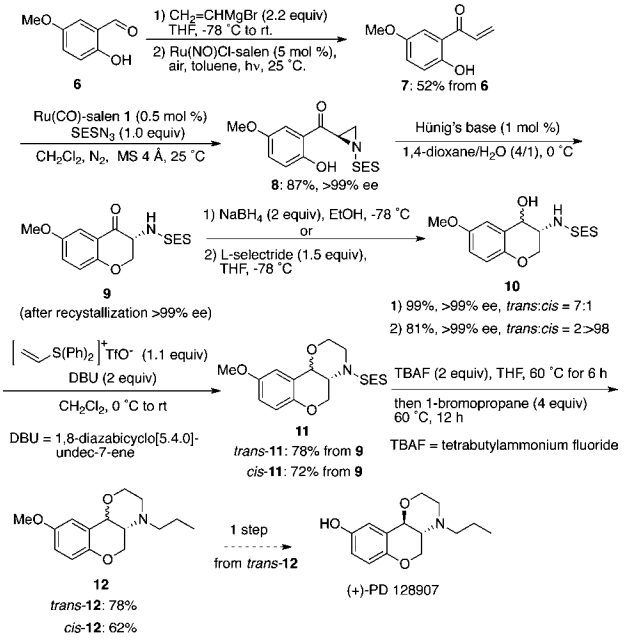
(+)-PD 128907 is a potent dopamin D_3 receptor agonist.[21] Although its structure is simple, only two racemic

Scheme 2. Deprotection of the *N*-SES Group of Aziridinyl Ketones



syntheses[22] and one chiral synthesis via resolution[22b] have been reported and no asymmetric synthesis based on the enantioselective method has been reported. With the present asymmetric aziridination as a key step, we achieved the formal but highly enantioenriched synthesis of (+)-PD 128907 (Scheme 3). The synthesis started with vinylation of commercial 5-methoxysalicylaldehyde **6**. The resulting vinyl alcohol is unstable, and oxidation using PCC, PDC, CrO_3/TBHP, or TEMPO/PhI$(OAc)_2$ did not give the desired product. The oxidation with excess MnO_2 (20 equiv) provided product **7** in moderate yield (37%). However, **6** was converted in one pot into vinyl ketone **7** at a yield of 52% via vinylation and subsequent Ru-catalyzed aerobic oxidation.[23] Aziridination of **7** gave almost enantiopure (*R*)-aziridinyl ketone **8** (>99% ee) in an acceptable yield (87%),[24] without protecting the phenolic hydroxyl group. Treatment of **8** with a catalytic amount of Hünig's base at 0 °C gave cyclic ketone **9**, though a slight decrease of the enantioselectivity to 96% ee was observed. Recrystallization of **9** from CH_2Cl_2/hexane gave enantiopure **9**.[24] Reduction

Scheme 3. Formal Asymmetric Synthesis of (+)-PD 128907



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of **9** with $NaBH_4$ gave the desired *trans*-hydroxy amine **10** preferentially, while the reduction with L-selectride afforded *cis*-hydroxy amine **10** exclusively. The mixture of *trans*- and *cis*-products **10** was converted without separation to the corresponding 4-protected 1,4-oxazine derivatives **11** by annulation using a diphenyl vinyl sulfonium reagent,[25] and the product mixture was chromatographed to give *trans*- and *cis*-oxazines **11**, respectively. Deprotection of the respective SES group in *trans*- and *cis*-oxazines **11** with TBAF and subsequent treatment of the resulting amines with 1-bromopropane gave the corresponding *trans*- and *cis*-oxazines **12** in good yields, respectively.[26] Since *trans*-**12** has been converted to (+)-PD 128907 in one step,[22] a formal asymmetric total synthesis of (+)-PD 128907 was achieved in eight steps with the synthesis of **12**.

In summary, we have demonstrated that ruthenium(CO)-salen complex **1** is an efficient catalyst for enantioselective aziridination of acid-sensitive vinyl ketones using $SESN_3$ as the nitrene precursor. The reaction proceeded with high yields even at a 0.5−1 mol % catalyst loading to give almost enantiopure aziridinyl ketones. The high synthetic utility of this aziridination was shown by the short step synthesis of (+)-PD 128907.

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Supporting Information Available. X-ray crystallographic data of compounds **4h**, **9**, and *trans*-**12** in CIF format; experimental procedures, spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.