Asymmetric synthesis of 4*H*-1,3-oxazines: enantioselective reductive cyclization of *N*-acylated β-amino enones with trichlorosilane catalyzed by chiral Lewis bases†

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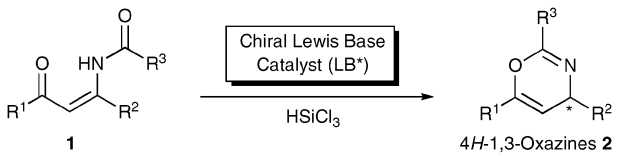
***N*-Acylated β-amino enones reductively cyclize by treatment with trichlorosilane and a chiral Lewis base catalyst to afford optically active 4*H*-1,3-oxazines, which can be transformed to other chiral compounds without racemization.**

4*H*-1,3-Oxazines are a class of six-membered heterocyclic compounds with one oxygen and one nitrogen in the ring structure.[1] These compounds have been synthesized *via* cyclization of *N*-acylated β-amino ketones using dehydrating agents,[2] or *via* reactions between nitriles and β-chloro ketones (or enones)[3] or between alkynes and *N*-acyl imines (or their equivalents).[4] However, to the best of our knowledge, the enantioselective synthesis of chiral 4*H*-1,3-oxazines possessing a stereogenic centre at the 4-position, as well as their biological activities, have yet to be studied.[5] During our studies on the asymmetric synthesis of *N*-acylated β-amino ketones, we unexpectedly found that optically active 4*H*-1,3-oxazines **2** could be directly obtained *via* reductive cyclization of *N*-acylated β-amino enones **1** using trichlorosilane and chiral Lewis base catalysts (Scheme 1). Herein, we describe this finding, as well as the potential utility of chiral 4*H*-1,3-oxazine products as synthetic intermediates.

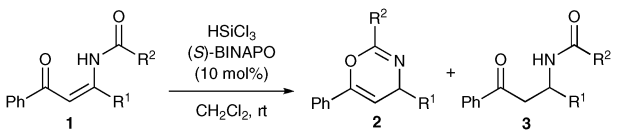


Scheme 1 Enantioselective reductive cyclization of *N*-acylated β-amino enones for asymmetric synthesis of 4*H*-1,3-oxazines.

We have recently reported that Lewis bases such as $Ph_3P{=}O$ and HMPA catalyze the conjugate reduction of simple enones with trichlorosilane, and that a chiral Lewis base can catalyze the reduction with a high enantioselectivity.[6] Therefore, we envisaged that optically active β-amino carbonyl compounds might be obtained *via* the enantioselective conjugate reduction of *N*-acylated β-amino enones **1** utilizing this method.[7]

First, (*Z*)-*N*-benzoyl enone **1a** (Table 1, entry 1), derived *via* the benzolylation of 3-amino-1-phenylbutane-1,3-dione, was treated with trichlorosilane (2 equiv.) in the presence of (*S*)-BINAPO (10 mol%, Fig. 1) in dichloromethane at rt. The consumption of **1a** was sluggish and incomplete. However,

Table 1 Enantioselective reductive cyclization of *N*-acylated β-amino enones **1** catalyzed by BINAPO[a]



Entry	R^1, R^2 (**1**)	Time/h	yield (%) (ee (%), config.) **2**	**3**
1[b]	Me, Ph (**1a**)	11	**2a**: 56 (71, *R*)	**3a**: 13 (4)
2	**1a**	24	**2a**: 68 (74, *R*)	**3b**: 17 (7, *S*)
3[c]	*i*-Pr, Ph (**1b**)	9	**2b**: 72 (47, *R*)	**3b**: 23 (42, *S*)
4[d]	Ph, Ph (**1c**)	9	**2c**: 75 (53, *S*)	**3c**: 12 (51, *S*)
5[e]	Me, *p*-$NO_2C_6H_4$ (**1d**)	24	**2d**: 38 (50, *R*)	**3d**: 20 (28, *S*)
6	Me, *p*-$MeOC_6H_4$ (**1e**)	5	**2e**: 68 (81, *R*)	**3e**: 18 (14, *S*)
7[b]	Me, Me (**1f**)	2	**2f**: 58 (26, *R*)[f]	**3f**: 27 (22, *S*)

[a] Unless otherwise noted, reactions were carried out using an *N*-acylated β-amino enone (0.25 mmol), trichlorosilane (3 equiv.), and (*S*)-BINAPO (10 mol%) in dichloromethane (1 mL) at rt, and quenched with water. [b] With trichlorosilane (2 equiv.). [c] *N*-(4-Methyl-1-phenylpent-1-en-3-yl)benzamide was obtained in 2% yield with 55% ee. [d] *N*-(1,3-Diphenylallyl)benzamide was obtained in 10% yield with 4% ee. [e] Enamide **1d** was recovered in 37% yield. [f] The yield and selectivity were determined after hydrolysis to keto amide **3f** (see text).

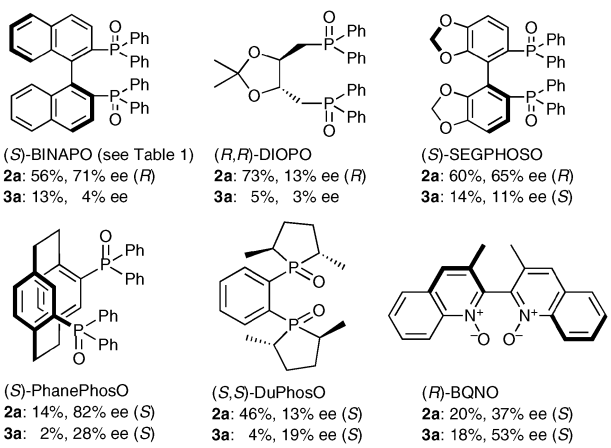


Fig. 1 Screening of Lewis base catalysts.

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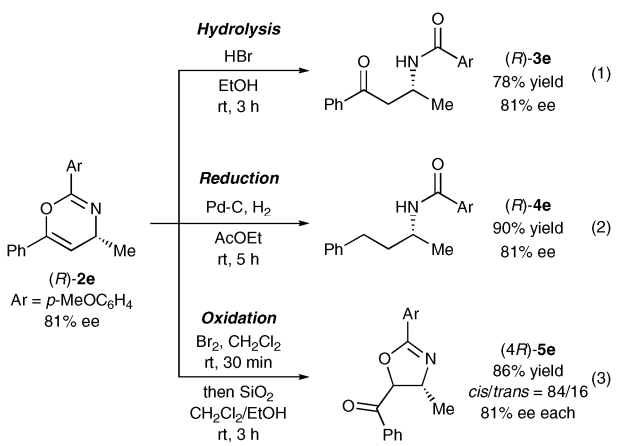
4*H*-1,3-oxazine **2a** was unexpectedly generated as the major product in moderate yield with good enantioselectivity (71% ee), whereas the yield and selectivity of anticipated keto amide **3a** were low. The use of a Lewis base catalyst is indispensable for the reaction, since no product was obtained in the absence of a catalyst. The quenching method was important; employing saturated aq. $NaHCO_3$ instead of water lowered the yield of **2a**. Changing the solvent to propionitrile also had a detrimental effect. Next, chiral Lewis bases other than BINAPO were tested for the reaction of **1a** (Fig. 1). Although (*R*,*R*)-DIOPO significantly improved the yield, the selectivity was disappointing. (*S*)-SEGPHOSO also enhanced the yield of **2a**, but with moderate enantioselectivity. Other types of phosphine oxides, (*S*)-PhanePhosO and (*S*,*S*)-DIOPO, could not improve both the activity and selectivity as well. With a chiral bisquinoline *N*,*N*′-dioxide, (*R*)-BQNO, the enantioselectivity for **2a** decreased, but that for **3a** increased, and reduction of BQNO with trichlorosilane was observed. Finally, the use of three equivalents of trichlorosilane with BINAPO catalyst and an extended reaction time proved to be the optimal conditions (Table 1, entry 2).

Under the conditions using (*S*)-BINAPO and trichlorosilane (3 equiv.), the reactions of *N*-benzoyl enones **1b** (R^1 = ^{i}Pr) and **1c** (R^1 = Ph) proceeded smoothly to give products **2b** and **2c** in good yields, and moderate enantioselectivities, respectively (Table 1, entries 3 and 4). On the other hand, an electron-donating R^2 group enhanced the formation rate of 4*H*-1,3-oxazines, as well as the enantioselectivity (entries 5 *vs.* 6). The coordination of the amide carbonyl to trichlorosilane may play an important role for both the rate- and enantio-determining steps. The reaction of enone **1f**, which has a similar electron-donating *N*-acetyl group, also rapidly afforded oxazine **2f** and keto amide **3f**, albeit with low selectivities (Table 1, entry 7). However, oxazine **2f** was unstable and readily hydrolyzed to **3f** during the workup.[8]

In almost all cases, the ee of **2** differed from that of **3**. Even the absolute configurations differed in many cases.[9] These observations imply that **2** is not generated from **3** *via* a simple dehydration (or formation of **3** from **2** *via* hydrolysis). It is plausible that 4*H*-1,3-oxazine **2** is generated *via* the conjugate reduction of *N*-acylated β-amino enone **1**, followed by cyclization of the resulting enolate and elimination of $HOSiCl_3$, whereas keto amide **3** originates from the 1,2-reduction of the *N*-acyl imine generated *via* equilibration of enamide **1**.[7] This mechanistic picture may explain the difference of the enantioselectivities between **2** and **3**. Further investigations are needed to clarify the detailed mechanism.



The synthetic utility of optically active 4*H*-1,3-oxazines **2** was preliminarily investigated. Treatment of **2e** (81% ee) with hydrobromic acid in ethanol gave β-amino ketone **3e** (eqn (1)). Pd/C-catalyzed hydrogenation of **2e** caused cleavage of the C–O bond of the oxazine to give saturated amide **4e** (eqn (2)).[10] On the other hand, oxidation of **2e** by bromine and subsequent treatment with silica gel generated 4,5-dihydro-oxazole **5e** (eqn (3)).[11] All these transformations proceeded without losing optical purity. The absolute configuration of **2e** was *R*, which was determined by transforming hydrogenated product **4e** into the known primary amine, (*R*)-4-phenylbutan-2-amine.[9]

In summary, we are the first to demonstrate that chiral Lewis bases catalyze the enantioselective reductive cyclization of *N*-acylated β-amino enones with trichlorosilane to afford optically active 4*H*-1,3-oxazines. In this reaction, trichlorosilane acts not only as a reductant, but also as a dehydrating agent. 4*H*-1,3-Oxazines can be converted *via* a variety of conditions to other chiral compounds without racemization. Further investigations to elucidate the reaction mechanism, synthetic utility and biological activity of chiral 4*H*-1,3-oxazines are currently in progress.

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8 The formation of oxazine **2f** was confirmed by checking the acidic aqueous extract by ^{1}H NMR analysis. However, **2f** was readily hydrolyzed to **3f** upon the addition of saturated aq. $NaHCO_3$. For details, see the ESI†.

9 The absolute configurations of **2c** and **2e** were assigned based on their transformations to known compounds (see the ESI†). Those of **2a**, **2b**, **2d** and **2f** were tentatively assigned by analogy. Because oxazine **2** is readily hydrolyzed to corresponding keto amide **3** without racemization (see eqn (1)), their configurations can be compared easily.

10 It has been reported that the PtO_2-catalyzed hydrogenation of racemic 4*H*-1,3-oxazines provides similar cleaved products, see: ref. 3*b*.

11 Formation of the corresponding *N*-acylated α-bromo-β-amino ketone followed by cyclization is assumed.