Asymmetric Henry Reactions of Aldehydes Using Chiral Biaryl-Based Bis(thiourea) Organocatalysts

Yuki Nakayama,[1] Yusaku Hidaka, Katsuji Ito*

Department of Chemistry, Fukuoka University of Education, Akama, Munakata, Fukuoka 811-4192, Japan
Fax +81(940)351711; E-mail: itokat@fukuoka-edu.ac.jp

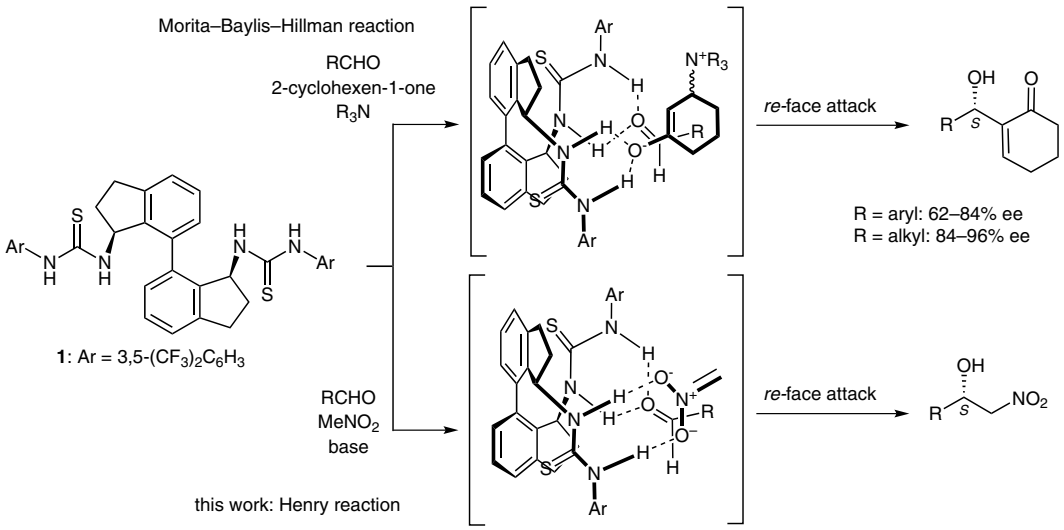
Received: 23.01.2013; Accepted after revision: 28.02.2013

Abstract: Biaryl-based bis(thiourea) was found to be an efficient organocatalyst for the asymmetric Henry reaction. High enantioselectivity of up to 93% ee was obtained for the reaction of nitromethane with aryl aldehydes when the combination of *N*,*O*-bis(trimethylsilyl)trifluoroacetoamide (BSTFA) with a catalytic amount of potassium acetate was used as the base.

Key words: asymmetric catalysis, bis(thiourea), Henry reaction, nucleophilic addition, enantioselectivity

The Henry (or nitroaldol) reaction is one of the most useful carbon–carbon bond-forming reactions because the reaction proceeds smoothly with high atom efficiency under mild conditions to yield β-nitro alcohols, which are key building blocks. In the field of organic synthesis, the asymmetric version of the Henry reaction has therefore received considerable interest.[2] In 1992, Shibasaki et al. reported the first example of a catalytic asymmetric Henry reaction, which used a chiral La–BINOL catalyst.[3] Subsequently, various chiral metal complexes have been extensively evaluated as catalysts.[4] In parallel with these approaches, methods using organocatalysts have also been developed. In 1994, Nájera et al. reported the first organocatalytic asymmetric Henry reaction using a chiral guanidine catalyst; however, only moderate enantioselectivity of 54% ee was obtained.[5] Ooi and Maruoka et al. reported that a Henry reaction of aldehydes with silyl nitronates that used chiral quaternary ammonium bifluorides was highly enantioselective.[6] Significant progress in the development of the asymmetric direct Henry reaction using organocatalyst was made with the introduction of Nagasawa's guanidine–thiourea bifunctional organocatalyst (up to 92% ee).[7] Other organocatalysts, including cinchona alkaloid based aminothioureas,[8] axially chiral bisarylthioureas,[9] axially chiral guanidines,[10] tetraaminophosphonium salts,[11] and polymeric cinchona alkaloids,[12] have all exhibited good to high enantioselectivities in reactions of aldehydes with nitromethane or nitroethane. Quite recently, Hong et al. developed [(bisurea-salen)Co] complexes, which are combined metallic and organocatalysts, for the asymmetric Henry reaction. These catalysts led to high enantioselectivities in reactions of both aliphatic and aromatic aldehydes.[13]

To achieve high enantioselectivity in the Henry reaction, the aldehyde and nitronate ion should both be captured in an appropriate chiral environment on the catalyst. Previously, we reported that the newly designed biaryl-based bis(thiourea) **1** is an effective organocatalyst for the asymmetric Morita–Baylis–Hillman reaction.[14] This reaction



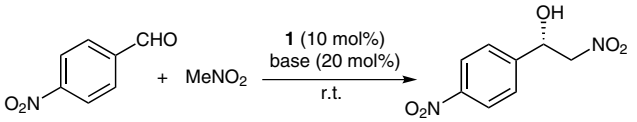
Scheme 1

SYNLETT 2013, 24, 0883–0885
Advanced online publication: 11.03.2013
DOI: 10.1055/s-0032-1318490; Art ID: ST-2013-U0077-L

was thought to proceed through a transition-state model as described in Scheme 1: two thiourea groups capture the carbonyl group of aldehyde and enolate. Therefore, it was expected that the Henry reaction would also proceed efficiently through the capture of both the aldehyde and nitronate ion by the two thiourea groups. To examine this possibility, we examined the asymmetric Henry reaction of aldehydes using bis(thiourea) **1**.

We first examined the reaction of 4-nitrobenzaldehyde with nitromethane in tetrahydrofuran (THF) performed at room temperature in the presence of a base (20 mol%) and catalyst **1** (10 mol%, Table 1). Both the reaction rate and enantioselectivity were largely dependent on the type of base. The reaction proceeded smoothly with 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base; however, the reaction yielded low enantioselectivity (Table 1, entry 1). Other tertiary amines, including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), *i*-Pr_2NEt, and 4-(dimethylamino)pyridine (DMAP), also resulted in low enantioselectivities (Table 1, entries 2–4).

Table 1 Asymmetric Henry Reaction of 4-Nitrobenzaldehyde and Nitromethane Using **1** as the Catalyst[a]



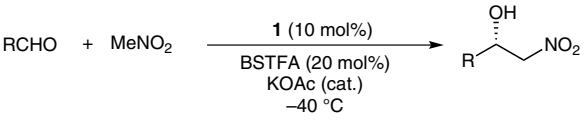
Entry	Base	Solvent	Time (h)	Yield (%)	ee (%)[b]
1	DABCO	THF	2	69	29
2	DBU	THF	1	69	2
3	*i*-Pr_2NEt	THF	1	95	20
4	DMAP	THF	0.5	79	18
5	imidazole	THF	16	98	68
6	imidazole	DMF	12	100	69
7[c]	BSA	DMF	3.5	91	68
8[c]	BSTFA	DMF	0.25	92	75
9[c,d]	BSTFA	DMF	11	82	88
10[c,e]	BSTFA	DMF	23	91	89

[a] All reactions were carried out at r.t. with molar ratios of aldehyde/nitromethane/**1**/base = 1:10:0.1:0.2, unless otherwise indicated.
[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AD-H; hexane–*i*-PrOH = 70:30).
[c] Catalytic amount of KOAc was added.
[d] Reaction was performed at –20 °C.
[e] Reaction was performed at –40 °C.

Enantioselectivity was improved to 68% ee when imidazole was used as a base, though the reaction rate was decreased (Table 1, entry 5). However, the reaction rate was improved to some extent by the change of solvent to DMF (Table 1, entry 6). The results of reactions in less polar solvents were unsatisfactory (toluene: 96 h, 13% yield, 52% ee; dichloromethane: 96 h, 26% yield, 68% ee). This may be partially due to the low solubility of bis(thiourea) **1** in less polar solvent. Fortunately, we found that the combination of *N*,*O*-bis(trimethylsilyl)acetoamide (BSA) with a catalytic amount of potassium acetate, which is a widely used base for palladium-catalyzed allylic substitutions,[15] led to a greatly increased reaction rate without a decrease in enantioselectivity (Table 1, entry 7). The reaction rate was further increased by using *N*,*O*-bis(trimethylsilyl)trifluoroacetoamide (BSTFA)[16] (Table 1, entry 8), which allowed the reaction to be carried out at low temperatures. As expected, enantioselectivity was increased with decreased reaction temperatures. A high enantioselectivity of 89% ee was obtained when the reaction was carried out at –40 °C (Table 1, entry 10).[17,18]

Under the optimized reaction conditions, we next examined asymmetric Henry reactions of several other aldehydes (Table 2).[19] A similarly high enantioselectivity of 92% ee was obtained for the reaction of 4-chlorobenzaldehyde, although the reaction proceeded somewhat slowly (Table 2, entry 1). The reactions of benzaldehyde and aryl aldehydes bearing an electron-donating group also exhibited high enantioselectivities (88–92% ee), but proceeded slowly and were not completed after 96 hours (Table 2, entries 2–4). On the other hand, the reactions of 2-naphthaldehyde and 4-biphenylcarboxaldehyde were completed within 47 hours and yielded the corresponding products with high enantioselectivities (Table 2, entries 5 and 6). In contrast, reactions of aliphatic aldehydes proceeded smoothly; however, their enantioselectivities were moderate (Table 2, entries 7 and 8).

Table 2 Asymmetric Henry Reaction of Aldehydes and Nitromethane Using **1** as the Catalyst[a]



Entry	R in RCHO	Time (h)	Yield (%)	ee (%)[b]
1	4-ClC_6H_4	96	70	92
2	Ph	96	50	92
3	4-MeC_6H_4	96	51	88
4	4-$MeOC_6H_4$	96	47	91
5	2-naphthyl	47	76	93
6	4-PhC_6H_4	47	70	91
7	*c*-Hex	19	99	58
8	$PhCH_2CH_2$	96	85	64

[a] All reactions were carried out at –40 °C with molar ratios of aldehyde/nitromethane/**1**/BSTFA = 1:10:0.1:0.2, unless otherwise indicated.
[b] Determined by HPLC analysis using chiral stationary-phase column according to the literature.[4b,g,j,9]

The absolute configuration of each product was determined to be *S*.[20] The observed stereochemistry was consistent with the postulated transition-state model depicted in Scheme 1, in which the *re* face of the aldehyde was preferentially attacked by the nitronate ion.[21]

In conclusion, we have demonstrated that biaryl-based bis(thiourea) **1** is an efficient chiral organocatalyst for the asymmetric Henry reaction. Further studies to expand the substrate scope and elucidate the reaction mechanism are under way in our laboratory.

Acknowledgment

We would like to thank Dr. Hiroshi Furuno, Institute for Materials Chemistry and Engineering (IMCE), Kyushu University, for the measurement of HRMS spectra and X-ray crystal structure analysis. We would also like to thank Ms. Keiko Ideta, Ms. Yasuko Tanaka, and Mr. Taisuke Matsumoto (Evaluation Center of Materials Properties and Function, IMCE, Kyushu University) for the measurement of NMR and HRMS spectra and X-ray analysis. This work was partially supported by JSPS KAKENHI Grant Number 24650532 and by the Cooperative Research Program of the 'Network Joint Research Center for Materials and Devices (IMCE, Kyushu University)'.

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(17) **Typical Experimental Procedure is Exemplified by Henry Reaction of 4-Nitrobenzaldehyde with Nitromethane**
Catalyst **1** (8.1 mg, 10.0 μmol) was placed in microtube under nitrogen and to this tube was added BSTFA (5.5 μL, 20.0 μmol) in DMF (100 μL), a catalytic amount of KOAc (0.4–0.5 mg, 4.1–5.1 μmol), and 4-nitrobenzaldehyde (16.1 mg, 0.1 mmol). After the mixture was cooled to –40 °C, $MeNO_2$ (55 μL, 1.0 mmol) was added at that temperature. After being stirred for 23 h at –40 °C, the mixture was quenched with H_2O and extracted with EtOAc. The organic extract was dried over anhyd $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane–Et_2O = 6:4) gave the desired product (19.3 mg, 91%). The ee of the product was determined to be 91% by HPLC using chiral stationary-phase column as described in the footnote of Table 1.

(18) Time-course studies suggested that the retro process is not involved in the reaction (3 h: 15% yield, 89% ee, 6 h: 35% yield, 88% ee, 12 h: 47% yield, 88% ee, 24 h: 90% yield, 89% ee). For the retro process in the asymmetric Henry reaction using organocatalyst, see ref. 7b.

(19) We also examined the reaction of aldehydes and $EtNO_2$, but the reaction did not proceed.

(20) Absolute configuration of all nitro alcohols were determined by comparison of elution order of HPLC and specific rotation with the reported value.[4b,g,j,9]

(21) (a) At the moment, we have no evidence that the nitronate anion is generated under the optimized conditions. However, we believe that the nitronate anion from $MeNO_2$ (pK_a = 10.2) is generated, because the imidate anion generated from BSA or BSTFA and KOAc can deprotonate dimethyl malonate (pK_a = 13). (b) For a review on the use of BSA in organic synthesis, see: El Gihani, M. T.; Heaney, H. *Synthesis* **1998**, 357.