Pergamon

Tetrahedron 57 (2001) 9309–9315

TETRAHEDRON

3-Acyl-2-(*N*-cyanoimino)oxazolidine derivative, a new asymmetric acylating agent for racemic secondary alkyl amines

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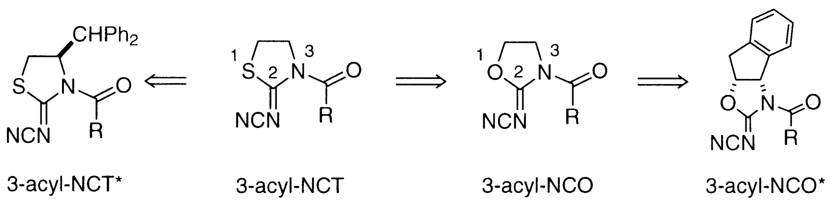
Received 29 June 2001; accepted 21 September 2001

Abstract—A 3-acyl-2-(*N*-cyanoimino)oxazolidine derivative was found to serve as an enantioselective acylating agent for *sec*-alkyl amines. These reagents differentiate the enantiomers of 1-phenylethylamine derivatives up to 85% ee, and the recovered chiral auxiliary is reusable.

1. Introduction

Optical resolution of racemic amines is a challenge in the field of recent organic chemistry, since the resulting chiral amines are useful chiral building blocks for diverse naturally occurring and synthetic molecules. Although enzymatic optical resolution has been well established,[1] the corresponding non-enzymatic methods regularly exhibited poor selectivity;[2] however a few effective non-enzymatic methods have been reported very recently.[3] In 1998, the first enantioselective acetylation of racemic amines was reported by Murakami et al., but the selectivity was less than 50%.[3d] A high level of enantioselective acetylation was recently realized by Ie and Fu using an *N*-acetylated 4-pyrrolinopyridine derivative, which showed lower enantioselectivity for transfer of other acyl groups.[3b] Two asymmetric benzoylations of racemic amines were independently reported by Atkinson et al.[3c] and by us.[3a] Atkinson's reagent was the first to differentiate the secondary amine with very high enantioselectivity. However, the application was limited to 2-methylpiperidine. A chiral 3-acyl-4-diphenylmethyl-2-(*N*-cyanoimino)thiazolidine (3-acyl-NCT*) recently developed by us is an asymmetric acylating reagent, which differentiated racemic *sec*-alkyl amines with moderate to good selectivity. In this reagent, the 2-(*N*-cyanoimino)thiazolidine moiety works not only as a leaving group but also as a recoverable chiral auxiliary. The strong electron-withdrawing ability of the *N*-cyanoimino group at C-2 activates the *N*(3)-acyl group transfer reaction. However, it has not been ascertained whether the sulfur atom in the thiazolidine ring is essential for the activation. We were interested in the participation of this part in achieving the acyl transfer reaction. Furthermore, if replacement of the sulfur atom with oxygen or nitrogen does not affect the ability for the acyl transfer reaction, a variety of chiral amino alcohols and ethylenediamines will serve as the material of new asymmetric acylating reagents.

In this paper, we describe the development of a new (*N*-cyanoimino)oxazolidine-type asymmetric acylating agent and its application to the kinetic resolution of *sec*-alkyl amines (Scheme 1).



Scheme 1.

Keywords: asymmetric reactions; resolution; acylation; amines.

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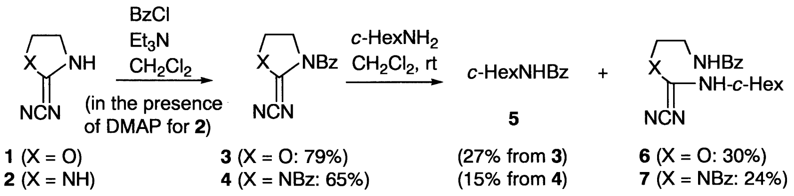
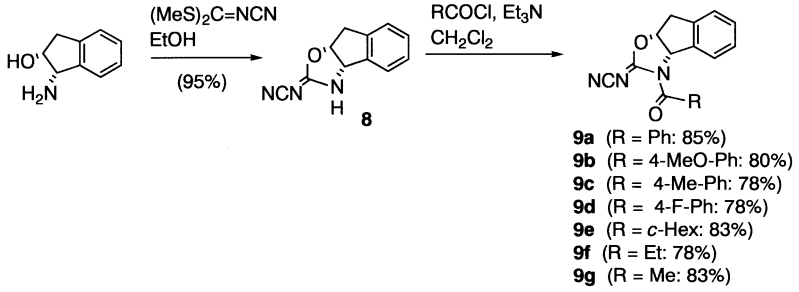
PII: S0040-4020(01)00933-4



Scheme 2.



Scheme 3.

2. Results and discussion

2.1. Acyl transfer reaction of 3-benzoyl-2-(*N*-cyanoimino)oxazolidine (3-benzoyl-NCO) and 1,3-dibenzoyl-2-(*N*-cyanoimino)imidazolidine (1,3-dibenzoyl-NCI) with cyclohexylamine

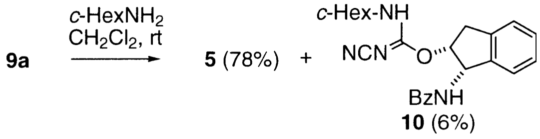
Benzoylation of known 2-(*N*-cyanoimino)oxazolidine **1** (NCO)[4] and 2-(*N*-cyanoimino)imidazolidine **2** (NCI)[5] easily affords 3-benzoyl-NCO **3** and 1,3-dibenzoyl-NCI **4** in 79 and 65% yields, respectively. Acylation of cyclohexylamine using **3** and **4** afforded *N*-cyclohexyl benzamide **5**[6] only in 27 and 15% yields, respectively. A considerable amount of the ring-aminolysis products **6** (30%) and **7** (24%) was formed (Scheme 2). This regioselectivity is in sharp contrast to that of 3-acyl-NCT,[7] which reacts at the carbonyl group exclusively. We assumed that the increased reactivity at the C_2-position of **3** and **4** results from higher electronegativity of oxygen and nitrogen than that of sulfur. Therefore, we had to circumvent the instability of the hetrocyclic rings to amines in order to develop these chiral analogs as acylating agents.

2.2. Asymmetric acylation using chiral 3-acyl-2-(*N*-cyanoimino)oxazolidine derivatives

Based on a preliminary experiment, we designed a chiral 2-(*N*-cyanoimino)oxazolidine derivative (NCO*) **8**. We expected that the oxazolidine ring involved in the fused ring system should be stabilized toward aminolysis, since the suitably oriented amino alcohol moiety would suppress ring-opening by the attack of amines. The chiral NCO* **8** was synthesized from commercially available (1*S*,2*R*)-1-amino-2-indanol and *S*,*S*′-dimethyl *N*-cyanodithioiminocarbonate in 95% yield. Then, the resulting NCO* **8** was subjected to benzoylation with BzCl and Et_3N in CH_2Cl_2 to give **9a** in 85% yield. In a similar manner, various 3-acyl-NCO* derivatives **9b–g** were synthesized (Scheme 3).

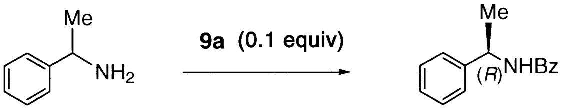
As we expected, the oxazolidine ring of **9a** having a fused ring structure is resistant to aminolysis by cyclohexylamine (1.1 equiv.) and the ratio of acylation was obviously increased comparing with monocyclic 3-benzoyl-NCO **3** (Scheme 4).

Next, we examined kinetic resolution of the racemic *sec*-alkyl amine using **9a** and 10 equiv. of (±)-1-phenylethylamine in MeCN[†] at various temperatures (Table 1). Both the yield and enantiomeric excess were increased with lowering



Scheme 4.

Table 1. Temperature effect on enantioselective benzoylation of (±)-1-phenylethylamine with **9a**



Entry	Temperature (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	rt	0.8	48	38
2	0	2.5	57	39
3	−20	6.5	65	48
4	−40	21	53	59
5	−70[c]	65	87	83

All reactions were carried out in MeCN unless otherwise stated.

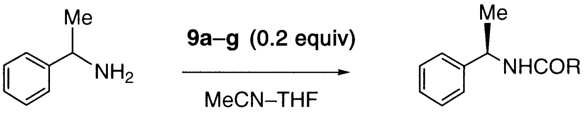
[a] Isolated yields based on **9a**.

[b] The enantiomeric excess and absolute configuration of the amide were determined by comparison of the specific rotation with the standard sample derived from the corresponding optically pure *sec*-alkyl amine.

[c] A 1:1 mixture of MeCN and CH_2Cl_2 was used as a solvent.

[†] In the previous work using 3-acyl-NCT*, we found that MeCN is the best solvent to achieve high enantioselectivity.[3a] In addition, this solvent is suitable to dissolve the polar 3-acyl-NCO* even at low temperature.

Table 2. Enantioselective acylation of (±)-1-phenylethylamine with various acylating agents **9a–g**



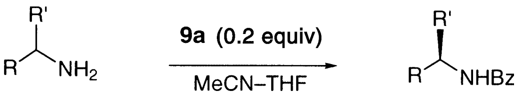
Entry	Reagent	R	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration
1	**9a**	Ph	−70	80	76	85	*R*
2	**9b**	4-MeO–Ph	−70	192	41	62	*R*
3	**9c**	4-Me–Ph	−70	192	87	78	*R*
4	**9d**	4-F–Ph	−70	108	90	74	*R*
5	**9a**	Ph	0	45	40	25	*R*
6	**9e**	*c*-Hex	0	48	43	10	*S*
7	**9f**	Et	0	21	70	17	*R*
8	**9g**	Me	0	53	68	64	*R*
9	**9g**	Me	−20	40	87	65	*R*
10	**9g**	Me	−40	168	trace	–	–

All reactions were carried out in a 1:1 mixture of MeCN–THF.

[a] Isolated yields based on 3-acyl-NCO* (**9**).

[b] The enantiomeric excess and absolute configuration of the amide were determined by comparison of the specific rotation with the standard sample derived from the corresponding optically pure *sec*-alkyl amine.

Table 3. Enantioselective benzoylation of racemic amines with **9a**



Entry	R	R′	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%)	Configuration
1	Ph	Me	−70	80	76	85	*R*
2	4-MeOPh	Me	−70	140	55	58[c]	*R*
3	2-MePh	Me	−70	288	42	16[c]	*R*
4	*c*-Hex	Me	−70	81	76	4	*R*
5	Ph	Et	−70	216	67	58[c]	*R*
6	Ph	Me	−70 to −40	38	53	40	*R*
7	Ph	CH_2OMOM	−70 to −40	252	49	65	*S*[e]

All the reactions were carried out in a 1:1 mixture of MeCN–THF.

[a] Isolated yields based on RCO–NCO* (**9**).

[b] The enantiomeric excess and absolute configuration of the amide were determined by comparison of the specific rotation with the standard sample derived from the corresponding optically pure *sec*-alkyl amine.

[c] The enantiomeric excess and absolute configuration of the amide were determined by comparison of the specific rotation with the reported values.[8–10]

[d] Change of absolute configuration stems from the change of the priority substituent at the stereogenic center.

the reaction temperature. The selectivity reached 83% ee at −70°C, wherein CH_2Cl_2 was employed as a co-solvent to prevent the solvent from freezing. At this temperature, the aminolysis of the oxazolidine ring was not observed.

Then, reaction of various 3-acyl-NCO*s **9a–g** with (±)-1-phenylethylamine was examined (Table 2). 5 equiv. of the racemic amine were used in a mixture of MeCN–THF (1:1), since these reaction conditions afforded higher recovery of NCO* than the conditions shown in Table 1 (the racemic amine (10 equiv.), MeCN–CH_2Cl_2 (1:1)). In the reaction of **9a** with (±)-1-phenylethylamine, asymmetric acylation proceeds smoothly at −70°C to give the benzoylated (*R*)-amine with 85% ee along with the recovered chiral NCO* **8** (95%), which was easily separated by column chromatography for reuse.[‡] Acyl transfer of 3-aroyl-NCO*s **9c–d** also proceeded at −70°C, but the yield of **9b** was low, presumably due to low solubility of **9b** in the solvent. The substituent on the phenyl group does not show remarkable effects on either the reactivity or the selectivity (entries 1–4). On the other hand, reactivity of the 3-alkylcarbonyl-NCO*s **9e–g** was lower than that of the 3-aroyl-NCO*s. Therefore, these reactions were conducted at 0°C. The selectivity decreased with the bulkiness of the alkyl group (entries 5–7). Interestingly, the 3-acetyl-NCO* **9g** showed higher selectivity at 0°C than that of the 3-benzoyl-NCO* **9a** (entry 8).[§] However, the selectivity was not increased by lowering the reaction temperature to −20°C (entry 9), and no reaction was observed at −40°C (entry 10). In all cases, except cyclohexylcarbonylation (entry 6), acylation of (*R*)-1-phenylethylamine proceeded mainly.

Next, kinetic resolution of other (±)-*sec*-alkyl amines using **9a** was examined (Table 3). The phenyl moiety in the amines is essential to achieve high selectivity (entries 1 and 2). Replacement of the phenyl group with a non-aromatic cyclohexyl group caused considerable decrease of selectivity (entry 4). The ee value was decreased in the

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[‡] The use of 2.5 equiv. of the racemic amine caused a considerable loss of the yield (43%) and ee (53% ee).

[§] Similar results were obtained in the case of 3-acetyl-NCT* derivative.[3a]

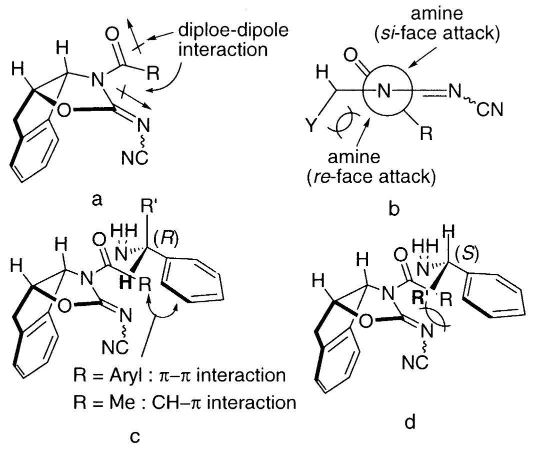

Figure 1. Plausible reaction mechanism of asymmetric benzoylation of (±)-phenylethylamine.

reaction with 1-(*o*-tolyl)ethylamine, in which the conformation of the aryl group is affected by the *o*-methyl group (entry 3). Replacement of the methyl group with an ethyl group decreased the reaction rate, but showed comparative selectivity (entry 5). Reaction of **9a** with the phenylglycinol *O*-methoxymethyl ether was sluggish at −70°C. However, the acylation proceeded at −40°C, giving higher ee than that of 1-phenylethylamine (entries 6 and 7).[¶]

The selectivity is speculated as follows. Stable conformation of the amide carbonyl group in the 3-benzoyl-NCO* **9a** would be depicted as Fig. 1a,b, in which the carbonyl group is oriented opposite to the *N*-cyanoimino group so as to minimize unfavorable dipole–dipole interaction and to avoid steric repulsion with the large indan ring (Y). In this conformation, the *re*-face of the carbonyl group is shielded by the large indan ring (Y). Therefore, approach of the amine would proceed mainly from the *si*-face. We have reported[3a] that attractive interaction between the benzoyl group in the acylating agent and the benzylamines seems to play an important role for differentiation of the enantiomeric isomers, that is, π–π interaction[11] for the chiral 3-aroyl-NCT and CH–π interaction[12] for that of the chiral 3-acetyl-NCT, respectively. The results obtained above indicate that the π–π or CH–π interaction would be similarly involved in the reaction of the 3-acyl-NCO*s as well as that of 3-acyl-NCT*s. That is, the racemic amines would approach the 3-aroyl-NCO* **9a–d** so as to overlap two phenyl groups by virtue of the π–π interaction (Fig. 1c,d). For the 3-acetyl-NCO* **9g**, CH–π interaction would attract the acetyl group and the phenyl group instead of the π–π interaction. Since the approach of the (*S*)-isomer suffers from larger steric repulsion between the R′ (Me, Et or CH_2OMOM) group and the 2-(*N*-cyanoimino)oxazolidine ring (Fig. 1d), the reaction of the (*R*)-isomer would be faster than that of the (*S*)-isomer.

3. Conclusion

In conclusion, we have developed new 2-(*N*-cyanoimino)oxazolidine-type asymmetric acylating agents for racemic *sec*-alkyl amines. 3-Benzoyl-NCO* **9a** is readily synthesized from a commercially available amino alcohol in two steps, and differentiates the enantiomeric isomers of the 1-phenylethylamine derivatives with considerably good enantioselectivity (up to 85% ee), and the resulting chiral auxiliary can be recovered and is reusable. Since the reagent **9a** shows opposite selectivity to that of the chiral NCT*, these reagents can be used complementarily.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured using a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 500 MHz with a JEOL JNM-GX500 spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ at 67.8 or 75 MHz with a JEOL JNM-EX270 spectrometer or a JEOL JMN-AL-300, respectively. All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value). IR spectra were measured with a Horiba FT-210 IR spectrometer. Mass spectra were taken with a Shimadzu QP-1000 mass spectrometer or a JMS-600 mass spectrometer. High resolution mass spectra were measured by a JEOL JMS-600H. Merck Kieselgel 60 was used as an adsorbent for column chromatography. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under N_2 atmosphere. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure.

4.1.1. 3-Benzoyl-2-(*N*-cyanoimino)oxazolidine (3). Benzoyl chloride (0.14 ml, 1.20 mmol) was added to a mixture of **1** (111 mg, 1.00 mmol) and Et_3N (0.16 ml, 1.24 mmol) in CH_2Cl_2 (3 ml) with stirring at 0°C under N_2. The stirring was continued at rt for 13 h. The reaction was quenched with 10% HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine prior to drying and solvent evaporation. The residue was recrystallized with AcOEt to give **3** (169 mg, 79%) as a colorless powder. Mp 179.5–180.0°C (AcOEt). ^{1}H NMR δ: 4.17 (t, J=7.9 Hz, 2H, CH_2N), 4.49 (t, J=7.9 Hz, 2H, CH_2O), 7.42–7.69 (m, 5H, Ar–H). ^{13}C NMR (d^6-DMSO) δ: 46.4, 67.9, 112.8, 127.9 (2C), 128.8 (2C), 132.3, 133.0, 161.9, 167.9. IR (KBr) 2200 (CN), 1670 (C=O) cm^{-1}. MS m/z (%): 215 (M$^+$, 19.4), 105 (100). HRMS (EI) Calcd for $C_{11}H_9N_3O_2$ (M$^+$): 215.0695. Found: 215.0693.

4.1.2. 1,3-Dibenzoyl-2-(*N*-cyanoimino)imidazolidine (4). Benzoyl chloride (0.22 ml, 2.00 mmol) was added to a mixture of **2** (110 mg, 1.00 mmol), Et_3N (0.26 ml, 2.00 mmol), DMAP (122 ml, 1.00 mmol) in CH_2Cl_2 (2 ml) with stirring at 0°C under N_2. The stirring was continued at rt for 1 d. The reaction was quenched with 10% HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine prior to drying and solvent evaporation. The residual solid was washed with MeOH to give **4** (206 mg, 65%) as a colorless powder. Mp 170.0–170.5°C

[¶] Kinetic resolution of 2-methylpiperidine was attempted, but failed due to low reactivity of **9a** with the *sec*-amine even at rt.

(AcOEt). ^{1}H NMR δ: 4.12 (s, 4H, CH$_2$N×2), 7.45–7.72 (m, 10H, Ar–H). ^{13}C NMR δ: 46.0 (2C), 111.2, 128.5 (4C), 129.1 (4C), 132.4 (2C), 133.2 (2C), 154.5, 168.7 (2C). IR (KBr) 2186 (CN), 1689 (C=O) cm^{-1}. MS *m/z* (%): 318 (M$^+$, 25.1), 105 (100). HRMS (EI) Calcd for $C_{18}H_{14}N_4O_2$ (M$^+$): 318.1116. Found: 318.1116.

4.1.3. *N*-[2-[(*N*-Cyanoimino)(cyclohexylamino)methoxy]-ethyl]benzamide (6). A mixture of **3** (108 mg, 0.50 mmol) and cyclohexylamine (0.050 ml, 0.55 mmol) in CH_2Cl_2 (3 ml) was stirred at rt for 5 d. The resulting precipitate was filtered off and the filtrate was washed with 1N NaOH, 5% HCl, and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel (CHCl$_3$–MeOH=50:1) to give **5** (28 mg, 27%) along with **6** (48 mg, 30%) each as a colorless powder. The data of **5**[6] is comparable to that reported. **6**: mp 164.5–165.0°C (AcOEt). ^{1}H NMR δ: 1.12–1.60 (m, 10H, cyclohexyl), 3.49 (d, *J*=7.9 Hz, 2H, CH$_2$N), 3.87 (d, *J*=7.9 Hz, 2H, CH$_2$O), 4.09 (m, 1H, cyclohexyl), 7.29–7.55 (m, 6H, CONH and Ar–H), 9.06 (d, *J*=7.9 Hz, 1H, cyclohexyl-N*H*). ^{13}C NMR δ: 24.6 (2C), 25.0 (2C), 39.1, 51.8 (2C), 67.5, 115.7, 126.9 (2C), 128.5 (2C), 131.7, 133.9, 167.6, 165.5. IR (KBr) 3317 (NH), 3284 (NH), 2200 (CN), 1641 (C=O) cm^{-1}. MS *m/z* (%): 314 (M$^+$, 0.5), 147 (100). HRMS (EI) Calcd for $C_{17}H_{22}N_4O_2$ (M$^+$): 314.1742. Found: 314.1743.

4.1.4. *N*,*N*′-Dibenzoyl-*N*-[(*N*-cyanoimino)(cyclohexyl-amino)methyl]ethylenediamine (7). A mixture of **4** (95 mg, 0.30 mmol) and cyclohexylamine (0.030 ml, 0.33 mmol) in CH_2Cl_2 (3 ml) was stirred at rt for 5 d. The resulting precipitate was filtered off and the filtrate was washed with 1N NaOH, 5% HCl, and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel (AcOEt) to give **5** (9 mg, 15%) along with **7** (30 mg, 24%) each as a colorless powder. **7**: mp 195.0–196.0°C (AcOEt). ^{1}H NMR δ: 1.13–1.70 (m, 10H, cyclohexyl), 3.48 (dd, *J*=7.9 Hz, 2H, CH$_2$NH), 3.75 (m, 2H, CH$_2$N), 4.09 (m, 1H, cyclohexyl), 7.24–7.73 (m, 11H, CONH and Ar–H), 9.06 (d, *J*=7.9 Hz, 1H, cyclohexyl-NH). ^{13}C NMR δ: 24.1 (2C), 25.0, 30.8, 39.1, 45.6, 52.2, 115.5, 126.8 (2C), 127.0 (2C), 128.3 (2C), 128.4 (2C), 131.2, 131.7 (2C), 133.1, 134.3, 159.1, 169.7, 169.9. IR (KBr) 3203 (NH), 2183 (CN), 1676 (C=O), 1599 (C=O) cm^{-1}. MS *m/z* (%): 303 (M$^+$, 5.5), 105 (100). HRMS (EI) Calcd for $C_{25}H_{29}N_5O_2$ (M$^+$): 431.2321. Found: 431.2320.

4.1.5. [(3a*S*,8a*R*)-3,3a,8,8a-Tetrahydro-2*H*-indeno[1,2-*d*]-[1,3]oxazol-2-ylidene]cyanamide (8). A solution of *S*,*S*′-dimethyl *N*-cyanodithioiminocarbonate (2.92 g, 20.0 mmol) in EtOH (60 ml) was added to a solution of (1*S*,2*R*)-*cis*-1-amino-2-indanol (3.28 g, 22.0 mmol) in EtOH (40 ml) with stirring at rt and the whole was refluxed over night. The solvent was evaporated and the residual solid was washed with EtOH and dried to give **8** as a pale yellow powder (3.78 g, 95%). Mp 212.0–213.0°C (EtOH). $[\alpha]_D^{27}=-190.2$ (*c* 1.00, CHCl$_3$). ^{1}H NMR δ: 3.45 (d, *J*=5.5 Hz, 2H, CH$_2$), 5.42 (d, *J*=7.3 Hz, 1H, CHN), 5.63 (t, *J*=4.9 Hz, 1H, CHO), 7.28–7.47 (m, 5H, NH and Ar–H). ^{13}C NMR δ: 37.7, 63.2, 85.5, 115.5, 125.1, 125.5, 127.7, 129.3, 139.6, 139.9, 164.9. IR (KBr) 3138 (NH), 2193 (CN) cm^{-1}. MS *m/z* (%): 199 (M$^+$, 100). Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.26; H, 4.68; N, 20.99.

4.2. General procedure of acylation of 8

Benzoyl chloride (0.060 ml, 0.55 mmol) was added to a mixture of **8** (100 mg, 0.50 mmol) and Et$_3$N (0.070 ml, 0.55 mmol) in CH_2Cl_2 (1 ml) with stirring at 0°C under N$_2$. The stirring was continued at rt for 2 d. The reaction was quenched with 10% HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel.

4.2.1. [(3a*S*,8a*R*)-3-Benzoyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9a). Pale yellow powder (85%). Mp 206.0–207.0°C (AcOEt). $[\alpha]_D^{27}=-15.0$ (*c* 1.00, CHCl$_3$). ^{1}H NMR δ: 3.53 (dd, *J*=6.1, 5.4 Hz, 1H, CH$_2$), 3.59 (d, *J*=6.1 Hz, 1H, CH$_2$), 5.66 (td, *J*=7.3, 1.8 Hz, 1H, CHO), 6.27 (d, *J*=6.7 Hz, 1H, CHN), 7.32–7.76 (m, 9H, Ar–H). ^{13}C NMR δ: 37.5, 66.5, 83.8, 112.1, 125.4, 126.9, 128.0 (2C), 128.5 (2C), 128.8, 130.5, 132.2, 132.7, 137.3, 139.1, 160.1, 168.4. IR (KBr) 2195 (CN), 1659 (C=O) cm^{-1}. MS *m/z* (%): 303 (M$^+$, 3.6), 105 (100). Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 71.30; H, 4.49; N, 13.81.

4.2.2. [(3a*S*,8a*R*)-3-(4-Methoxybenzoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9b). Colorless powder (80%). Mp 195.0–196.0°C (AcOEt). $[\alpha]_D^{27}=-12.2$ (*c* 0.50, CHCl$_3$). ^{1}H NMR δ: 3.53 (dd, *J*=6.1, 5.5 Hz, 1H, CH$_2$), 3.59 (d, *J*=6.1 Hz, 1H, CH$_2$), 3.87 (s, 3H, OCH$_3$), 5.64 (td, *J*=7.9, 1.8 Hz, 1H, CHO), 6.25 (d, *J*=7.3 Hz, 1H, CHN), 6.89–7.66 (m, 8H, Ar–H). ^{13}C NMR δ: 37.8, 55.6, 66.6, 83.6, 113.4, 123.8, 125.4 (2C), 126.8, 128.4, 130.4 (2C), 131.8, 137.3 (2C), 139.0, 163.6 (3C). IR (KBr) 2208 (CN), 1647 (C=O) cm^{-1}. MS *m/z* (%): 333 (M$^+$, 2.2), 135 (100). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.27; H, 4.72; N, 12.46.

4.2.3. [(3a*S*,8a*R*)-3-(4-Methylbenzoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9c). Colorless powder (78%). Mp 216.5–217.0°C (AcOEt). $[\alpha]_D^{23}=-15.2$ (*c* 0.93, CHCl$_3$). ^{1}H NMR δ: 2.42 (s, 3H, CH$_3$), 3.48 (dd, *J*=6.1, 5.5 Hz, 1H, CH$_2$), 3.55 (d, *J*=6.1 Hz, 1H, CH$_2$), 5.63 (td, *J*=7.9, 1.8 Hz, 1H, CHO), 6.25 (d, *J*=7.3 Hz, 1H, CHN), 6.89–7.66 (m, 8H, Ar–H). ^{13}C NMR δ: 21.7, 37.6, 66.6, 83.7, 112.1, 125.3, 126.8, 128.4, 128.6 (2C), 129.1 (2C), 130.3 (2C), 137.3, 139.0, 143.7, 160.0, 168.1. IR (KBr) 2219 (CN), 1652 (C=O) cm^{-1}. MS *m/z* (%): 317 (M$^+$, 30.4), 119 (100). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.65; H, 4.98; N, 13.17.

4.2.4. [(3a*S*,8a*R*)-3-(4-Fluorobenzoyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9d). Colorless powder (78%). Mp 146.0–147.0°C (AcOEt). $[\alpha]_D^{22}=-4.15$ (*c* 1.25, CHCl$_3$). ^{1}H NMR δ: 3.53 (dd, *J*=6.7, 4.9 Hz, 1H, CH$_2$), 3.59 (d, *J*=6.7 Hz, 1H, CH$_2$), 5.65 (td, *J*=7.9, 2.4 Hz, 1H, CHO), 6.27 (d, *J*=6.7 Hz, 1H, CHN), 6.89–7.66 (m, 8H, Ar–H). ^{13}C NMR δ: 37.6, 66.5, 83.9, 111.9, 115.4, 125.4 (2C), 126.8, 128.4, 130.4 (2C), 131.8 (2C), 137.3, 139.0, 163.3, 167.0, 167.1. IR (KBr) 2208 (CN), 1645 (C═O) cm^{-1}. MS *m/z* (%): 321 (M$^+$, 3.0), 123 (100). HRMS (EI) Calcd for $C_{18}H_{12}N_3O_2F$ (M$^+$): 321.0913. Found: 321.0914.

4.2.5. (3a*S*,8a*R*)-3-Cyclohexylcarbonyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9e). Colorless powder (83%). Mp 161.5–162.5°C (AcOEt). $[\alpha]_D^{27}$=+47.1 (*c* 0.71, $CHCl_3$). ^{1}H NMR δ: 1.23–1.89 (m, 11H, cyclohexyl), 3.41 (dd, *J*=6.1, 5.5 Hz, 1H, ArCH_2), 3.51 (d, *J*=6.1 Hz, 1H, ArCH_2), 5.49 (t, *J*=6.7 Hz, 1H, CHO), 6.14 (d, *J*=6.7 Hz, 1H, CHN), 7.28–7.51 (m, 4H, Ar–H). ^{13}C NMR δ: 25.2, 25.6, 28.6, 29.2, 37.4, 42.5, 65.8, 83.3, 112.4, 123.8, 125.4, 126.7, 128.6, 130.4, 137.9, 138.9, 158.5, 175.8. IR (KBr) 2208 (CN), 1635 (C═O) cm^{-1}. MS *m/z* (%): 309 (M$^+$, 4.2), 83 (100). Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.83; H, 6.26; N, 13.50.

4.2.6. (3a*S*,8a*R*)-3-Propionyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9f). Colorless powder (78%). Mp 179.0–180.0°C (AcOEt). $[\alpha]_D^{26}$=+15.2 (*c* 0.91, $CHCl_3$). ^{1}H NMR δ: 1.20 (t, *J*=7.3 Hz, 3H, CH_2CH_3), 2.94 (q, *J*=7.3 Hz, 2H, CH_2CH_3), 3.42 (dd, *J*=6.1, 5.5 Hz, 1H, ArCH_2), 3.51 (d, *J*=6.1 Hz, 1H, ArCH_2), 5.53 (t, *J*=6.1 Hz, 1H, CHO), 6.14 (d, *J*=6.7 Hz, 1H, CHN), 7.27–7.59 (m, 4H, Ar–H). ^{13}C NMR δ: 8.2, 30.2, 37.4, 65.7, 83.6, 112.2, 125.3, 126.9, 128.4, 130.3, 137.7, 138.9, 160.1, 173.3. IR (KBr) 2212 (CN), 1713 (C═O) cm^{-1}. MS *m/z* (%): 255 (M$^+$, 32.7), 115 (100). HRMS (EI) Calcd for $C_{14}H_{13}N_3O_2$ (M$^+$): 255.1008. Found: 255.1006.

4.2.7. [(3a*S*,8a*R*)-3-Acetyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*][1,3]oxazol-2-ylidene]cyanamide (9g). Colorless powder (83%). Mp 207.0–208.0°C (AcOEt). $[\alpha]_D^{27}$=+48.5 (*c* 0.97, $CHCl_3$). ^{1}H NMR δ: 2.60 (s, 3H, CH_3), 3.43 (dd, *J*=6.1, 5.5 Hz, 1H, CH_2), 3.52 (d, *J*=6.1 Hz, 1H, CH_2), 5.53 (t, *J*=6.7 Hz, 1H, CHO), 6.13 (d, *J*=6.7 Hz, 1H, CHN), 7.27–7.60 (m, 4H, Ar–H). ^{13}C NMR δ: 24.8, 37.4, 65.6, 83.6, 112.0, 125.1, 126.8, 128.2, 130.1, 137.5, 138.8, 160.1, 169.0. IR (KBr) 2190 (CN), 1635 (C═O) cm^{-1}. MS *m/z* (%): 241 (M$^+$, 10.2), 199 (100). Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.57; H, 4.66; N, 17.32.

4.3. General procedure for asymmetric acylation of racemic *sec*-alkyl amines with the 3-acyl-NCO* 9a–e

A mixture of **9a** (60.0 mg, 0.20 mmol) and (±)-1-phenylethylamine (0.12 ml, 1.0 mmol) in a 1:1 mixture of MeCN–THF (2 ml) was stirred at −70°C for 80 h under N_2. The mixture was diluted with AcOEt and washed 10% HCl and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel (hexane–AcOEt=1:1) to give *N*-(1-phenylethyl)benzamide (35 mg, 76%, 85% ee) along with **8** (38 mg, 95%) each as a colorless powder.

4.3.1. (1*S*,2*R*)-1-Benzoylamino-2-[(cyanoimino)(cyclohexylamino)methoxy]-2,3-dihydro-1*H*-indene (10). Colorless powder (6%). Mp 212.0–213.0°C (AcOEt). $[\alpha]_D^{24}$=−108.9 (*c* 0.40, $CHCl_3$). ^{1}H NMR δ: 0.88–1.67 (m, 10H, cyclohexyl), 3.18 (dd, *J*=12.2, 2.4 Hz, 1H, ArCH_2), 3.36 (m, 1H, cyclohexyl), 3.38 (dd, *J*=12.2, 5.5 Hz, 1H, ArCH_2), 5.49 (d, *J*=6.7 Hz, 1H, cyclohexyl-N*H*), 5.69 (m, 1H, CHN), 5.86 (t, *J*=5.5 Hz, 1H, CHO), 6.33 (m, 1H, CONH), 7.29–7.95 (m, 9H, Ar–H). ^{13}C NMR δ: 24.4 (2C), 24.8 (2C), 32.7, 37.5, 51.6, 55.8, 80.2, 115.6, 124.1, 125.2, 126.9 (2C), 127.6, 128.7 (2C), 128.9, 132.0, 133.6, 139.1, 139.6, 162.6, 167.1. IR (KBr) 3365 (NH), 3265 (NH), 2202 (CN), 1643 (C═O) cm^{-1}. MS *m/z* (%): 402 (M$^+$, 0.8), 235 (100). HRMS (EI) Calcd for $C_{24}H_{26}N_4O_2$ (M$^+$): 402.2055. Found: 402.2054.

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