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Improved organocatalytic electrophilic α-cyanation of β-keto amides with 1-cyanato-4-nitrobenzene

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ABSTRACT

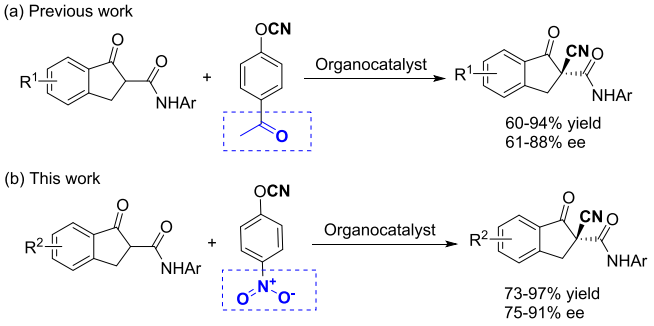
By using a readily accessible, new and safe cyano-transfer reagent, 1-cyanato-4-nitrobenzene, the enantioselectivity of the direct electrophilic α-cyanation of 1-indanone-derived β-keto amides was greatly improved as a result of an enhanced double-hydrogen bonding. Thus, in the presence of cinchonine as the bifunctional organocatalyst, a series of α-cyano β-keto amides were produced in excellent yields (73–97%) and good to high enantioselectivities (75–91% ee) under mild reaction conditions.

Introduction

Cyano-containing compounds, as the significant intermediates in organic synthesis, exist extensively nitriles in natural products and synthetic drugs due to the amazing bioactivities and diverse inter-conversion of functional groups.[1] Therefore, much attention has been paid to the development of efficient methods for their synthesis, such as nucleophilic substitution or addition with anionic cyanides, affording cyanohydrins[2] and aliphatic nitriles,[3] correspondingly. In the past decades, various cyanating reagents such as aryl cyanate,[4] 3-cyano-2-(*N*-cyanoimino)thiazolidine,[5] 2-cyanopyridazin-3(2*H*)-one,[6] and 1-cyanobenzotriazole[7] have been used in the electrophilic cyanation of β-keto carbonyl compounds. However, the synthetic applications are limited by the substrate scope and use of strong base.

In 2013,[8] Ibrahim and co-workers reported a simple, efficient, and high-yielding procedure for the electrophilic cyanation of 1,3-dicarbonyl compounds with TsCN in the presence of K_2CO_3 as the base. In 2015, we first revealed a new procedure to synthesize racemic α-nitriles from active hydrogen substitution with hypervalent iodinate cyanobenziodoxole (CBX) as the electrophile.[9] Accordingly, Waser reported the asymmetric version with moderate enantioselectivity with cinchona alkaloid catalysts.[10a] In the same year, Zheng documented the study with higher enantioselectivities by using a cinchonidine-derived phase transfer catalyst (PTC),[10b] in which the use of DMAP is crucial for the high enantioselectivity. In 2017, Feng and Liu reported the enantioselective α-cyanation of indan-1-one-derived β-keto esters and amides using a chiral *N*, *N*′-dioxide organocatalyst.[11] In these reactions, hypervalent iodine(III) reagents were used in common.[12,13]

Attributing to the good solubility and mild reactivity of aryl cyanate,[4,15,16] we succeeded in the enantioselective electrophilic α-cyanation reaction of β-keto esters and β-keto amides (**1**) by Lewis acid catalysis and organocatalysis with 4-acetylphenyl cyanate (**2g**).[14,17] Among these reactions, the ee for β-keto amides is a little bit low (Scheme 1a).[10,17] Moreover, compared with β-keto esters,[18] the α-functionalization of problematic β-keto amides has been much less investigated.[14,18–20] Herein, we reported the



Scheme 1. Asymmetric α-cyanation of β-keto amides.

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improved enantioselective α-cyanation reaction of β-keto amides (**1**) by using 1-cyanato-4-nitrobenzene (**2e**) bearing a nitro group with enhanced hydrogen bonding capability (Scheme 1b) rather than the previous **2g** with an acetyl group.

Results and discussion

Based on the preliminary work,[17] the reaction was carried out using 1-indanone-derived racemic β-ketoamide (**1a**) as the model substrate and natural cinchonine **C3** as the organocatalyst in the presence of 4 Å molecular sieves (MS) in CH_2Cl_2 at 0 °C under an argon atmosphere. As shown in Table 1, we first screened seven electrophilic cyano transfer reagents (**2a**–**g**). When 4-cyanatobenzaldehyde **2a** was employed, pleasantly the cyanated product **3a** was obtained in 84% yield and 60% ee whereas **2b**, **2c** and **2d** furnished the desired product with lower yields and ee values (entries 1–4). In terms of enantioselectivity, it was found 1-cyanato-4-nitrobenzene (**2e**) was the best electrophilic reagent (72% yield, 79% ee) in the model reaction (entry 5), while **2f** resulted in a significant reduction in enantioselectivity because of the steric hindrance of *ortho*-Me on the phenyl ring (entry 6). Notably, **2g** afforded cyano product **3a** with lower yield and enantioselectivity (entry 7).[17] It implies that the H-bond acceptor *para*-nitro group had stronger interaction than a *para*-carbonyl group, typically an acetyl, with the free C9-OH H-bonding donor, which may be responsible for the increased enantioselectivity.

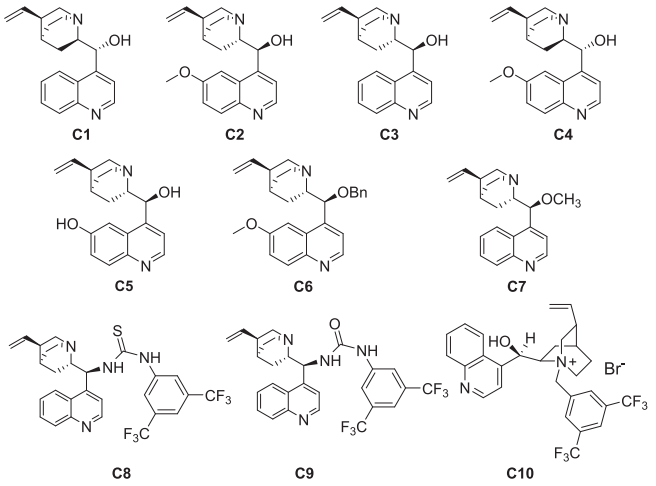
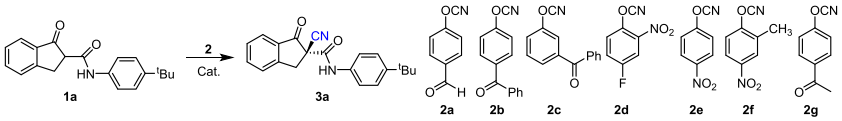


Fig. 1. Evaluated organocatalysts in this study.

Next, a small library of organocatalysts (Fig. 1) was evaluated for this reaction (Table 1, entries 8–16). Natural cinchonidine (**C1**) provided moderate 62% ee (Table 1, entry 8). Among other naturally accessible cinchona alkaloids such as quinidine (**C2**), cinchonine (**C3**) and quinine (**C4**), **C3** showed the most promising 79% ee (entry 5 *vs* entries 9 and 10). To elucidate the possible

Table 1
Establishment and optimization of the model reaction of **1a**.[a]



Entry	Cyano source	Cat. (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**2a**	C3 (20)	CH_2Cl_2	0	12	84	60
2	**2b**	C3 (20)	CH_2Cl_2	0	12	64	43
3	**2c**	C3 (20)	CH_2Cl_2	0	12	65	46
4	**2d**	C3 (20)	CH_2Cl_2	0	12	72	46
5	**2e**	C3 (20)	CH_2Cl_2	0	12	72	79
6	**2f**	C3 (20)	CH_2Cl_2	0	12	68	56
7	**2g**	C3 (20)	CH_2Cl_2	0	12	32	54
8	**2e**	C1 (20)	CH_2Cl_2	0	12	75	−62
9	**2e**	C2 (20)	CH_2Cl_2	0	12	48	−3
10	**2e**	C4 (20)	CH_2Cl_2	0	12	60	11
11	**2e**	C5 (20)	CH_2Cl_2	0	12	54	0
12	**2e**	C6 (20)	CH_2Cl_2	0	12	63	−8
13	**2e**	C7 (20)	CH_2Cl_2	0	12	68	16
14	**2e**	C8 (20)	CH_2Cl_2	0	12	57	4
15	**2e**	C9 (20)	CH_2Cl_2	0	12	69	0
16	**2e**	C10 (20)	CH_2Cl_2	0	12	66	7
17	**2e**	C3 (20)	$CHCl_3$	0	12	59	60
18	**2e**	C3 (20)	$ClCH_2CH_2Cl$	0	12	54	75
19	**2e**	C3 (20)	CH_3CHCl_2	0	12	69	68
20	**2e**	C3 (20)	THF	0	12	60	39
21	**2e**	C3 (20)	CH_3CN	0	12	57	29
22	**2e**	C3 (20)	Toluene	0	12	63	41
23	**2e**	C3 (20)	CH_2Cl_2	RT	12	62	65
24	**2e**	C3 (20)	CH_2Cl_2	−20	36	73	84
25	**2e**	C3 (20)	CH_2Cl_2	−40	36	97	91
26	**2e**	C3 (20)	CH_2Cl_2	−78	36	67	82
27[d]	**2e**	C3 (10)	CH_2Cl_2	−40	36	66	81
28[e]	**2e**	C3 (20)	CH_2Cl_2	−40	36	89	88
29[f]	**2e**	C3 (20)	CH_2Cl_2	−40	36	90	88

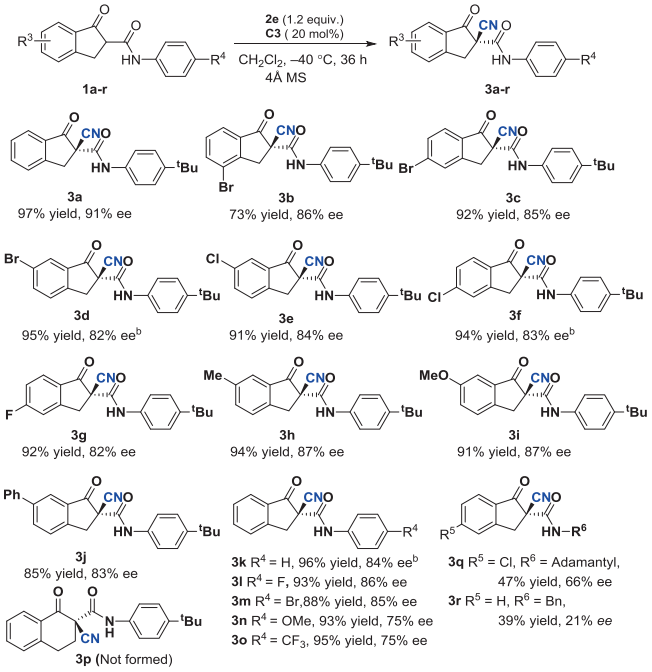
[a] Reaction conditions: **1a** (30.7 mg, 0.1 mmol), **2e** (19.7 mg, 0.12 mmol, 1.2 equiv.), cat. (0.02 mmol, 20 mol%), 4 Å MS (5 mg), solvent (1.0 mL), argon atmosphere.
[b] Isolated yield.
[c] Enantiomeric excess (ee) was determined by chiral HPLC analysis on Chiralpak AD-H.
[d] 10 mol% catalyst.
[e] 10 mg 4 Å MS.
[f] 2.5 mg 4 Å MS.

H-bonding donor role of C9-OH group in **C3**, two types of structural modifications were designed by either introduction of a second C6′-OH (**C5**) or protection of C9-OH with Bn (**C6**) and Me (**C7**). However, both the additional C6′-OH in **C5** and protected C9-OH in **C6** and **C7** gave inferior ee values (entry 11 *vs* 9 for **C5**, entry 12 *vs* 8 for **C6**, entry 13 *vs* 5 for **C7**, respectively). It indicates the H-bond donor C9-OH predominates the stereochemistry outcome. In addition, other derivatives like thiourea **C8**, urea **C9** and PTC **C10** were also investigated but leading to low ee values (entries 14–16).

Subsequent screening of solvent revealed CH_2Cl_2 was still the best solvent with respect to both yield and enantioselectivity (Table 1, entry 5 *vs* entries 17–22). However, other chlorinated alkane solvents eroded the enantioselectivity to different extents (entries 17 and 19) while polar CH_3CN (entry 20) and less polar toluene and THF (entries 21–22) resulted in a sharp decrease in the enantioselectivity of **3a**.

To further optimize the results, other reaction parameters such as the amount of catalyst loading, additives, and reaction temperature were investigated. Temperature was found to have a significant influence on the enantioselectivity. Higher reaction temperature other than 0 °C decreased the ee value (Table 1, entry 23 *vs* entry 5). On the other hand, lowering the temperature from 0 °C to −20 °C and −40 °C the enantioselectivity was increased stepwise to 91% ee (entry 25 *vs* entry 24) for a longer reaction time, while further decreasing to −78 °C eroded the enantioselectivity (entry 26). When the catalyst loading was reduced to 10 mol%, **3a** was generated in low yield and reduced enantioselectivity (entry 27). Nevertheless, more or less amount of 4 Å MS rather than 5 mg is unbeneficial to this reaction (entries 28 and 29). Therefore, the optimal reaction conditions are as follows: 20 mol% of **C3** as the catalyst, 1.2 equiv. of cyano reagent **2e**, and stirring for 36 h in CH_2Cl_2 at −40 °C.

With the optimal reaction conditions in hand, the substrate scope was explored with results shown in Scheme 2. All these ee values are higher than the results employing the cyano reagent



Scheme 2. Substrate scope of the organocatalyzed α-cyanation of β-keto amides.[a] [a]All reactions were performed on the scale of 0.1 mmol of the substrate with 4 Å MS (5 mg) in CH_2Cl_2 (1.0 mL) at −40 °C for 36 h under an argon atmosphere. The results are listed with isolated yields and ee values determined by chiral HPLC analysis on Chiralpak AD-H. [b]30 mol% of **C3** used.

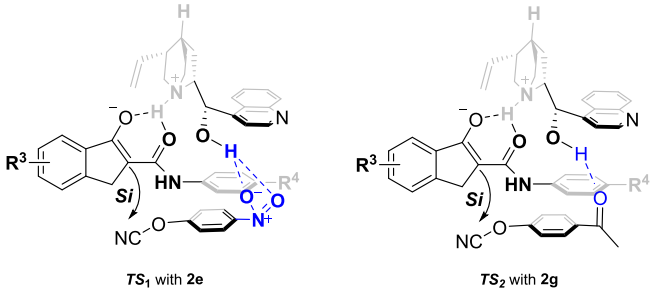


Fig. 2. The transition state to explain the enhanced enantioselectivity.

2g instead.[17] A series of halogenated 1-indanone-derived β-keto amides bearing Cl, F and Br on the benzene ring at C4, C5, or C6-position were readily converted into the corresponding products with enantioselectivity ranging from 82% to 86% ee (**3b**–**g**). However, electron-donating substituents such as C6-Me, C6-MeO and C6-Ph gave a little higher 87% ee (**3h**–**j**). Furthermore, substituent at the amide side also affected the catalytic consequences. Aniline-derived substrates containing C4′-MeO, C4′-F, C4′-Br, C4′-CF_3 groups could be transformed into the corresponding products **3k**–**o** in excellent yields (88–96%) and good to high enantioselectivities (75–86% ee) whereas the product bearing a six-membered ring (**3p**) was not formed.[10a,b] However, the substrate scope of β-keto amides still limited for phenyl-ring fused aromatic amides which is benefit to the thermodynamic active enol species in the transition state ***TS*$_1$**, while bulky *N*-adamantyl amide (**3q**) gave little lower 66% ee and *N*-benzyl amide (**3r**) much less 21% ee implying a possible π-π interaction between cyano reagent and amide (*vide infra* ***TS*$_1$**).

Based on the above experimental observations as well as our previous report,[17] we proposed a plausible transition state (***TS*$_1$**) to explain the observed enhanced enantioselectivity with the new cyano reagent. As illustrated in Fig. 2, cinchonine acts as a dual functional catalyst and activates both the substrate and the cyanate reagent *via* hydrogen bonding. Firstly, the β-keto amide **1a** coordinates to the quinuclidine amine moiety of the catalyst through H-bonding *via* enolate form in almost planar geometry. Secondly, C9-OH of cinchonine connects the nitro group of **2e** by a double H-bond[21] thus activating the O–CN bond. Then, the β-keto amide **1a** attacks CN preferentially from the *Si* face, leading to the formation of the predominant (*S*)-enantiomer **3a**. The OH—O double hydrogen bonds between the nitro of **2e** and C9-OH of the catalyst play the crucial role to arrange the preferred ***TS*$_1$** more tightly than ***TS*$_2$** in the case of acetyl cyano reagent **2g** leading to the improved enantioselectivity.

Conclusion

In summary, the enantioselectivity was greatly improved in the direct electrophilic α-cyanation of 1-indanone-derived β-keto amides by using a new cyano transfer reagent, 1-cyanato-4-nitrobenzene, as a result of an enhanced double-hydrogen bonding. With cinchonine as the bifunctional organocatalyst, it gave a series of α-cyano β-keto amides in excellent yields (up to 97%) and higher enantioselectivities (up to 91% ee) than 1-cyanato-4-acetylbenzene.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.032.

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