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

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ABSTRACT

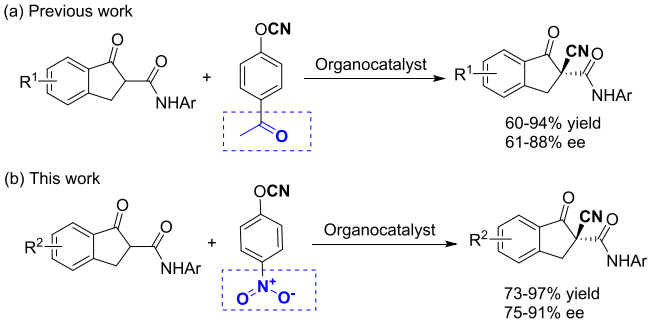
By using a readily accessible, new and safe cyano-transfer reagent, 1-cyanato-4-nitrobenzene, the enantioselectivity of the direct electrophilic α-cyanation of 1-indanone-derived β-keto amides was greatly improved as a result of an enhanced double-hydrogen bonding. Thus, in the presence of cinchonine 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 hyperiodinate 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.

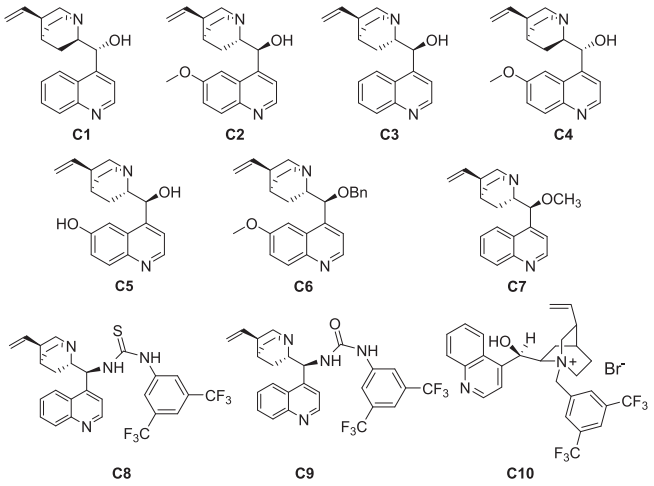
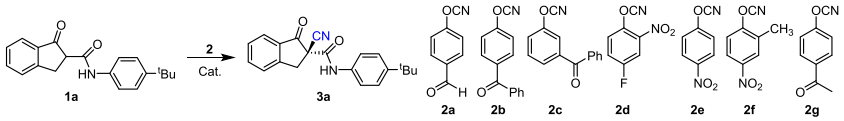


Fig. 1. Evaluated organocatalysts in this study.

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.