Organocatalysis

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Direct Asymmetric α Benzoyloxylation of Cyclic Ketones**

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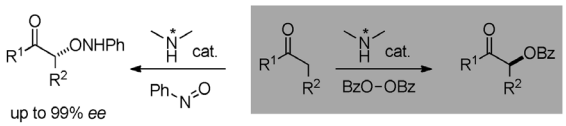
Enantiomerically pure α-oxygenated carbonyl compounds are ubiquitous structures in natural products and pharmaceuticals, and important building blocks in organic synthesis. Consequently, the enantioselective introduction of an oxygen moiety at the α position of carbonyl groups continues to be an intensely investigated field.[1] In this context, enamine catalysis recently became a powerful approach for the direct asymmetric α oxygenation of ketones and aldehydes, thus avoiding the need of preforming an enolate equivalent.[2] In particular, the α aminoxylation of aliphatic ketones and α-unbranched aldehydes with nitrosobenzene has been established as a reliable oxidation method.[3] However, despite the excellent enantioselectivity of this method, limitations remain. Most importantly, a several-fold excess of the carbonyl substrate is typically required, thus limiting the method to inexpensive starting materials and the early stages of a multistep synthesis.[4] Furthermore, reactions with α-branched aldehydes invariably give inseparable mixtures of aminoxylation and nitroso aldol products, favoring the latter and resulting in only moderate enantioselectivity for the α-oxygenated product (up to 45% *ee*).[5] Recently, Maruoka and co-workers, and others have introduced benzoyl peroxide as a useful, readily available, and inexpensive reagent for the asymmetric α benzoyloxylation of simple α-unbranched aldehydes.[6] Herein we report a highly enantioselective α benzoyloxylation of stoichiometric amounts of cyclic ketones catalyzed by readily available cinchona-alkaloid-derived primary amines.

In the previous methods for the α benzoyloxylation of aldehydes, bulky secondary amine catalysts were used to avoid catalyst decomposition by oxidation.[2c,6a] This may well be the reason why no other, more sterically demanding substrate classes have been applied to this catalyst system to date [Eq. (1); Bz = benzoyl]. We have recently established cinchona-alkaloid-derived primary amines in the catalytic asymmetric epoxidation of enones and α-branched enals,[7] thus demonstrating the excellent stability and reactivity of these catalysts toward challenging substrate classes. Indeed, the observed robustness of the primary amine moiety may be attributed to its lower reactivity toward oxidation compared to secondary amines,[8] which are classically used in organocatalysis. Nevertheless, while numerous secondary amine catalysts have been employed in the α oxygenation of aldehydes and ketones,[2] the use of primary amines in this transformation has been virtually non-existent.[9] This is surprising in light of the growing use of primary amine catalysts for the functionalization of diverse substrate classes, including ketones, enones, α-branched enals, and aldehydes.[10]

On the basis of these considerations, we envisioned that the readily available primary amines of type **9**, derived in a single step from cinchona alkaloids, could catalyze a direct enantioselective α oxygenation of ketones. In particular, we wished to develop a method that is stoichiometric in the carbonyl reagent and introduces a usefully protected oxygen functionality.



(1)

We began our investigation using cyclohexanone (**1a**) as the model substrate, a slight excess (1.5 equiv) of anhydrous benzoyl peroxide (**2**), and 10 mol% of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT; **3**) to avoid possible benzoyl radical side reactions. Initial catalyst studies confirmed our expectation that the commonly used secondary amines are ineffective catalysts, presumably because of their low activity and concurrent decomposition. Thus, 10 mol% of (*S*)-proline (**5**) gave the desired product with 11% conversion after 24 hours, and this conversion did not increase over the next 5 days, while the diarylprolinols **6** and **7** resulted in no conversion[11] (Table 1, entries 1–3). In contrast, a trichloroacetic acid salt of the quinine-derived catalyst **9** catalyzed the α benzoyloxylation of cyclohexanone with an encouraging 56% yield and excellent enantioselectivity (97:3 e.r.), the remaining reaction mixture consisting only of the unreacted starting materials (entry 4).

Encouraged by this result, we set out to further optimize the reaction conditions. Increasing the concentration to 1M had a positive effect on conversion (Table 1, entry 5); however, further increase in the concentration led to appreciable formation (11%) of the dibenzoyloxylation product (entry 6). A screen of acid co-catalysts revealed that both the amount and the nature of the acid influenced the enantioselectivity. In particular, higher loading of trichloroacetic acid (40 mol%) led to partial racemization of product **4a** (entry 7). Substituting the acid co-catalyst with diphenyl hydrogen phosphate improved the conversion but slightly

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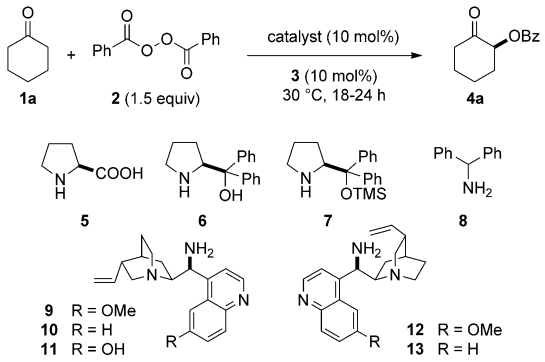
Table 1: Evaluation of the reaction conditions for the asymmetric benzoyloxylation of cyclohexanone **1a**.



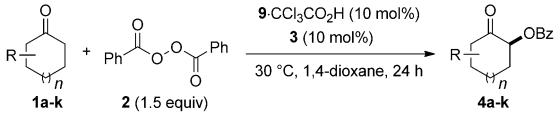
Entry	Catalyst (amine, acid)	Solvent	Conc. [M]	Yield [%][a]	e.r.[b]
1	**5**	DMSO	0.5	11	–
2	**6**	THF	0.5	0	–
3	**7**	THF	0.5	0	–
4	**9**·Cl_3CCO_2H	THF	0.5	56	97:3[c]
5	**9**·Cl_3CCO_2H	THF	1	67	97:3
6	**9**·Cl_3CCO_2H	THF	2	66[d]	97:3
7	**9**·4 Cl_3CCO_2H	THF	1	56	85:15
8	**9**·$(PhO)_2PO_2H$	THF	1	83	96:4
9	**10**·$(PhO)_2PO_2H$	THF	1	48	93:7
10	**11**·$(PhO)_2PO_2H$	THF	1	65	89:11
11	**12**·$(PhO)_2PO_2H$	THF	1	51	8:92[e]
12	**13**·$(PhO)_2PO_2H$	THF	1	88	12:88[e]
13	**9**·Cl_3CCO_2H	1,4-dioxane	1	76	97:3
14	**8**·(*R*)-TRIP	THF	1	29	57:43

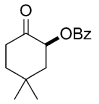
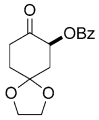
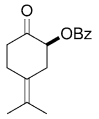
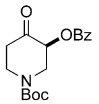
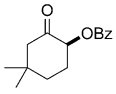
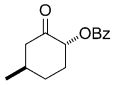
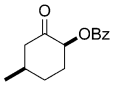
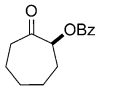
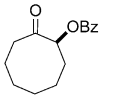
[a] Determined by ^{1}H NMR spectroscopy using triphenylmethane as an internal standard. [b] Determined by HPLC analysis using a chiral stationary phase. [c] The absolute configuration (*S*) was determined by comparison of the optical rotation of **4a** with the literature value.[13] [d] 11% of the dibenzoyloxylated product was also observed. [e] Product obtained with the *R* configuration. DMSO = dimethylsulfoxide, THF = tetrahydrofuran, TMS = trimethylsilyl, TRIP = 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-bi-2-napththol cyclic monophosphate.

diminished the enantioselectivity (entry 8). An examination of related cinchona-derived amines showed no improvement in the reaction (entries 9–12). After a screen of solvents,[12] 1,4-dioxane was chosen as the optimal reaction medium (entry 13). We also tested a combination of the achiral amine **8** to activate the ketone as an enamine, and the chiral Brønsted acid (*R*)-TRIP for the activation of benzoyl peroxide (entry 14). Intriguingly, while the chemical yield was low, some enantioselectivity (57:43 e.r.) was observed.

With the optimized reaction conditions in hand, we explored the scope of the asymmetric α benzoyloxylation with respect to ketone substrates (Table 2). Various six-, seven-, and eight-membered carbocyclic and heterocyclic ketones cleanly underwent α benzoyloxylation, thus affording the desired products **4** with good yields and excellent enantioselectivities. By using the related pseudoenantiomeric catalyst **13**, products with the opposite configuration could be generated with equal efficiency (entries 3 and 4). A range of functional groups were tolerated in the reaction, including an acetal, an olefin, and a carbamate (entries 5–7). The β,β-disubstituted substrate **1g** afforded product **4g** as a single

Table 2: Scope of the asymmetric α benzoyloxylation of ketones.



Entry[a]	Product[b]		Yield [%][c]	e.r.[d]
1		**4a**	67 61[f]	97:3 (>99:1)[e] 96.5:3.5[f]
2		**4b**	78	94.5:5.5
3[g]		**4c**	66	95:5
4[g,h]		*ent*-**4c**	63	95:5
5		**4d**	52 (89 brsm)	95.5:4.5
6		**4e**	63	94:6
7		**4f**	45	92:8
8		**4g**	77 (>20:1 r.r.)[i]	96:4
9[j]		**4h**	60 (18:1 d.r.) (12:1 r.r.)[i]	>99:1[k]
10		**4i**	57 (18.5:1 d.r.) (2:1 r.r.)[i]	>99:1[k]
11[g,l]		**4j**	74	98:2
12[g,l]		**4k**	81[m]	98:2

[a] Reaction scale: 0.4 mmol. [b] The absolute configuration of products **4** was assigned by comparison of the optical rotation with the literature values or by analogy (see the Supporting Information for details). [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] After a single recrystallization. [f] Using 2-methyltetrahydrofuran as solvent. [g] Using $(PhO)_2PO_2H$ as the acid co-catalyst. [h] Using catalyst **13**. [i] r.r. = regioisomeric ratio. [j] Using catalyst **12**. [k] Enantiomerically pure starting material **1h** was used. [l] Using 2 equiv of the ketone. [m] Contains 11% of the dibenzoyloxylated product. Boc = *tert*-butoxycarbonyl, brsm = based on recovered starting material.

regioisomer (entry 8), whereas the enantiopure substrate **1h** underwent a highly regioselective and *trans*-diastereoselective benzoyloxylation (entry 9) with the pseudoenantiomeric catalyst **12**. Highly *cis*-selective α benzoyloxylation was also possible for this substrate with catalyst **9**, albeit with reduced regioselectivity (entry 10). In all cases, less than 5% of the dibenzoyloxylated ketone was observed as the only by-product, except for cycloheptanone and cyclooctanone (entries 10 and 11), where overoxygenation was a competitive process that could be effectively suppressed by using two equivalents of the starting material. We also examined the compatibility of our reaction with the environmentally benign and industrially valuable solvent 2-methyltetrahydrofuran. Gratifyingly, the reaction with ketone **1a** afforded the product with similar yield and enantioselectivity (entry 1).

Acyclic and large ring-sized ($n > 8$) ketones currently represent a limitation of this method, as they undergo α benzoyloxylation with very poor conversion (< 5%), possibly owing to the low nucleophilicity of the generated unstrained enamine intermediates.

To probe the utility of our method in preparative synthesis, we performed the reaction with ketone **1a** on a fivefold scale (2 mmol, 0.4 g) and were pleased to obtain the corresponding product **4a** with a good yield (76%) and essentially uncompromised enantioselectivity (95.5:4.5 e.r.), which could be readily improved to 99.5:0.5 e.r. by a single recrystallization. Furthermore, we tested a substrate with a complex pre-existing architecture, where use of stoichiometric amounts of the ketone is particularly valuable. From cholestanone (**1l**), we could successfully obtain the corresponding benzoyloxylated product **4l**[14] with excellent regio- and diastereocontrol, and a high yield [Eq. (2)].

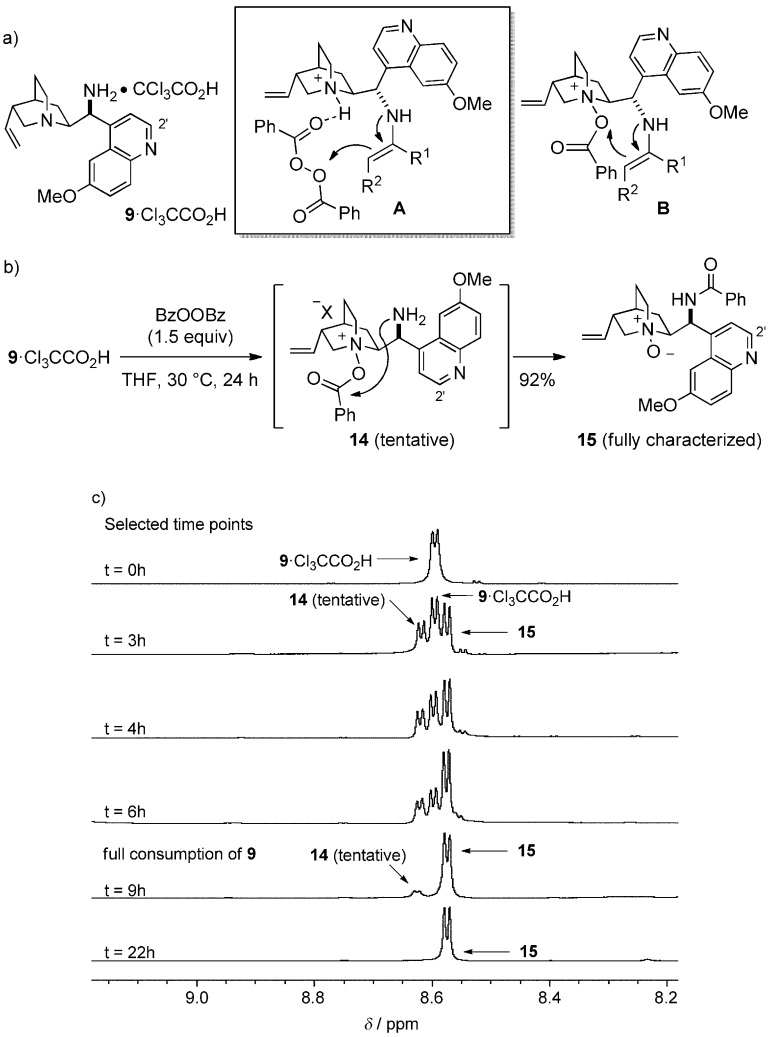
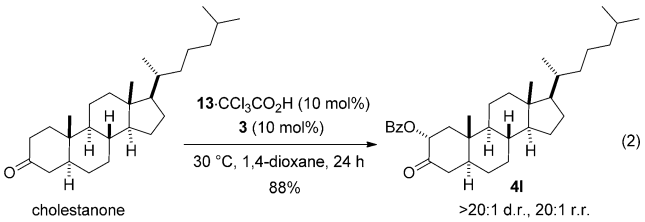


Figure 1. a) Proposed transition state. b) Behavior of the catalyst salt **9**·Cl_3CCO_2H toward benzoyl peroxide in the absence of a ketone substrate. c) ^{1}H NMR study of the conversion of **9**·Cl_3CCO_2H into **15** over time (peak corresponds to proton 2′ of **15** in [D_8]THF).



(2)

Mechanistically, we propose that the primary amine catalyst **9** activates ketones as enamines that nucleophilically attack benzoyl peroxide. In particular, we believe that the transition state involves an intermolecular attack of the enamine onto benzoyl peroxide, which is activated by the protonated quinuclidine nitrogen atom of the catalyst **9** (Figure 1a, transition state **A**). ^{1}H NMR studies of the catalyst salt **9**·Cl_3CCO_2H treated with benzoyl peroxide in the absence of a ketone substrate suggest that the quinuclidine nitrogen atom is transiently benzoyloxylated (structure **14**), but slowly rearranges to form compound **15** (Figure 1b,c).[12,15] Although **15** is completely inactive, quinuclidine benzoyloxylation of catalytically relevant intermediates cannot be ruled out at this point. As such, a transfer of the benzoyloxy moiety from the quinuclidine nitrogen atom onto the enamine through an intramolecular rearrangement[6a] could be envisioned (transition state **B**). Detailed mechanistic studies aimed at elucidating the structure of the active enamine intermediates are currently underway in our laboratories.

In conclusion, we have developed an operationally safe and simple methodology for the α benzoyloxylation of ketones, which delivers valuable benzoyl-protected hydroxyketones **4** with good yields and high enantioselectivities. This transformation utilizes a readily available salt of a primary amine catalyst and stoichiometric amounts of various functionalized ketones, and can be scaled up without loss of yield or enantioselectivity. In addition, preliminary investigations

on challenging α-branched aldehydes have identified a highly promising catalytic system that delivers aldehydes containing an α-quaternary stereocenter with very good yields and promising enantioselectivities. Results on the studies of this substrate class will be reported in due course.

Experimental Section

α Benzoyloxylation of ketones **1**: A 2 mL vial, equipped with a magnetic stirring bar, was charged with 2,6-di-*tert*-butyl-4-methylphenol (BHT) (9.0 mg, 0.0408 mmol, 10 mol%), catalyst **9** (13.3 mg, 0.408 mmol, 10 mol%), trichloroacetic acid (6.6 mg, 0.0408 mmol, 10 mol%), ketone **1** (0.408 mmol), and 1,4-dioxane (0.4 mL) and then stirred for 5 min before adding anhydrous benzoyl peroxide (147 mg, 0.612 mmol, 1.5 equiv). The reaction mixture was stirred at 30 °C for 24–48 h, diluted with dichloromethane, and treated with a saturated aqueous solution of $NaHCO_3$, extracted three times with dichloromethane, washed with brine, dried over Na_2SO_4, filtered, concentrated to approx. 1 mL and purified by flash column chromatography on silica gel eluting with a specified mixture of *n*-pentane and Et_2O. The enantioselectivity was determined by HPLC analysis using a chiral stationary phase.

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