Synthetic Methods

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Organocatalytic Asymmetric α-Halogenation of 1,3-Dicarbonyl Compounds**

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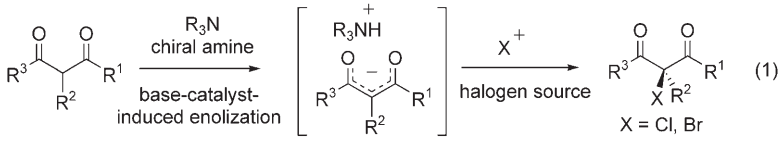
The enantioselective construction of carbon–halogen stereogenicity belongs to the topical area of current asymmetric catalysis[1] by virtue of the fact that halogen atoms attached to a chiral stereocenter can serve as a linchpin for further stereospecific manipulations.[2] Moreover, optically active halogen-containing compounds are increasingly important targets in drug discovery and material sciences.[3] Despite this, different efficient catalytic asymmetric halogenation strategies have been developed only in the last few years.[1a,b] To date, the most notable advances have been made in the α-halogenation of carbonyl compounds by using mild and stable sources of electrophilic halogens. All the reported asymmetric catalytic methodologies, from the first Lewis acid catalyzed asymmetric α-fluorination of β-keto esters reported by Hintermann and Togni,[4] to several highly practical metal-free (organocatalytic)[5] approaches, involve the transient formation of an enolate (enol) that can be halogenated to generate the desired product. The crucial enolization process can be efficiently promoted through 1) coordination of chiral Lewis acids with 1,3-dicarbonyl compounds;[6] 2) formation of an enamine intermediate derived from the reaction between a secondary chiral amine and enolizable aldehydes and ketones;[7] 3) attack of a chiral nucleophile on a ketene intermediate to generate a zwitterionic enolate;[8] and 4) ionic association of a phase-transfer catalyst with the enolate.[9]

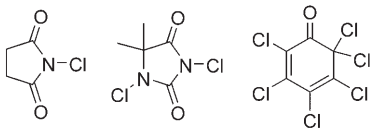
Recently, chiral tertiary amines have been successfully applied in various organocatalytic transformations, acting as chiral-base catalysts.[10] However, this concept has not yet been applied to asymmetric halogen–carbon bond-forming reactions. Herein, we describe a new effective approach that uses a cinchona alkaloid derivative as a chiral base for promoting the enolization of 1,3-dicarbonyl compounds and the subsequent highly enantioselective electrophilic α-chlorination and α-bromination of the enol derivative [Eq. (1)].

Despite the considerable recent advances, the development of a novel halogenation system of 1,3-dicarbonyl compounds that displays satisfactory selectivity as well as generality is still in high demand, as the reported Lewis acid catalyzed asymmetric chlorinations and brominations of β-keto esters are efficient only with selected substrates.[6a–c] The organocatalytic halogenation presented herein is effective with both cyclic and acyclic β-keto esters and with cyclic β-diketones to afford highly optically enriched α-halogenated compounds (up to 96% *ee*) in good yields using inexpensive benzoylquinidine (BQd) as the catalyst and easy-to-prepare polyhalogenated quinolinones as new sources of the halogen.



(1)

To verify the feasibility of such an organocatalytic asymmetric halogenation strategy, we examined the reaction of ethyl 2-oxo-cyclopentanecarboxylate **1a** with *N*-chlorosuccinimide (NCS, **3a**) as the halogen source in the presence of some cinchona alkaloid derivatives as the chiral-base catalyst. Representative results of the extensive screening of reaction conditions are listed in Table 1. Several solvents were inves-


3a **3b** **3c**

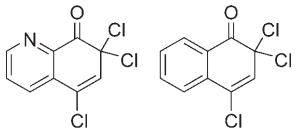

3d **3e**

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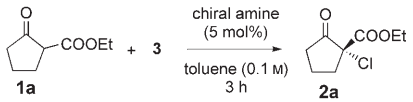
Table 1: Screening of reaction conditions for the organocatalytic asymmetric chlorination of **1a**.[a]



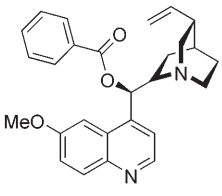
1a **2a**

Entry	Catalyst[b]	3	*t* [h]	*T* [°C]	Conv. [%][c]	*ee* [%][d]
1	$(DHQ)_2PYR$	**3a**	2	RT	>95	21 (*R*)
2	$(DHQD)_2PHAL$	**3a**	2	RT	>95	33 (*S*)
3	$(DHQ)_2AQN$	**3a**	2	RT	>95	46 (*R*)
4	cinchonidine	**3a**	2	RT	>95	10 (*R*)
5	quinine	**3a**	2	RT	>95	18 (*R*)
6	**4a**	**3a**	2	RT	>95	60 (*R*)
7	**4a**	**3a**	3	−78	>95	58 (*R*)
8	**4a**	**3b**	3	RT	>95	36 (*R*)
9	**4a**	**3c**	3	RT	>95	57 (*R*)
10	**4a**	**3d**	3	RT	>95 (98)[e]	79 (*R*)
11	**4a**	**3e**	3	RT	58	78 (*R*)
12	**4a**	**3d**	24	−78	70	95 (*R*)
13[f]	**4a**	**3d**	24	−78	74	95 (*R*)
14[g]	**4a**	**3d**	24	−78	80 (68)[e]	95 (*R*)
15[g]	**4b**	**3d**	3	RT	>95 (96)[e]	85 (*S*)
16[g]	**4b**	**3d**	24	−40	>95 (98)[e]	95 (*S*)

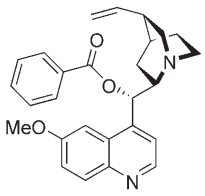
[a] Experimental conditions (0.4-mmol scale): open-air reactions run in undistilled solvent (0.1 M) using a 1:1.2 ratio of **1a** to **3**, and 5 mol% of catalyst. [b] $(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, $(DHQ)_2AQN$ = hydroquinine anthragquinone-1,4-diyl diether. See Supporting Information for structures of catalysts. [c] Conversion determined by ^1H NMR spectroscopy of the crude mixture. [d] Determined by GC analyses on commercially available chiral stationary phases; the absolute configuration reported in parentheses was determined by comparison of values of optical rotation with those reported in the literature. [e] Number in parenthesis indicates yield of the isolated product **2a**. [f] Reaction carried out with 1 equivalent of $NaHCO_3$. [g] Reaction carried out with 1 equivalent of $NaHCO_3$ in toluene (0.25 M).

tigated, and toluene was selected as the solvent of choice, although ethereal solvents afforded analogous results (see Supporting Information for details).

In the initial studies, benzoylquinine (BQ, **4a**) proved to be the most promising catalyst among the chiral amines tested by affording the *R* chloro derivative **2a** in moderate enantio-



4a (BQ)



4b (BQd)

meric excess (60% *ee*, Table 1, entry 6). However, a slight decrease in enantioselectivity was observed when the BQ-catalyzed reaction was performed at −78 °C (entry 7). We speculated that, under these reaction conditions, the uncatalyzed background reaction of the enol form effectively competes with the stereoselective pathway, even at low temperature. Thus, the primary goal was to employ a less-reactive, finely tuned chlorinating agent that displays a minimal rate of background reaction with the substrate **1a**.

Along these lines, a series of electrophilic halogens was screened, employing BQ (**4a**) as the catalyst (entries 8–11). The trichloroquinolinone **3d**, which is easily prepared from 8-hydroxyquinoline and 3 equivalents of *tert*-butylhypochlorite, gave the best result, with the product **2a** obtained in 79% *ee*. The structurally related chlorinating agent **3e** provided the same stereochemical outcome with a significant decrease in reactivity. Performing the reaction at −78 °C in the presence of **3d** led to a dramatic increase in enantioselectivity, albeit at the expense of reactivity (95% *ee*, entry 12), which indicates that under these conditions the discrimination between the background reaction and the asymmetric catalyzed chlorination was maximized.[11] Importantly, the capacity of the trichloroquinolinone **3d** to function in highly enantioselective enolate halogenations is disclosed here for the first time.[12]

Halogen transfers involving quinolinone **3d** are expected to release stabilized aromatic phenolate anion **5** in a thermodynamically favorable process (Figure 1). We envis-

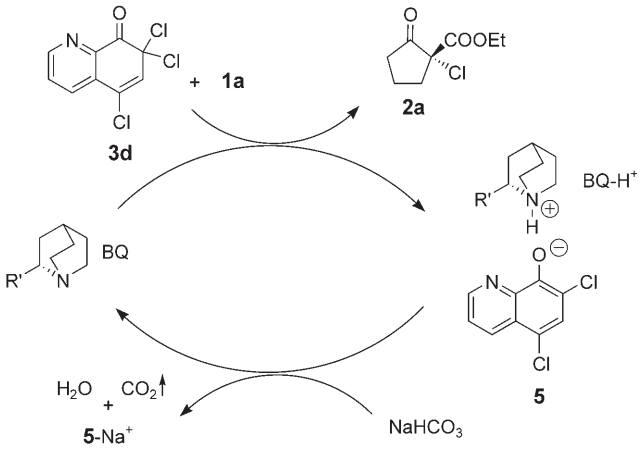


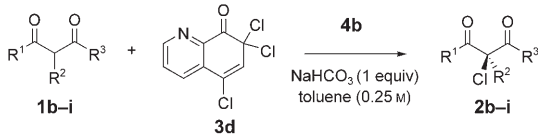
Figure 1. Halogen transfer from quinolinone **3d** to **1a** catalyzed by BQ (**4a**).

aged that the plausible tight ionic association of **5** with the protonated chiral amine catalyst may affect the efficiency of the system. We reasoned that an inorganic base that is able to facilitate the proton transfer from the protonated chiral amine ($BQ\text{-}H^+$) to thus regenerate the active catalyst without promoting a racemic chlorination path could have a beneficial effect on the reaction rate.[13] With this consideration in mind, a survey of reaction conditions was performed which revealed that the BQ-catalyzed asymmetric chlorination of **1a** was accelerated by using 1 equivalent of $NaHCO_3$ in a more concentrated solution (toluene, 0.25 M; Table 1, entries 13–14).[14] Noteworthy, when the "pseudoenantiomeric" BQd (**4b**) was used as catalyst the opposite enantiomer (*S*)-**2a** was obtained in significantly higher enantiomeric excess (entry 15). Such a selectivity allowed the reaction to be performed at higher temperature without affecting the optical purity of the product, which was isolated in quantitative yield (95% *ee*, entry 16).

The superior levels of induction and efficiency exhibited by BQd (**4b**) in the presence of $NaHCO_3$ (1 equiv) and toluene (0.25 M), prompted us to select these conditions to

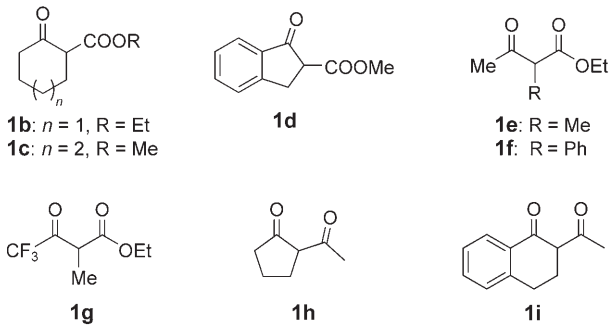
examine the scope of the 1,3-dicarbonyl substrates in this asymmetric chlorination protocol. As highlighted in Table 2, cyclic β-keto esters **1b–d** were all converted into the corresponding chloro derivatives in fairly good yields and with excellent optical purity (Table 2, entries 1–3). The

Table 2: Organocatalytic asymmetric chlorinations of β-keto esters and β-diketones.[a]



Entry	Product	**4b** [mol%]	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**2b**	15	−40	40	83	96
2	**2c**	15	−40	52	48[d]	90
3	**2d**	5	−78	36	80 (75)	93 (91)
4	**2e**	20	RT	48	75	76 (69)
5	**2f**	15	−10	36	99	80
6[e]	**2g**	15	−78	52	44[f]	89
7[g]	**2h**	5	−78	30	90 (87)	51 (56)
8[g]	**2i**	15	−40	48	74 (78)	59 (58)

[a] Experimental conditions (0.4-mmol scale): open-air reactions run in undistilled toluene (0.25 M) using a 1:1.2 ratio of **1** to **3d**, 1 equivalent of $NaHCO_3$, and benzoylquinidine (**4b**) as catalyst. Results in parentheses were obtained by using BQ (**4a**) as catalyst to give the opposite enantiomer. [b] Yield of isolated products **2**. [c] *ee* values of **2** were determined by HPLC or by GC analyses on commercially available chiral stationary phases (see Supporting Information for details). [d] Conversion = 65%. [e] Reaction carried out in *tert*-butyl methyl ether. [f] Conversion = 80%; the lower yield is due to the volatility of **2g**. [g] Performed in the absence of $NaHCO_3$.



asymmetric chlorination of different substituted acyclic β-keto esters also afforded the desired products with good enantioselectivity, although a decreased reactivity was observed (entries 4–6). In the presence of a more-reactive substrate such as **1g**, the possibility to perform the reaction at low temperature allowed the generation of the chlorinated adduct **2g** in high optical purity (89% *ee*, entry 6).[15]

We next investigated the efficiency of the method with β-diketones, a particularly challenging class of substrates for which, to our knowledge, just one example of low-enantioselective chlorination has been reported.[6b] Reactions of cyclic diketones **1h–i** proceeded smoothly to give the expected products with moderate enantioselectivity (entries 7–8).

Last, the extension of the presented organocatalytic protocol to asymmetric brominations was evaluated. We presumed that the newly synthesized tribromoquinolinone **6** (Figure 2), structurally related to the chlorinating agent **3d**, might have been a useful source of bromine for the organo-

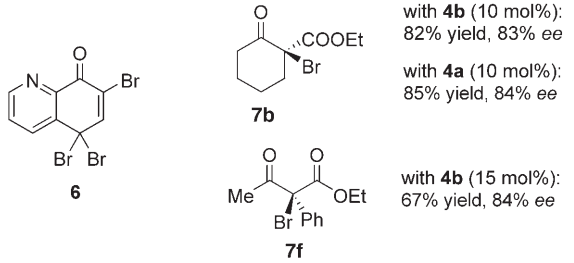


Figure 2. The organocatalytic asymmetric bromination of β-keto esters **1b,f** in the presence of 1.2 equivalents of **6** as the halogen source (toluene (0.25 M), −78 °C, 30 h) to afford **7b** and **7f**.

catalytic enantioselective α-bromination. Proof-of-principle was provided through BQd-catalyzed reactions of β-keto esters **1b** and **1f**: the corresponding bromo derivatives **7b** and **7f** were obtained in good yields and with good enantioselectivity (up to 84% *ee*, Figure 2).[16] Further studies to improve the efficiency and the applicability of the organocatalytic enantioselective bromination reaction are ongoing in our laboratories.

In summary, we have developed the first organocatalytic asymmetric α-chlorination and α-bromination reactions of 1,3-dicarbonyl compounds by using an inexpensive chiral amine as the catalyst and a mild, operationally simple protocol that allows direct access to highly enantiomerically enriched halogen-containing compounds. The use of polyhalogenated quinolinones as new sources of halogen electrophiles was essential to achieve high enantioselectivity.

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[11] The uncatalyzed background chlorination reaction of **1a** was demonstrated to proceed to different extents depending on the chlorinating agent; that is, under conditions of 1:1 **1a**/**3**, in toluene for 3 h at room temperature, the conversion of **1a** is 100% with **3a**, 58% with **3c**, and 12% with **3d**.
[12] It was reported that the use of trichloroquinolinone **3d** in the asymmetric catalytic α-chlorination of acid halides resulted in poor chemical and optical yields; see reference [8b].
[13] For a similar system in which the proton transfer from the protonated benzoylquinine to $NaHCO_3$ represents a key step of catalysis, see the α-chlorination of acid halides in reference [8b].
[14] The beneficial effect of $NaHCO_3$ on reactivity is more appreciable with less-reactive substrates such as linear β-keto esters. The effects of various bases on the asymmetric halogenation were evaluated (see Supporting Information).
[15] The absolute configurations of **2a–b** and **2e** were determined to be *S* by comparison of the specific optical rotations with those reported in the literature. All other absolute configurations were assigned by analogy. Although it is premature to provide a detailed mechanistic explanation at this level, the sense of stereochemical induction suggests the formation of a BQd–enolate ionic complex in which the *Re* face is effectively shielded by the chiral organocatalyst.
[16] The use of different brominating agents such as *N*-bromosuccinimide and 2,4,4,6-tetrabromo-2,5-cyclohexadione resulted in very low enantioselectivities.

