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Catalytic, Asymmetric α-Chlorination of Acid Halides

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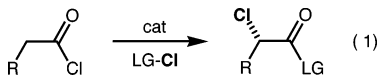
Abstract: We present a full account of a tandem catalytic, asymmetric chlorination/esterification process that produces highly optically enriched α-chloroesters from inexpensive, commercially available acid halides using cinchona alkaloid derivatives as catalysts and polychlorinated quinones as halogenating agents. We have performed kinetics and control experiments to investigate the reaction mechanism and establish conditions under which the reactions can be best performed. We have developed NaH and $NaHCO_3$ shuttle base systems as the easiest and most cost-effective ways of conducting the reactions, rendering the methodology economically competitive with known chiral halogenation procedures. We have also demonstrated the utility of our reactions by converting the products to synthetically useful derivatives.

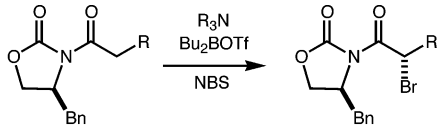
Introduction

Halogenations of organic molecules constitute a synthetically important and historically significant class of chemical reactions. Every student of organic chemistry learns from the earliest stages of his chemical education that diatomic halides are among the most ubiquitous (and reactive) of halogenating agents. As far as many textbooks are concerned, the story seems to stop there. Diatomic halides are known to be highly reactive and generally nonselective species, proving to be incompatible with a variety of functionality within complex molecules, as well as being unsuitable reagents for enantioselective reactions. Fortunately, in recent years, a vast number of milder, alternative halogenating agents have appeared in the literature,[1] making the study of stereoselective, catalyzed halogenations more feasible. Recently, we have become interested in the possibility of catalytic, enantioselective halogenation reactions. Specifically, α-halogenations of carbonyl compounds,[2] which historically have employed diatomic halides as an electrophilic source of halogen, posed an appealing challenge. For example, enantioselective α-halogenation could result in compounds that serve as intermediates in the construction of valuable functionalized molecules.[3] In this full paper, we report our work on catalytic, enantioselective α-chlorination reactions (eq 1) that utilize inexpensive acid chlorides as starting materials and chiral nucleophiles as catalysts, as well as employing polyhalogenated quinones as finely electronically tuned chlorinating agents.

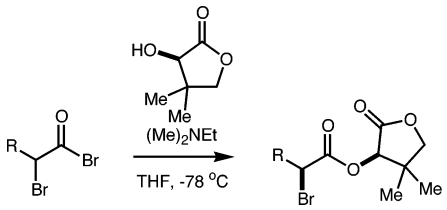


(1)

Much recent work in the field of selective α-halogenation of carbonyl compounds has centered on the development of mild sources of electrophilic halogenating agents. Electrophilic α-fluorination has been the most intensely developed, with reagents (including Selectfluor) attaining widespread use.[4] Many stereoselective α-halogenations have been achieved using chiral auxiliary-based methods. For example, Evans has developed an auxiliary-based route to α-bromoimides (eq 2).[5]



(2)

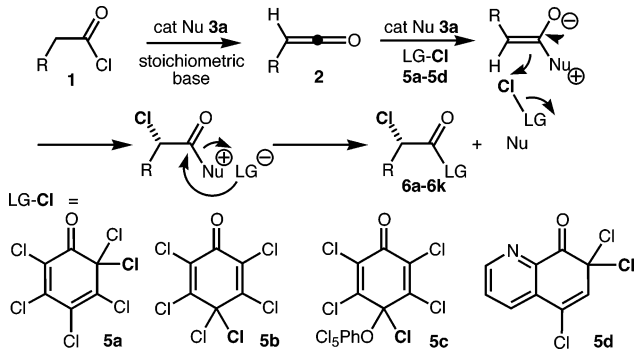


(3)

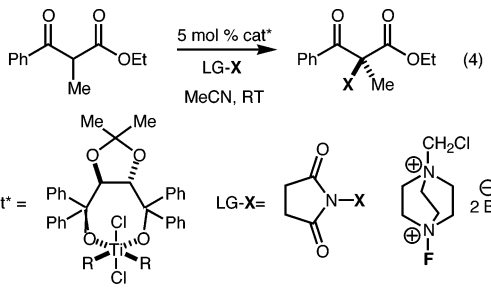
A diastereoselective chlorination using diacetone glucose as the chiral auxiliary has also been published;[6] similarly, a diastereoselective bromination was reported using chiral glycosides.[7] Also, while not technically an α-halogenation, Durst

(1) (a) Rappe, C. *Acta Chem. Scand*. **1968**, *22*, 219−230. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (c) Patai, S. *The Chemistry of the Carbon−Halogen Bond*, Part 1; Wiley: New York, 1988.
(2) (a) House, H. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; pp 459−478. (b) De Kimpe, N.; Verche, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*; John Wiley & Sons: New York, 1988.
(3) (a) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; John Wiley & Sons: New York, 1992. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum: New York, 1990.
(4) (a) Muñiz, K. *Angew. Chem., Int. Ed*. **2001**, *40*, 1653−1656. (b) Kim, D. Y.; Park, E. J. *Org. Lett*. **2002**, *4*, 545−547.
(5) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123−1126.
(6) (a) Duhamel, L.; Angibaud, P.; Desmurs, J. R.; Valnot, J. Y. *Synlett* **1991**, 807−808. (b) Angibaud, P.; Chaumette, J. L.; Desmurs, J. R.; Duhamel, L.; Ple, G.; Valnot, J. Y.; Duhamel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1919−1932. (c) Duhamel, P. *Bull. Soc. Chim. Fr*. **1996**, *133*, 457−459.

Scheme 1. Tandem Catalytic Asymmetric Chlorination/ Esterification



has developed an important diastereoselective synthesis of a series of α-bromo- and α-iodoesters from *in situ* generated α-halogenated ketenes (eq 3).[8]

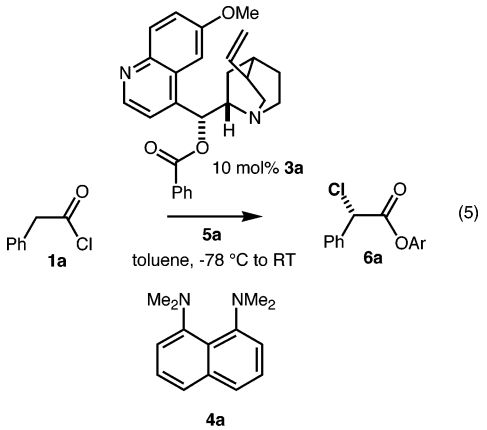


Recent attention has focused on the development of catalytic asymmetric methods for generating halogenated compounds. Ultimately, the design of a catalytic, enantioselective α-halogenation reaction would effectively utilize a very mild source of halogen that could be easily manipulated. The very first step in this nascent field was reported by Togni, who has developed a titanium-taddol-catalyzed halogenation procedure (eq 4).[9] This protocol is effective for the halogenation of highly enolizable α-alkyl-1,3-dicarbonyl compounds, which can readily form titanium-based enolates *in situ*.[10] A similar protocol has been recently developed by Sodeoka et al., who used a Pd(II)−BINAP complex to achieve the asymmetric fluorination of α-keto esters.[11]

As Togni's initial report appeared, we had begun work on our own catalytic, asymmetric halogenation (particularly chlorination) reactions. We envisioned a process in which *in situ* generated ketenes[12] would react with chiral nucleophiles such as cinchona alkaloid derivatives to form zwitterionic enolates.[13] These would in turn react with a mild electrophilic halogen source in a tandem halogenation/esterification reaction (Scheme 1). The electrophilic halogen would add to the α-position of the enolate, producing an acylammonium salt that subsequently undergoes transacylation with the leaving group of the electrophile. This process produces a series of chiral α-chloroesters with two new points of potential functionalization (the α-halogen atom and the active ester), that could serve as intermediates for the conversion to optically active amines, amides, ethers, alcohols, esters, and sulfides. Through the use of mild halogenating reagents, we could introduce enantioselectivity into our products. The challenge was multifold: to establish a new chlorination reaction, to observe catalysis, and to impart enantioselectivity.

Results and Discussion

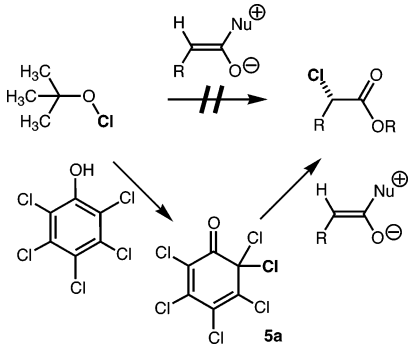
Catalytic Asymmetric Chlorination Using Proton Sponge as the Stoichiometric Base. The initial strategy was influenced by our earlier, successful development of a catalytic, asymmetric synthesis of β-lactams through the cycloaddition of ketenes and imines[14] employing various chiral nucleophiles, including cinchona alkaloid derivatives[15] such as benzoylquinine (BQ) **3a**, as dual catalysts and "shuttle" bases, and proton sponge as the initial dehydrohalogenating agent.[16] In the subsequent improvement of the β-lactam reaction,[17] we found that small amounts of metal cocatalysts, including salts of In(III) and Zn(II), could dramatically improve the yields of these reactions, and also other, less expensive bases, such as NaH, could be employed. One key aspect of the β-lactam reactions concerns the putative formation of a chiral, zwitterionic enolate from *in situ* generated ketenes (or sometimes more directly from the acid chlorides themselves) and chiral nucleophiles. In the case of the β-lactam chemistry, the enolate reacts with imines, but at that time there was reason to believe that these species could also condense with other electrophiles of appropriate reactivity, such as chlorinating agents. In the beginning, the most important question concerned the choice of chlorinating agent. Diatomic chlorine was deemed too reactive, whereas most other agents proved to be completely unreactive. Surprisingly, sources of halogen that are too mild pose the biggest problem, as they are unable to react with the weakly nucleophilic zwitterionic enolate. It was clear to us that only a very narrow window of reactivity existed in which a desirable chlorinating agent could operate and that reaction development would be more difficult than originally anticipated.



Nevertheless, we were encouraged by the results of the β-lactam reaction and began screening sources of electrophilic

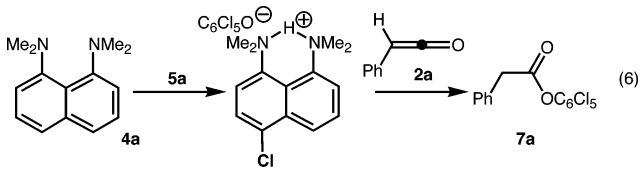
(7) Belucci, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron: Asymmetry* **1995**, *6*, 221−230.
(8) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799−6802.
(9) (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362. (b) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425−2453.
(10) It is useful to distinguish between asymmetric processes in which halogen adds as either an electrophile or a nucleophile. The latter category includes the enantioselective opening of meso epoxides: Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.
(11) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 14530−14531.
(12) (a) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235. (c) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792−3796.
(13) Chiral ammonium enolates have been shown to be the reactive intermediates in a number of asymmetric transformations. For examples, see: (a) Wynberg, H.; Staring, E. G. *J. Am. Chem. Soc*. **1982**, *104*, 166−168. (b) Calter, M. A. *J. Org. Chem*. **1996**, *61*, 8006−8007.

Scheme 2. Chlorination Using *t*-BuOCl

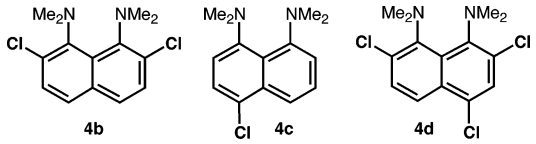


halogen, such as alkylhypochlorites,[18] *N*-chlorosuccinimide (NCS), and various *N*-chloroamides with *in situ* generated phenylketene using BQ **3a** as a catalyst. Phenylacetyl chloride **1a** was added to a solution of 10 mol % catalyst and 1.1 equiv of proton sponge **4a** at −78 °C to generate the zwitterionic enolate (eq 5). In most cases, *N*-halosuccinimides and *N*-chloroamides were unsuccessful, yielding no detectible products, as were a multitude of other candidates, such as chlorinated pyridones, iodanes, and sulfonamides. *tert*-Butylhypochlorite, on the other hand, proved to be too reactive, chlorinating almost anything in the reaction mixture, including solvent (Scheme 2). After much effort, we finally turned our attention to the polyhaloquinone-derived reagents, including **5a**−**5d**.[19] Polyhalogenated quinones have a long history as often unanticipated byproducts of aromatic halogenation reactions. Hundreds of them are known in the literature, and they are often easy to make (or in certain cases, purchase). For example, pentachlorophenol reacts readily with *tert*-butylhypochlorite to produce quinone **5a** in quantitative yield;[20] this substance is available commercially. We have also undertaken the development of an enantioselective α-bromination reaction, facets of which are different enough to be reported separately.[21]

Halogen transfers involving polyhaloquinones are expected to release stabilized aromatic phenolate anions in a thermodynamically favorable process; we envisaged that the phenolate could then react with the resulting acylammonium salt (Scheme 1) and regenerate the catalyst to yield the final product. In our first attempt using the perchlorinated quinone **5a** and phenylacetyl chloride, with 10 mol % BQ as catalyst and 1.1 equiv of proton sponge, α-chloroester **6a** was formed in moderate yield (40%) but with high enantioselectivity (95% ee). Also isolated from the reaction mixture, however, was a fair amount of the achiral ester **7a**, the product resulting from the formal alcoholysis of phenylketene by pentachlorophenol (eq 6). Further investigation revealed that pentachlorophenol was being generated *in situ* by an undesired side reaction, the chlorination of electron-rich proton sponge by the quinone **5a**. These results constituted our first (and very ominous) encounter with byproduct halogenations that ultimately result in undesired ketene phenolysis and prompted us to investigate intensively other "clean" methods of ketene generation that would result in minimal exposure of the halogenating agents to other substrates (*vide infra*).



We started by using various chlorinated proton sponge derivatives **4b**−**d**[22] as stoichiometric bases, reasoning that they would be resistant to further halogenation. However, they proved to be deactivated as bases, affording products in low yield, although the amount of undesired byproduct also dropped considerably. At this point, we deemed it necessary to investigate entirely different classes of more effective stoichiometric bases for the reaction.



Ketene Formation I: Generation Using BEMP. Our first attempt at "clean" ketene generation using an alternative base involved the use of the powerful, resin-bound, phosphazene base BEMP, which could be filtered off after reaction to leave behind a solution of pure ketene. We found that when a solution of phenylacetyl chloride in THF is passed through an addition funnel containing at least 1 equiv of BEMP at −78 °C, phenylketene is produced quantitatively.[23] The ketene solution was allowed to drip slowly into a flask (−78 °C) containing **3a** (10 mol %), and to this was added a solution of **5a**. After this solution had stirred at −78 °C for 4 h, quenching and column chromatography yielded the product (*S*)-**6a**[24] in 80% yield and 99% ee (eq 7).[25] A number of other acid chlorides were screened using this procedure with similar results as summarized in Table 1. As can be seen, a wide range of acid chlorides was successfully employed, including those that possess either aliphatic or aromatic substituents, to afford products in high enantioselectivity and moderate to good chemical yields. Whereas BQ (**3a**) forms one series of enantiomers in reliably stereoregular fashion, benzoylquinidine, or BQd (**3b**, the "pseudoenantiomer of BQ"), consistently affords the opposite set (for example, products (*R*)-**6a** and (*R*)-**6b**). Notable is the compatibility of acid chloride **1b**, possessing an electron-rich (and "halogenatable") phenoxy

(14) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(15) For other timely uses of cinchona alkaloids in catalytic asymmetric synthesis and others contained therein: France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012.

(16) Cinchona alkaloid derivatives have recently been used as stoichiometric reagents for asymmetric halogenation: (a) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699−3701. (b) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728−10729.

(17) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 1603−1605.

(18) Walling, C.; Padwa, A. *J. Org. Chem.* **1963**, *28*, 2976−2977.

(19) Denivelle, L. *Bull. Soc. Chim. Fr.* **1957**, 724−728.

(20) Guy, A.; Lemaire, M.; Guette, J.-P. *Synthesis* **1982**, *12*, 1018−1020.

(21) Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051.

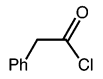
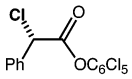
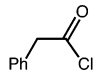
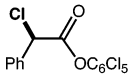
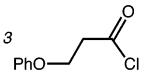
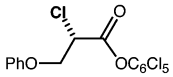
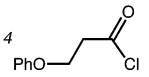
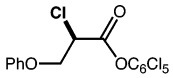
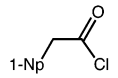
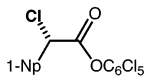
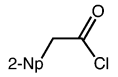
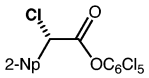
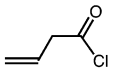
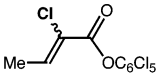
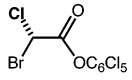
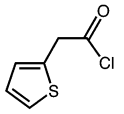
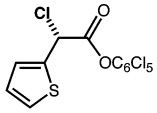
(22) (a) Ozeryanskii, V. A.; Pozharskii, A. F.; Vistorobskii, N. V. *Russ. J. Org. Chem.* **1997**, *33*, 251−256. (b) Glowiak, T.; Majerz, I.; Malarski, Z.; Sobczyk, L.; Pozharskii, A. F.; Ozeryanskii, V. A.; Grech, E. *J. Phys. Org. Chem.* **1999**, *12*, 895−900.

(23) (a) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853−10859. (b) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J.; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965.

(24) Proofs of absolute configuration were determined on the basis of conversion to the known methyl ester and a known α-thio derivative. Stereoregularity was inferred for other products on the basis of these proofs as well as on the basis of computational models. See Supporting Information.

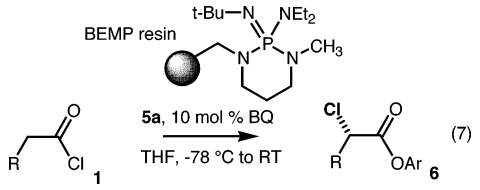
(25) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532.

Table 1. Alkaloid-Catalyzed Reactions of Acyl Halides **1** Using BEMP as a Dehydrohalogenating Agent

entry	*acid chloride*		*product*		*% ee*	*% yield*[a]
1		**1a**		**(*S*)-6a**	99	80
2		**1a**		**(*R*)-6a**	99	81
3		**1b**		**(*S*)-6b**	97	57
4		**1b**		**(*R*)-6b**	96	58
5		**1c**		**(*S*)-6c**	95	57
6		**1d**		**(*S*)-6d**	94	63
7		**1e**		**6e**	--	65
8		**1f**		**(*S*)-6f**	97	51
9		**1g**		**(*S*)-6g**	80	66

[a] Reactions run with 10 mol % catalyst, 0.13 mmol of ketene, 0.065 mmol of **5a** at −78 to 25 °C for 4 h in THF. Yield based on **5a** after chromatography.

group, with the chlorinating agent. Also noteworthy is the use of α-bromoacetylbromide **1f** to afford the α-bromo-α-chloro ester **6f** as the product in 51% yield and 97% ee, a molecule in which two different halogen atoms are attached to one chiral center. Finally, with BEMP as base, the thiophen-2-yl-acetyl chloride **1g** can be converted smoothly into its corresponding α-chloroester (*S*)-**6g** in 66% yield and 80% ee, an uncharacteristically low degree of optical induction for this series of reactions.



(7)

Ketene Formation II: "Shuttle" Deprotonation Using the Sodium Hydride/Crown Ether System. In an attempt to develop a more cost-effective way to generate ketenes (5 g of BEMP costs about 800 times more than NaH), we began to test hydride salts that could act as stoichiometric bases in the dehydrohalogenation of acid chlorides. We also sought a procedure that is amenable to larger scale halogenations (in large amounts, BEMP, besides being costly, is difficult to handle and "gums" up reaction flasks preventing smooth stirring); we examined the use of the inexpensive and low molecular weight sodium hydride as a stoichiometric base for ketene generation.

Scheme 3. Sodium Hydride Shuttle Deprotonation System

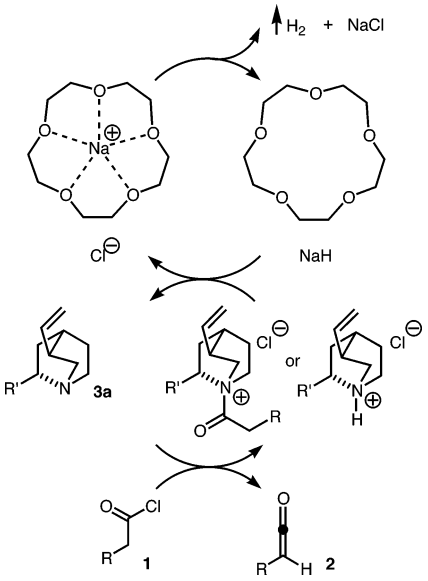
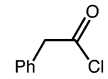
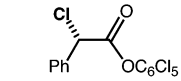
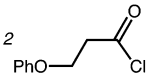
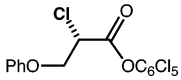
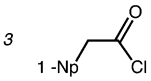
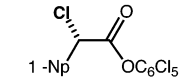
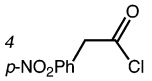
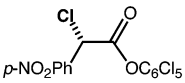
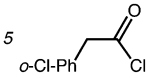
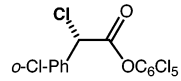
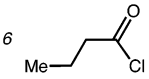
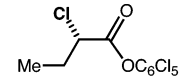


Table 2. Alkaloid-Catalyzed Reactions of Acyl Halides **1** Using NaH

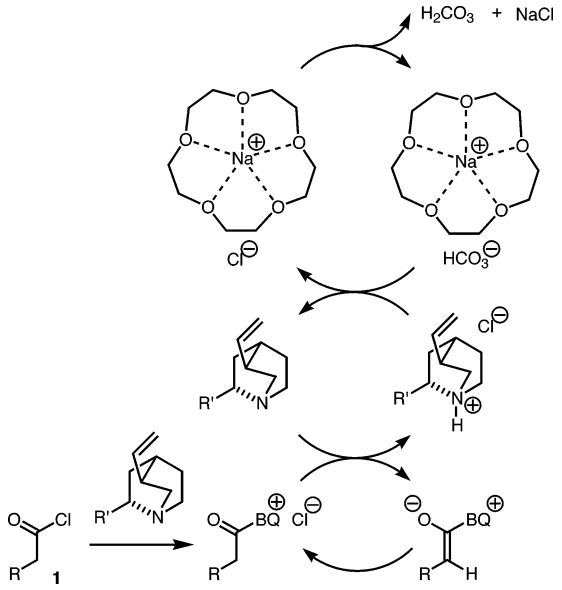
entry	*acid chloride*		*product*		*% ee*	*% yield*[a]
1		**1a**		**(*S*)-6a**	95	63
2		**1b**		**(*S*)-6b**	92	61
3		**1c**		**(*S*)-6c**	92	61
4		**1h**		**(*S*)-6h**	99	58
5		**1i**		**(*S*)-6i**	90	79
6		**1j**		**(*S*)-6j**	98	43

[a] Reactions run with 10 mol % catalyst, 2.7 mmol of ketene, 1.3 mmol of **5a** at −78 to 25 °C for 4 h in THF. Yield based on **5a** after chromatography.

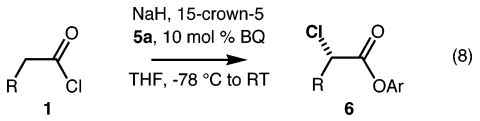
In this case, ketene is generated through a shuttle deprotonation system that employs BQ and 15-crown-5 as a phase transfer cocatalyst to help solubilize NaH (Scheme 3). Phenylacetyl chloride was added to a stirred suspension of NaH and catalytic amounts of 15-crown-5 and BQ in THF at −78 °C. A solution of **5a** in THF was added slowly over 3 h by syringe pump, and the reaction was warmed to room temperature over 4 h (eq 8).[26] Workup and chromatography yielded the α-chlorinated product (*S*)-**6a** in 63% yield and 95% ee. We proceeded to examine the system on other acid chloride substrates (Table 2) with results that are comparable to BEMP (ee's 90−99%; yields 58−79%), but at a fraction of the cost. Most importantly, we were able to

(26) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627−629.

Scheme 4. Generation of Zwitterionic Enolates Using Sodium Bicarbonate



prepare compound **6a** on a larger, multigram scale using this methodology.

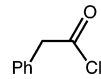
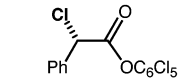
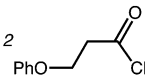
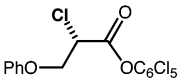
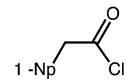
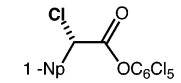
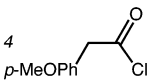
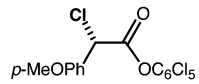


(8)

Ketene/Enolate Formation III: Chlorinations Using Sodium Bicarbonate. Although cost-effective, NaH presents some disadvantages as a stoichiometric base. For example, NaH requires a ketene "preformation" step that can be difficult to manage. High concentrations of ketene can be prone to dimerization and other side reactions; so a method that would involve a very slow, "time release" ketene or zwitterionic enolate generation might be more appealing. Along those lines, we have found that we can effect halogenation of acid chlorides using an excess of the mild base sodium bicarbonate as a dehydrohalogenating reagent along with catalytic amounts of BQ and 15-crown-5.[27] Sodium bicarbonate is extremely cheap, readily available, very mild, and air stable. It is potentially more advantageous than the use of potassium carbonate because racemization due to excess base or byproduct sodium salts is much less likely, allowing for a one-pot procedure and eliminating the need for a filtration step. Furthermore, we presumed that proton transfer from protonated BQ (or an acylammonium salt) to the bicarbonate should be slower, due to the mild basicity of bicarbonate, thus ensuring a proportionately slower formation of ketene (or, perhaps more plausibly, the zwitterionic enolate). In contrast to our proposed ketene generation with sodium hydride, it is less likely that free ketene is being generated with sodium bicarbonate, as the preformation step has been obviated. In fact, when we attempt (even lengthy) preformation steps with bicarbonate as stoichiometric base and BQ as the shuttle, no free ketene (monitored by ReactIR) is formed (*vide infra*). A plausible mechanism is illustrated in Scheme 4. After initial transacylation by one molecule of BQ, a second molecule of catalyst abstracts the α-proton to form the zwitterionic enolate directly. The hydrochloride salt of BQ then transfers its proton to the bicarbonate, thus regenerating the catalyst.

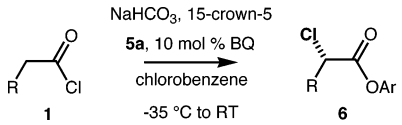
(27) Shah, M. H.; France, S.; Lectka, T. *Synlett* **2003**, *12*, 1937−1939.

Table 3. Alkaloid-Catalyzed Reactions of Acyl Halides **1** Using $NaHCO_3$

entry	*acid chloride*		*product*		*% ee*	*% yield*[a]
1		**1a**		**(S)-6a**	90	68
2		**1b**		**(S)-6b**	88	56
3		**1c**		**(S)-6c**	91	60
4		**1k**		**(S)-6k**	88	58

[a] Reactions run with 10 mol % catalyst, 2.7 mmol of acid chloride, 1.3 mmol of **5a** at −35 to 25 °C for 5 h in chlorobenzene. Yield based on **5a** after chromatography.

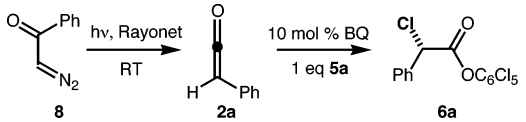
To support our hypothesis, we conducted the experiment at room temperature (where monosubstituted ketenes are usually unstable) and isolated product in 65% yield, with albeit lowered enantioselectivity (56% ee). When we attempted to perform the corresponding reaction with NaH as stoichiometric base at room temperature, no desired products were observed. During optimization, we discovered that an excess of sodium bicarbonate (>10 equiv), in the presence of catalytic amounts of BQ and 15-crown-5 cocatalyst at −35 °C in chlorobenzene, afforded α-haloester (*S*)-**6a** in 68% yield with 90% ee (eq 9). Although we have not screened a full range of acid chloride candidates using this protocol, we have reason to believe it should be as applicable as the earlier methodology, albeit with slightly lower ee's at the present time (Table 3).



(9)

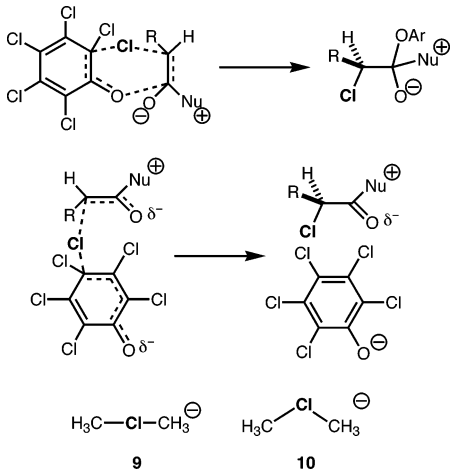
Scale-Up Reactions. In an attempt to probe the utility of our methodology, we focused our attention on the scale-up of the halogenation/esterification using either sodium hydride or sodium bicarbonate. Using 2 g of **5a**, we obtained α-chloroester **6a** in 65% yield and in 91% ee for NaH and 60% yield with 90% ee for $NaHCO_3$.

Direct Ketene Formation IV: Generation via Wolff Rearrangement. Another common method for generating free ketene is the Wolff rearrangement.[28] When diazoketone **8** is photolyzed, it produces phenylketene through a standard Wolff rearrangement (eq 10). We photolyzed **8** in the presence of quinone **5a** and 10 mol % BQ in THF and afforded α-chloroester **6a** in 45% yield and 85% ee, demonstrating that alternative sources of ketenes are viable in the reaction.



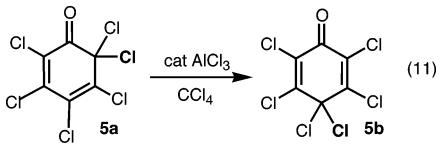
(10)

Scheme 5. Proposed Transition States of Chlorination Using **5a** versus **5b**



9 **10**

Mechanistic Considerations. It occurred to us that it is possible that the asymmetric chlorinations are operating through either of two reactive assemblies. One can imagine a process by which α-chlorination and transacylation occur simultaneously through a six-membered transition state, or else a mechanism in which these two steps are separated (Scheme 5). The ortho relationship between the carbonyl oxygen and the electrophilic chlorine atom in **5a** makes the concerted option a possibility. To test this theory, we converted **5a** to its corresponding para-substituted isomer **5b** under $AlCl_3$ catalysis (eq 11).[29] A six-membered transition state is not possible for reaction of **5b** with an enolate for steric reasons. When **5b** was substituted for **5a** in the chlorination of phenylacetyl chloride using NaH as the base, α-chloroester **6a** was formed in 68% yield and only 56% ee. This result can be rationalized through two possibilities: one based on transition state ordering, and the other on thermodynamics. With **5a**, the six-membered transition state allows for facile transfer of the chlorine with simultaneous ester formation in a rigid transition state assembly. Because this assembly is not geometrically possible for **5b**, only a less ordered stepwise process is involved, and the selectivity might be diminished. Alternatively, **5b** is lower in energy than **5a**, and perhaps less reactive as a halogenating agent. Consequently, the reaction rate is slowed and the selectivity similarly is decreased as higher temperatures are needed to ensure reaction. It is difficult to imagine a practical experiment to differentiate the two possibilities, so we turned to theoretical calculations to shed light on the question.



5a **5b** (11)

For example, the transition state of the chlorine transfer step in the concerted mechanism must be highly bent. However, the bridged μ-chloro anion **9** shows a strong preference for a linear geometry at B3LYP/6-31G*;[30] a bent starting geometry (**10**) results in convergence to a linear geometry or else dissociation to the methyl anion and chloromethane upon optimization. Species **9** can serve as a model for the electrophilic chlorine transfer process of our system, and it would seem to disfavor the concerted option on this basis.

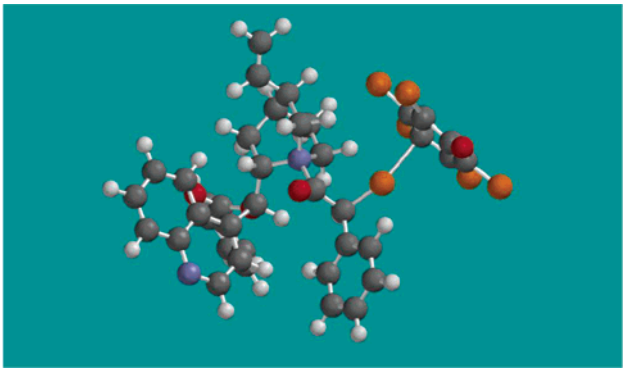


Figure 1. PM3 transition state assembly of the reaction of **5a** with the BQ·phenylketene derived enolate.

Stereochemical Models and Transition States. To determine good starting geometries for molecular orbital-based transition state calculations, we first turned to molecular mechanics (MM) given the size and the "all organic" nature of the putative reactive enolate complex. The MM model that we propose to account for the sense of induction that we observe in our cinchona alkaloid-catalyzed halogenation reactions is also similar to the model proposed for the asymmetric β-lactam forming process. For example, MM calculations using modified MMFF or AMBER force fields[31] on model ketene-**3a** (the complex derived from reaction of BQ with phenylketene) reveal a low energy structure in which the *re* face is exposed to the approach of the halogenating agent, whereas the *si*-face approach is 2.5−7 kcal/mol higher in energy, depending on the force field used in the calculation.[32]

Next, we calculated transition states at the semiempirical PM3 level of the complex derived from phenylketene and BQ during its reaction with **5a** (Figure 1) using the low energy MM conformation as a starting geometry. While admittedly crude, this level of theory was deemed necessary given the size of the reactive assembly. No stable concerted TS's were found in this case; in contrast, the chlorine transfer process occurs nearly linearly (bond angle 162°) in a "late" TS (distance enolate/Cl = 1.84 Å; distance quinone/Cl = 2.40 Å) in a fashion that favors a stepwise mechanism. When the geometry is constrained to a cyclic array, it is evident that substantial steric hindrance between the enolate and **5a** would be expected. In the linear, stepwise transition state, however, an interaction between the carbonyl/phenolic oxygen on **5a** and the hydrogen atoms alpha to the bridgehead nitrogen on the BQ catalyst constitutes an apparent stabilizing (rigidifying) Lewis acid/Lewis base (LA−LB) interaction.[33] Thus, at this point, we favor the thermodynamic explanation for the difference in selectivity between **5a** and **5b** (with perhaps a minor LA−LB interaction to stiffen

(28) Chiang, Y.; Kresge, A. J.; Popik, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5930−5932.
(29) Denivelle, L. *Bull. Soc. Chim. Fr.* **1956**, 1834−1836.
(30) Calculations were performed using the Titan Program, version 2.0. On the other hand, the μ-bridged chloro cation $[H_3C-Cl-CH_3]^+$ shows a strong preference for a bent geometry.
(31) We used the program Macromodel (version 7.0) for the calculations (Schrodinger, Inc.).
(32) Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002**, *58*, 8351−8356.

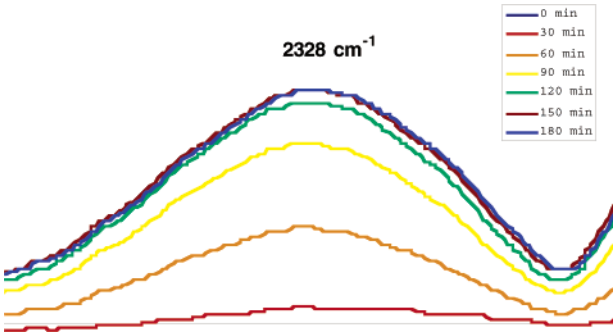
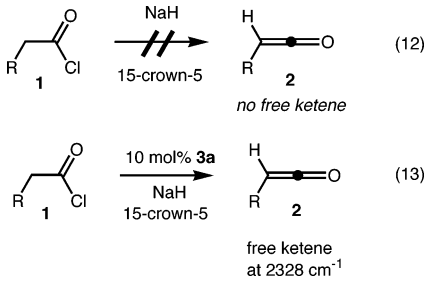


Figure 2. Growth of the phenylketene stretch at 2328 cm^{-1} over time.

the transition state) and a stepwise mechanism in which a tight ion pair recombines in a fast acylation step.

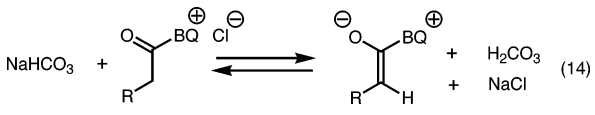
Spectroscopic Evidence of Ketene Formation. We conducted a series of spectroscopic experiments to provide evidence for the putative "preformation" of ketene when sodium hydride is used as the stoichiometric base. Our previous investigations led us to similar conclusions about the irreversible BEMP method of ketene generation.[34] Our initial shuttle deprotonation system utilized proton sponge as the stoichiometric base and did not require the generation of free ketene to proceed; the zwitterionic enolate was also found to form reversibly under these conditions. Similarly, the use of bicarbonate bases does not necessarily mandate the preformation of ketenes.



To shed light on this issue, we examined the formation of phenylketene from sodium hydride and BQ catalyst by a ReactIR experiment. With the addition of 10 mol % BQ to the acid chloride, sodium hydride, and 10 mol % 15-crown-5, free ketene is gradually formed, as witnessed by the observed IR frequency for the ketene carbonyl stretch at 2328 cm^{-1} (Figure 2). The reaction of BQ with phenylacetyl chloride itself is very fast, with a small, but noticeable, ketene hump (2328 cm^{-1}) forming immediately after addition. The broad phenylketene stretch then grows in fairly rapidly before it levels off and begins to diminish as the BQ present slowly catalyzes the formation of ketene dimer. Interestingly enough, the phenylacetyl chloride carbonyl stretch (1799 cm^{-1}) never completely goes away, thus explaining why an excess of acid chloride may be needed. As mentioned, ketene formation is not observed with HCO_3^- as base, even in the presence of BQ.

To confirm the pivotal role of BQ with regard to the ketene forming reaction, several control reactions were also conducted and monitored by ReactIR. At −35 °C in chlorobenzene, sodium hydride alone does not produce any visible amount of ketene (eq 12). Even the addition of 2 equiv of NaH has no visible effect on the phenylacetyl chloride carbonyl stretch. Similarly, the addition of 10 mol % 15-crown-5 to a mixture of 1.0 equiv of NaH and phenylacetyl chloride in chlorobenzene at −35 °C produces no detectible free ketene. It is not until both of these reactions warm to near 0 °C that the free ketene signal becomes apparent, with the 15-crown-5 reaction producing ketene earlier and to a greater extent, but not nearly to the extent to which the BQ catalyst induces ketene formation. When BQ is added to the NaH solution at lowered temperatures, the phenylketene stretch at 2328 cm^{-1} then grows in over time (eq 13 and Figure 2).

Kinetics of the NaH and the HCO_3^- Promoted Reactions. If the use of NaH as stoichiometric base involves a ketene preformation step, whereas the use of bicarbonate does not, it stands to reason that the dependence of the reaction rate of each shuttle base system on various reaction components could be different. To our surprise, we determined that the reaction rates of both the NaH and the bicarbonate promoted halogenation reactions are proportional to the concentration of halogenating agent for the standard reaction of phenylacetyl chloride **1a** with **5a** in THF at −78 °C.[35] This result is in marked contrast to the β-lactam cycloaddition reaction, whose rate is dependent on the concentration of acid chloride and catalyst, but not imine. These facts run counter to our intuition that in the case of the bicarbonate shuttle, slow enolate formation should be the rate-determining step (RDS), not reaction of enolate with chlorinating agent, as our results imply. Still, our intuition can be reconciled with the kinetics if we assume that the rate of enolate formation in the bicarbonate shuttle is comparable to the rate of reaction with zwitterionic enolate, or else that enolate formation is reversible, so that its concentration does not build up over the course of time (eq 14). Given the basicity of bicarbonate, this scenario is very plausible, and, as stated, reversible enolate formation is observed in the β-lactam cycloaddition reaction with proton sponge as base. Interestingly, we observed no direct dependence of the catalyst concentration on the rates of product formation above 10 mol % loading. This is due to the apparent fact that with higher catalyst concentrations, there is a dramatic observed increase in competitive phenol formation in the early stages of reaction, an event which necessarily leads to formation of nonhalogenated byproduct **7**.

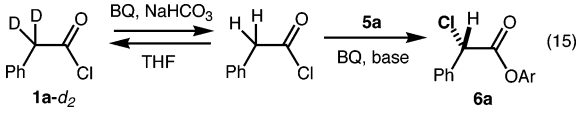


The postulate of reversible enolate formation is consistent with the observation that α,α-dideuteriophenylacetyl chloride (**1a**-d_2) undergoes fast α-proton exchange in the presence of BQ catalyst and bicarbonate in THF solvent, resulting in formation of α-chloro-α-protio product **6a** (eq 15).

(33) Short C−H−O distances have been identified in organic compounds and also in nucleic acid molecules. These interactions have been studied in detail, with an emphasis on the application of crystal correlation studies. Due to their influence in crystal packing, studies are underway to ascertain the extent to which these interactions affect C−H approach to an oxygen atom. For mechanistic and theorical discussions of C−H−O interactions, see: (a) Calhorda, M. J. *Chem. Commun*. **2000**, 801−809. (b) Desiraju, G. R. *Acc. Chem. Res*. **1991**, *24*, 290−296. (c) Gu, Y.; Kar, T.; Scheiner, S. *J. Am. Chem. Soc*. **1999**, *121*, 9411−9422. (d) Steiner, T. *Chem. Commun*. **1997**, 727−734.

(34) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc*. **2002**, *124*, 6626−6635.

(35) Kinetics experiments were performed by varying the concentration of chlorinating agent **5a**, BQ catalyst, and acid chloride substrate, and measuring the percent conversion at various times (see Supporting Information).

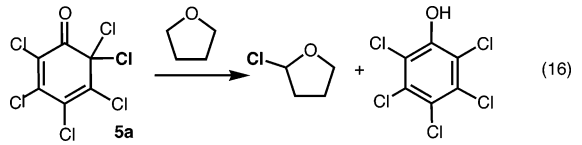


(15)

Mechanistic and Practical Implications of Nonhalogenated Byproducts. Throughout the development of these reactions, we were intermittently plagued by the capricious formation of undesired nonhalogenated achiral ester byproducts **7** in quantities varying from trace amounts to >50%. The byproducts can be thought of in a formal sense as resulting from the reaction of pentachlorophenol with *in situ* generated ketenes. Pentachlorophenol, for example, must arise from the reduction of quinone **5a** by species within the reaction mixture that contain active hydrogen. As explained above, high catalyst loadings paradoxically promote the formation of byproduct through quinone reduction. Other possibilities for reductants include: (1) the solvent, (2) the stoichiometric base, (3) the catalysts and cocatalysts, (4) the substrate (which can conceivably react with the quinone through a remote position, as well as the desired α-position), (5) impurities such as water, and (6) light (which may induce radical pathways). To minimize (or eliminate) byproduct formation, each of these possibilities was investigated individually. Because both the acid chloride and the chlorinating agent are incorporated into the byproduct, its suppression could potentially increase our yields. The mechanism of the formation of this product is also of interest; one could imagine that pentachlorophenol is being formed *in situ* and this reacts with either a free ketene or the acid chloride to give the ester.

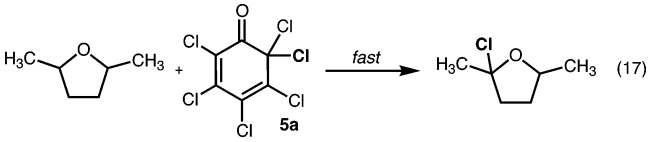
Our initial investigation centered on the potential formation of free pentachlorophenol involving each of the aforementioned scenarios:

(1) Solvent. This seemed one of the more likely culprits due to its overwhelming presence in the reaction. Additionally, THF, a solvent of choice, is known to react readily with certain active halogenating agents.[36] We stirred quinone **5a** in THF both in the presence and in the absence of BQ at temperatures ranging from −78 °C to reflux (eq 16). Only at room temperature and above was formation of phenol observed in quantities sufficient to account for production of the byproduct, and BQ had only a small effect on promoting phenol formation under these conditions. The THF is presumably converted into the α-chloride, as is precedented in published work on THF chlorinations.[37]



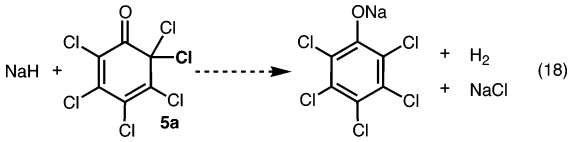
(16)

Note that the reaction temperatures for phenol formation are higher than those for desired product formation, suggesting that careful temperature control could alleviate problems. However, putative phenol formation occurs at much lower temperatures in the actual reactions. When the more easily oxidized solvent 2,5-dimethyl-THF was employed in the standard reaction, an enhanced yield of phenol was observed, implicating the solvent as a potential substrate (eq 17), and suggesting the use of an appropriate proton free solvent in some cases.



(17)

(2) The Stoichiometric Base. We have observed byproducts with the use of several different stoichiometric bases, including proton sponge, $NaHCO_3$, and NaH. As we stated earlier, proton sponge reacts readily with quinone **5a** to liberate pentachlorophenol. Potassium carbonate affords much reduced quantities of byproduct relative to proton sponge, but for practical reasons carbonate bases are inferior to NaH, as a filtration step is needed. When prolonged times are employed in the reaction of NaH and acid halides to produce putative ketenes, ensuring consumption of all NaH, the relative quantities of byproduct are reduced, suggesting that residual NaH can react with quinone **5a**. However, when NaH is mixed with **5a** in CCl_4 in the presence of 15-crown-5 and BQ, only trace amounts of phenol were observed after 24 h at room temperature, suggesting that quinone reduction by NaH is probably not a major contributor in the production of the achiral ester **7** (eq 18).



(18)

(3) The Catalysts and Cocatalysts: ***N*-Chloro Species 3c.** In our initial report, we demonstrated that *N*-chlorination of resin-bound BQ deactivated the catalyst, although *N*-chlorination seemed to be less of a problem using soluble catalysts. Upon recharacterization of the quinine moiety, we discovered derivative **3c**. We set up a test reaction to see if *N*-chlorination could be plausibly occurring in solution under any circumstances, in light of our catalyst concentration experiments. We employed 2-(*N*,*N*-dibenzylaminomethyl)naphthalene **11** to catalyze the halogenation reaction in place of BQ, assuming that if *N*-chlorination were to occur, dehydrohalogenation would follow yielding an iminium salt **13**.

Hydrolysis of **13** should yield naphthaldehyde **14**, an easily identifiable marker (Scheme 6) that provides a convenient test for *N*-chlorination. In the event, naphthaldehyde was formed in 30% yield and α-haloester **6a** was formed in 30% yield, confirming that under select conditions *N*-chlorination can play a deleterious role in the reaction, although fortunately BQ seems to be fairly resistant to *N*-chlorination under normal reaction conditions, except perhaps in high concentrations.

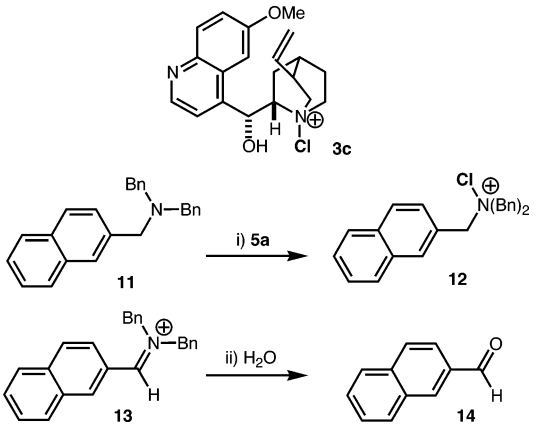
Finally, even the role that the cocatalyst 15-crown-5 may play in byproduct formation was investigated. Quinone **5a** was treated with 15-crown-5 in the inert solvent CCl_4 and monitored from −78 °C to room temperature. No phenol formation was observed in this case.

(4) Substrates. Under no conditions have we observed remote chlorination of a substrate that would account for phenol formation.

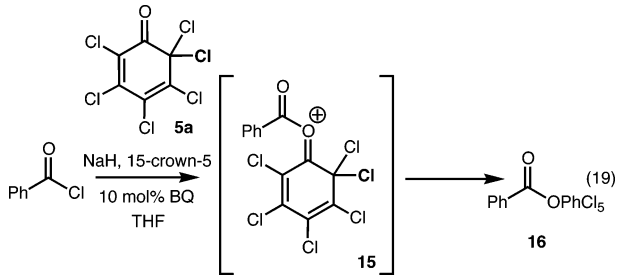
(5) Impurities. The most likely impurity in the reaction is water, especially with the use of hygroscopic solvents such as THF. To elucidate the role that water could be playing, we have conducted our reactions under conditions ranging from scrupulously dry to wet (1 equiv or more of water). A definite trend could be discerned: in reactions with little or no water,

(36) (a) Koole, G. A.; Nelson, W. L.; Gioannini, T. L.; Angel, L.; Simon, E. J. *J. Med. Chem.* **1984**, *27*, 1718−1723. (b) Crombie, L.; Wyvill, R. D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1971−1982.
(37) Gross, H. *Angew. Chem.* **1960**, *72*, 268−269.

Scheme 6. Deactivation of Catalyst Due to *N*-Chlorination

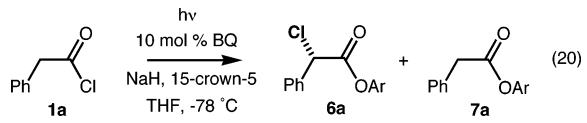


drastically reduced amounts of byproduct were obtained, whereas in "high" water reactions, substantial amounts of byproduct were isolated. Under the conditions of the reaction, it is possible that water could react with quinone **5a** to form hypochlorite and phenol, thus accounting for the observed results, although this would seem, based on prior observations, to be contrathermodynamic.



A control experiment in which benzoyl chloride was substituted for phenylacetyl chloride under normal reaction conditions also revealed that ketene formation is not necessarily a prelude to the byproduct (eq 19). Benzoyl chloride has no α-protons, yet was found to undergo transacylation by pentachlorophenol giving the ester **16**.[38] This suggests that the acid chloride activates phenol formation in some manner, perhaps by transient formation of acyloxonium ion **15**, which we expect to be a much more reactive halogenating species toward not only the substrate, but the solvent and other reaction components as well. We view this to be a very significant control experiment, suggesting that acid chloride itself can play a deleterious role.

(6) Light. Another plausible explanation for the reduction of **5a** could be the formation of chlorine atoms from the homolytic cleavage of C−Cl bond due to light. To determine the validity of this hypothesis, we conducted a series of experiments in the presence and absence of light. First, the normal reaction (NaH) was performed under a 60-W lamp over a period of 5 h. α-Chloroester **6a** was obtained in 58% yield with 35% of the nonhalogenated byproduct **7a** (eq 20). In the presence of light and AIBN, a radical initiator, α-chloroester was formed in 55% yield with 30% byproduct.



When the reaction was performed purely in the dark, product was obtained in 58% yield with only 10% of the byproduct.

Table 4. Solvent Effects on the Asymmetric Chlorination of Phenylacetyl Chloride Using NaH under Standard Conditions

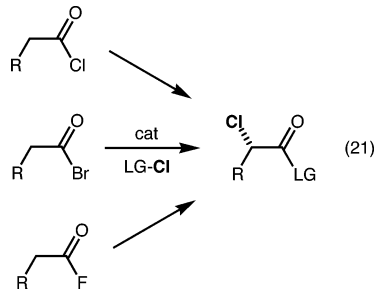
solvent	% ee	% yield[a]	% byproduct **7a**
THF	92	65	31
toluene	92	65	27
CH_2Cl_2	92	65	25
benzotrifluoride	-	0	90
$CFCl_3$	65	40	55
chlorobenzene[b]	93	70	-
CCl_4[c]	85	45	25

[a] Reactions run with 10 mol % catalyst, 0.13 mmol of ketene, 0.065 mmol of **5a** at −78 °C to room temperature for 4 h in THF. Yield based on **5a** after chromatography. [b] Reaction preformed at −35 °C. [c] Reaction preformed at −0 °C.

Trying the normal reaction in the presence of a radical scavenger (cumene) afforded product in 58% yield with 20% of the unwanted byproduct. Therefore, we can conclude that light is not significantly affecting the amount of desired product, although it seems to have an effect on the amount of byproduct in some cases.

(7) Alternative Solvents. We screened a number of solvents under the normal conditions, ranging from those with no protons (CCl_4, $CFCl_3$) to those with protons present on deactivated aromatic rings (chlorobenzene, benzotrifluoride), and compared the results to those obtained using common solvents such as THF and toluene (Table 4). Chlorobenzene proved to be the most compatible with our method, although the reaction temperature had to be raised to −35 °C to avoid freezing. Upon the replacement of THF in the published NaH procedure with chlorobenzene, chloroester **6a** was formed in 70% yield with 93% ee, with no detected byproduct. Benzotrifluoride results in a spectacular failure (>90% byproduct) for unknown reasons. It must be pointed out that the formation of byproduct otherwise had little correlation to the presumed reactivity (especially oxidizability) of the solvent, aside from the case of THF and dimethyl-THF.

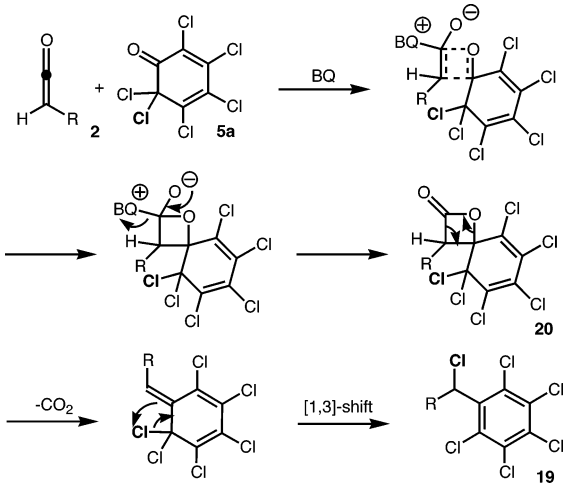
In summary, it is unlikely that any one factor can completely account for the formation of the nonhalogenated byproduct. Instead, a complex interplay of potential reasons can conspire to produce large amounts of byproduct, rendering the reaction of reduced utility. To minimize its formation, we propose a number of precautions, including the use of alternative proton free solvents, NaH as an inexpensive stoichiometric base in which ketene formation occurs under more extended (>2 h) time periods, or else $NaHCO_3$ as another, "slow release base" alternative, and scrupulously water-free conditions. Also, catalyst loadings should be kept to 5−50 mol %.



Other Acid Halides. We have also used acid fluorides and acid bromides with varying degrees of success in the chlorination reaction (eq 21). Under no circumstances is bromine or fluorine

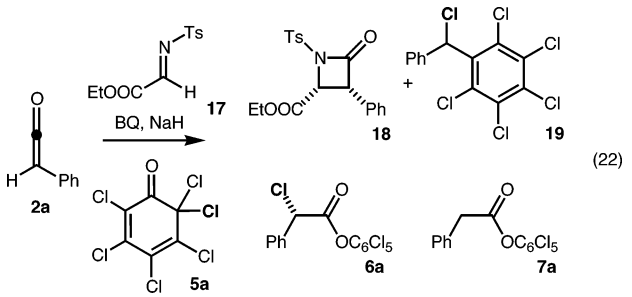
(38) Igolen, J.; Morin, C. *J. Org. Chem.* **1980**, *45*, 4802−4804.

Scheme 7. Proposed Mechanism of the Formation of **19**



incorporated into the α-position instead of chlorine, facts that confirm the origin of the chlorine atom to be in the polyhaloquinone. Whereas acid bromides work as well as acid chlorides, acid fluorides, on the other hand, generally afford low yields of product. We attribute this result to the sluggish acylation of the chiral nucleophilic catalyst by the acid fluoride, which is a less reactive acylating agent.

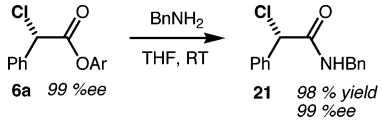
A Mysterious Byproduct. To gain insight into competition between halogenation and *β*-lactam formation, reactions presumed to follow similar mechanisms, we conducted an experiment in which the chlorinating agent **5a** and α-imino ester **17** were added in equal amounts to a preformed solution of phenylketene and a stoichiometric amount of BQ at −78 °C (eq 22). After the mixture was warmed to room temperature, four different products were observed and isolated from the reaction mixture. In addition to the α-chlorinated ester **6a**, *β*-lactam **18**, and the corresponding nonhalogenated ester **7a**, variable amounts (from 5% to 50%) of the chlorinated compound **19** were observed. Characterization of **19** led us to the following proposed mechanism, involving cycloaddition of phenylketene (or its enolate) with chlorinating agent **5a** to form lactone **20** (Scheme 7).



(22)

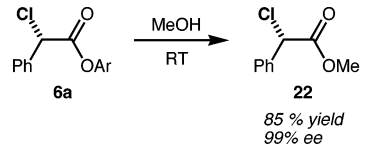
Decarboxylation and rearomatization with a concomitant 1,3-chloro-shift thus provides the product. Note that this mechanism does not take into account the presence of imine **17**, which is mysteriously necessary to the formation of the byproduct. Thus, the precise reason this product forms is still not totally understood.

Conversion to Useful Optically Active Compounds; Alternative Halogenating Agents. The fact that the products of the asymmetric halogenations are active esters allows facile derivatization to other esters and amides, at least in theory. In practice, amidation of α-chloropentachlorophenyl esters proceeds well with primary amines, affording α-chloroamide **21** through room-temperature reactions that retain their optical purity (eq 23).



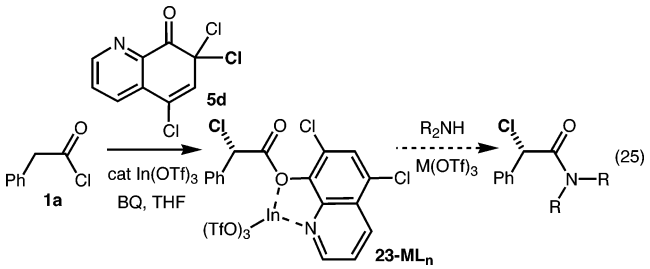
(23)

Similarly, when alcohols are stirred with our activated α-chloroesters, transesterification occurs readily without racemization to afford the α-chloro methyl ester **22** (eq 24).



(24)

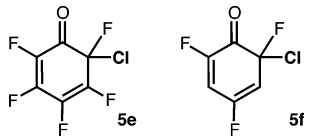
However, more vigorous conditions are required for amidation with secondary amines and anilines; racemization may result in these cases. At this point, we sought to develop new quinone-based halogenating agents in which the active ester product would contain a binding site that could be activated toward amidation by a metal cocatalyst (eq 25). The halogenating agent itself could be made more reactive by metal binding, perhaps enhancing chemical yields in the asymmetric process. The trichloroquinolinone **5d** was easily prepared from 8-hydroxyquinoline and 3 equiv of *tert*-butylhypochlorite. When this reagent was added to a solution of phenylacetyl chloride (**1a**), sodium hydride, and catalytic amounts of 15-crown-5, BQ, and $In(OTf)_3$ in THF at −78 °C, the α-chloroester **23** was observed in only 22% yield. Whereas the product starts out optically active, it racemizes rapidly (presumably due to metal coordination to the active ester), unfortunately rendering this protocol unviable. Performing the experiment without metal catalyst yields no product, at least confirming that Lewis acid catalysis is feasible. Product **23** does undergo very fast transacylations with a variety of secondary amine substrates under $Sc(OTf)_3$ catalysis, but we decided not to pursue this transformation intensively, due to the lack of enantioselectivity and yield in the initial reaction (dashed arrow, eq 25).



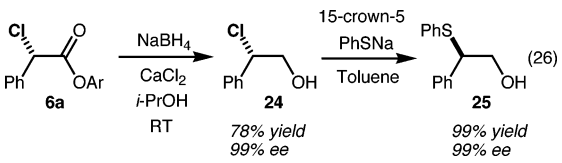
(25)

The second strategy involved making a pentafluorophenyl ester product through the polyfluorinated chloroquinone **5e**. Chlorine should transfer over fluorine, leading to desired product. In our hands, pentafluorophenyl esters are an order of magnitude more reactive toward amidation than the corresponding pentachlorophenyl counterparts. The perfluorinated α-chloroquinone (**5e**) and the α-chloro-2,4,6-trifluoroquinone (**5f**) were easily synthesized from sodium or potassium phenolate and

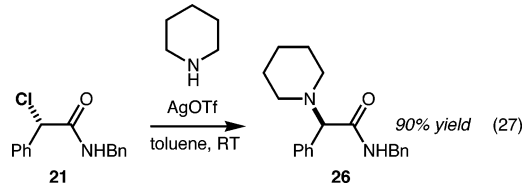
chlorine gas.[39] Regrettably, treatment of either reagent with a preformed solution of phenylketene failed to yield any product. We began to realize that we were very lucky indeed to have chosen quinone **5a**, whose reactivity is apparently optimal, for screening. For example, a simple substitution of a Cl atom by a phenolate group also results in an inactive agent (witness quinone **5c**).



Synthesis of Optically Pure 2-Chloro Alcohols: Reduction by $NaBH_4$. It has been demonstrated in the literature that optically pure α-chloroacids and esters can be reduced by various means to the corresponding chloro alcohols without loss of optical induction.[40] Intrigued by this knowledge, we converted α-chloroester **6a** to the alcohol **24**. Using $NaBH_4/CaCl_2$ as our reductant, we successfully obtained the (*S*)-chloro alcohol **24** with no loss of selectivity (eq 26). Furthermore, conversion to the known chiral sulfide **25** could be accomplished by treatment with thiophenol with complete inversion.



Displacement of Chlorine Promoted by Silver(I) Salts. D'Angeli and co-workers have published a report on the stereoselective nucleophilic substitution of 2-bromoamides by amines in the presence of Ag^+ or Ag_2O.[41] The authors observed inversion of configuration in the presence of AgOTf or powdered Ag_2O as a promoter under sonication (eq 27). We applied a similar procedure using our α-chloroamides as substrates. For example, when optically enriched amide **21** is mixed with AgOTf and an amine such as piperidine, the corresponding α-amino amide **26** is produced in high yield with net inversion (although about 10% of the optical purity was lost).



Conclusion

In summary, we have developed a catalytic, enantioselective synthesis of α-chloroesters using inexpensive acid chlorides as starting materials and cinchona alkaloid derivatives as catalysts. We discovered that polychlorinated orthoquinones are superior chlorinating agents for our reactions, whereas most other mild chlorinating agents fail completely. We have also improved upon our originally published methodology by reducing the amounts of nonhalogenated byproducts and have developed the use of cost-effective stoichiometric bases to achieve an overall process possessing considerable synthetic utility, and one that by any measure is at least competitive with existing chiral auxiliary methodology.

Experimental Section

General Procedure for the Synthesis of α-Chloroesters 6 Using Sodium Hydride. To a suspension of NaH (2.7 mmol), BQ **3a** (0.13 mmol), and 15-crown-5 (0.13 mmol) in 20 mL of THF at −78 °C was added phenylacetyl chloride **1a** (2.7 mmol) in THF (1 mL). A solution of the chlorinating agent **5a** (1.35 mmol) in 20 mL of THF was added via syringe pump over 3 h, and the reaction was subsequently allowed to warm to room temperature. It was then quenched with 150 mL of water, and the aqueous layer was extracted twice with 25 mL of diethyl ether and once with 20 mL of CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$, filtered, and concentrated. The residue was taken up in chloroform and adsorbed on silica gel before undergoing flash column chromatography (100% hexanes), affording (*S*)-**6a** in 63% yield and 95% ee.

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Supporting Information Available: General procedures for using proton sponge, BEMP, NaH, and $NaHCO_3$ as the stoichiometric base, compound characterization, kinetic, and control experiment data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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