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Reactive Ketenes through a Carbonate/Amine Shuttle Deprotonation Strategy: Catalytic, Enantioselective α-Bromination of Acid Chlorides

Ahmed M. Hafez, Andrew E. Taggi, Harald Wack, Julie Esterbrook, and Thomas Lectka*

Department of Chemistry, Johns Hopkins University, 3400 North Charles St., Baltimore, Maryland 21218

lectka@jhunix.hcf.jhu.edu

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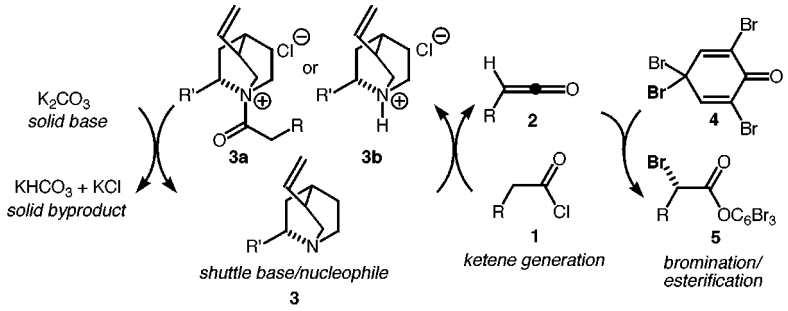
ABSTRACT



We have developed an efficient methodology for the generation of ketenes by employing a catalytic shuttle base and potassium carbonate as a stoichiometric base. We have applied this technology to the catalytic, asymmetric α-bromination of acid chlorides.

Although there exist many ways to synthesize pure ketenes, known methods usually require cumbersome apparatus, difficult conditions, or esoteric starting materials.[1] In synthetic chemistry, reactive ketenes are often accessed in situ from inexpensive acid chlorides through amine-promoted dehydrohalogenation reactions,[2] where they are invariably stirring with precipitated and solubilized ammonium salt byproducts. In some cases, the presence of these salts poses no problem; however, in other instances, they are deleterious to the course of the desired reactions.[3] The drawbacks of the present methodology have prompted us to look at powdered carbonates as stoichiometric bases for monosubstituted ketene formation from acid chlorides using a "shuttle" deprotonation strategy in which a small amount of a catalytic dehydrohalogenation base or a derived complex relays its proton to a stoichiometric base (Scheme 1). To apply this new ketene synthesis, we have chosen to investigate the tandem catalytic, enantioselective α-bromination−esterification of acid chlorides using chiral nucleophilic amines as catalysts.[4]

(1) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.

(2) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223−3235. (b) 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.

(3) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(4) We published a preliminary report focusing primarily on α-chlorinations: (a) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532. For other representative asymmetric α-halogenation reactions, see: (catalytic) (b) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359−4362. (auxiliary-based) (c) Enders, D.; Klein, D. *Synlett* **1999**, 719−720. (d) Enders, D.; Potthoff, M.; Raabe, G.; Runsink, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2362−2364. (e) Oppolzer, W.; Dudfield, P. *Tetrahedron Lett.* **1985**, *26*, 5037−5040. (f) Evans has developed an auxiliary-based route to α-chloroimides: Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123−1126.

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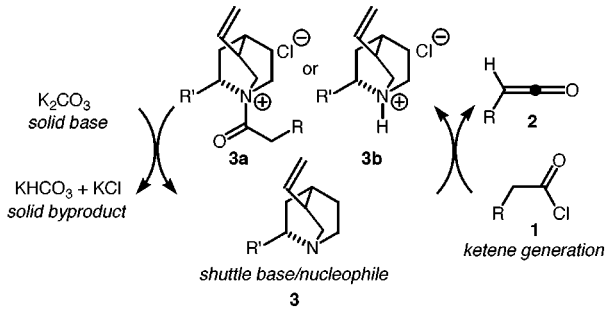
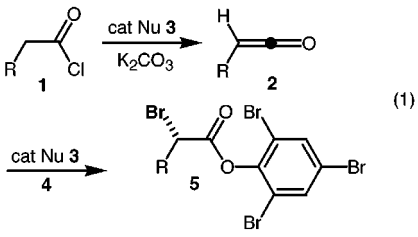
Scheme 1. Relay Deprotonation with Carbonate Salts



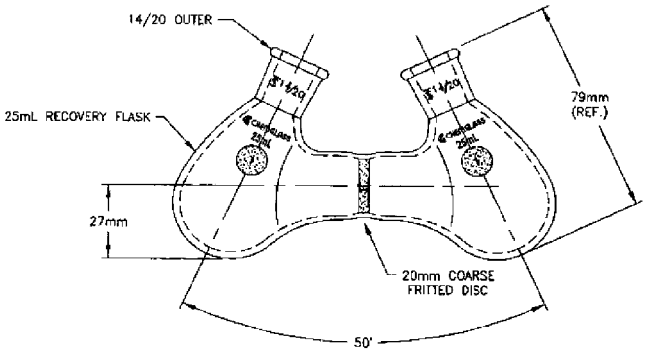
Carbonate salts are very inexpensive commodity chemicals,[5] have low toxicity, and are easy to dispose of after use. Because of their insolubility in organic media, there exists precedent for their use as stoichiometric bases in phase transfer reactions.[6] Scheme 1 shows how the shuttle deprotonation system works. Fine mesh K_2CO_3 is in contact with an organic phase (e.g., toluene solvent at −78 °C), in which are dissolved an acid chloride **1** and a small amount of a chiral nucleophilic catalyst (e.g., benzoylquinine **3**) that doubles as a shuttle base. After 12 h, the preponderance of acid chloride is consumed and replaced by a solution of the putative ketene.

Precisely how the catalytic shuttle base effects monosubstituted ketene formation is not known at the moment; however, two subtly different mechanisms come to mind. The first involves direct deprotonation of acylammonium salt **3a** by carbonate with attendant elimination of the catalyst **3**. The second mechanism involves formation of the hydrochloride salt **3b** through acid chloride dehydrohalogenation and subsequent deprotonation of **3b** to regenerate **3**. In either case, the catalyst (or its derived complexes) serve as effective proton "shuttles" for ketene formation. Byproduct bicarbonate and alkali metal halides then precipitate. Once the ketene has formed stoichiometrically, it can easily be separated from the solid phase by filtration if necessary.



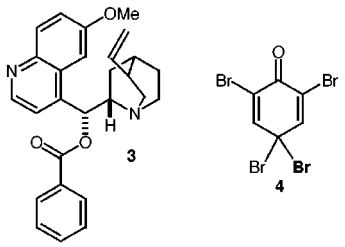
We have designed a simple piece of glassware to facilitate the ketene generation experiment and subsequent filtration (Scheme 2).[7] The apparatus consists of two recovery flasks

Scheme 2. Dual Reaction/Filtration Flask



linked by a fritted disk. The disk is located as low as possible in the assembly to allow it to be conveniently submerged in a cold bath. By canting the assembly in one direction, the reaction liquor can be transferred from one side to another without removing the piece from the bath, thus preserving the thermally unstable monosubstituted ketenes and leaving product salts and unreacted carbonate behind.

With an efficient in situ synthesis in hand, we turned our attention to catalytic asymmetric ketene brominations, screening a number of reagents for this purpose (NBS, an obvious choice, is inactive in these applications).[8] We found that the polybrominated *p*-quinone 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one **4** works best in the reaction (eq 1). The brominating agent **4**, which is commercially available, is also easily and inexpensively made in gram quantities by treatment of 2,4,6-tribromophenol with Br_2 in acetic acid in 90% yield. It is stable for extended periods when stored under N_2 in a refrigerator.



In our preliminary report on catalytic chlorinations, we proposed that the reaction proceeds through intermediate ketenes formed from dehydrohalogenation reactions using proton sponge[3] or a highly basic resin (BEMP)[9] as a base. In the interim, we identified two factors that would improve the utility and economy of the proposed reactions. The first was to substitute less expensive carbonate salts for the original dehydrohalogenating base (5 g of BEMP costs about

(5) Fine mesh size K_2CO_3 is available from Aldrich and several other companies.

(6) (a) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583−1585. For other dual uses of amine/carbonate base systems, see: (b) Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 297−300. (c) Sasson, Y.; Bilman, N. *J. Chem. Soc., Perkin Trans. 2* **1989**, 2029−2033.

(7) This flask will soon be commercially available from ChemGlass.

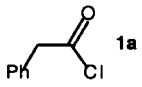
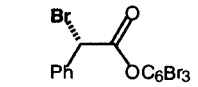
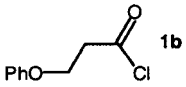
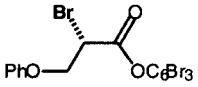
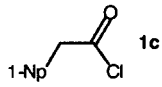
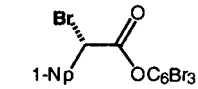
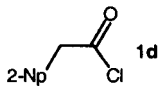
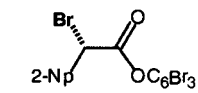
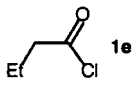
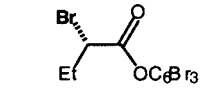
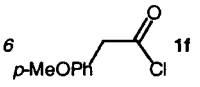
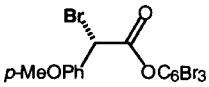
(8) (a) Bright, R.; Freeman, S.; Hayes, D.; Smith, G.; Tapolczay, D.; Coote, S. J. *Synth. Comm.* **1996**, *26*, 4195−4209. (b) Khan, G, R.; Leahy, D. E.; Katrizky, A. R. *J. Org. Chem.* **1984**, *49*, 4784−4786.

(9) (a) Hafez, A. M.; Taggi, A. E.; Wack, H. W.; Drury, W. J., III; Lectka, T. *Org. Lett.* **2000**, *2*, 3963−3965. (b) Schwesinger, R.; Willaredt, J.; Schempler, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435−2454.

$120), and the second was to focus on the synthesis of generally useful chiral α-bromoesters to complement our original submission.

A number of commercially available and easy-to-make acid chlorides were screened in the reaction (Table 1).[10] Once the ketene has been formed on one side of the dual flask, filtration of the solution into the other side was followed by addition of the brominating agent at −78 °C. The reaction was allowed to warm slowly to room temperature overnight and then worked up. For example, phenylacetyl chloride gave the brominated product **5a** in 76% yield and 91% ee (entry 1). 3-Phenoxypropionyl chloride also reacted well to afford product **5b** in 68% yield and 98% ee (entry 2). Naphthyl groups, appended to the acid chloride in the 1 and 2 positions, afforded products in good yield and high enantioselectivity (entry 3, 98% ee and entry 4, 94% ee, respectively). Importantly, aliphatic acid chlorides such as butyryl chloride also afforded enantioselective products such as **5e** in fair to good yield (entry 5, 58% yield, 86% ee). *p*-Methoxyphenylacetyl chloride (entry 6) afforded **5f** in 73% yield and 89% ee.

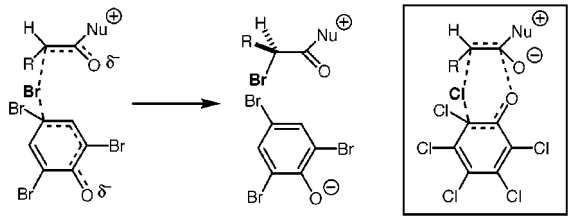
Table 1. Catalytic, Enantioselective α-Bromination of Acid Chlorides

entry	acid chloride	product	% ee	% yield[a]
1	 **1a**	 **(S)-5a**	91	76
2	 **1b**	 **(S)-5b**	98	68
3	 **1c**	 **(S)-5c**	98	71
4	 **1d**	 **(S)-5d**	94	68
5	 **1e**	 **(S)-5e**	86	58
6	 **1f**	 **(S)-5f**	89	73

[a] Reaction run with 10 mol % catalyst (0.13 mmol ketene, 0.065 mmol **4**) at −78 → 25 °C for 24 h in toluene. Yield based on **4** after chromatography.

A mechanistic point about the bromination reaction can also be made. The fact that a *p*-bromo quinone was successfully used mandates, for steric reasons, that the bromination step and the acylation step be separated (Scheme 3). Thus, a discrete ion pair is expected to form in the reaction. The situation with *o*-quinone chlorination may be different, involving simultaneous halogenation and transacylation through a tight six-membered transition state. One can also imagine that the 2,4,6-tribromophenolate anion could diffuse away from the ion pair to attack another molecule of ketene. The derived enolate could then undergo nonenantioselective bromination. The fact that our product enantioselectivities are high suggests that this pathway interferes little, if at all. Additional experiments to shed light on this intriguing mechanistic point are currently being conducted.

Scheme 3. Possible Mechanistic Differences between *para*- and *ortho*-Halogenated Quinones



Further studies on the asymmetric halogenation of organic molecules and other efficient procedures for the generation of ketenes are underway and will be reported in due course.

Acknowledgment. T.L. thanks Eli Lilly, DuPont, and the Sloan and Dreyfus Foundations for support. H.W. thanks Johns Hopkins for Sonnenborn and Whittaker Chambers Fellowships. The authors thank ChemGlass for providing a diagram of the reaction flask.

Supporting Information Available: General experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Product yields are based on the most expensive component in the reaction, usually the brominating reagent. See the Supporting Information for details and a general procedure.