JOC Notes

Scalable Methodology for the Catalytic, Asymmetric α-Bromination of Acid Chlorides

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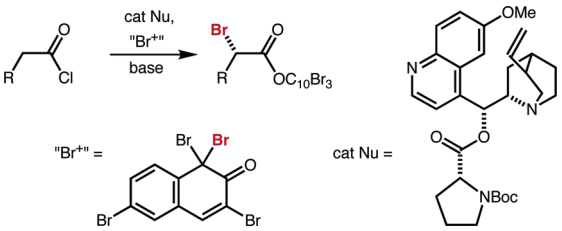


The optimization of a practical, catalytic, asymmetric process for the α-bromination of acid chlorides to produce synthetically versatile, optically active α-bromoesters is reported. A range of products is produced in high enantioselectivity and moderate to good chemical yields with retention of both upon scale-up. The reactions herein are catalyzed by cinchona alkaloid derivatives, with the best performance achieved by the use of a proline cinchona alkaloid conjugate designed in a de novo fashion.

We recently documented a catalytic, enantioselective α-bromination reaction that proceeds first by the generation of reactive ketenes via a carbonate/amine shuttle deprotonation strategy followed by the bromination of the derived ketene enolate by a selective brominating agent.[1] In this preliminary work, we encountered a number of obstacles that initially limited the synthetic utility of the bromination reaction, the main problem being the loss of enantioselectivity and yield upon scale-up of the reaction. In this note, we overcome these drawbacks through a mechanistically based approach to yield a reaction of expanded scalability. We have extended our α-bromination methodology, yielding a wide range of products with the easily displaceable bromide substituent. The general reaction sequence (Scheme 1) begins with the acid chloride starting material (**1**), which is converted to a zwitterionic enolate intermediate by the action of our catalyst (**3**) and a stoichiometric base. This transient, chiral nucleophile abstracts Br^+ from the brominating agent, producing an ion-paired intermediate (**5**) that undergoes transacylation to produce the desired product (**6**) and regenerate the catalyst (**3**) for another cycle. The enhanced S_N2 reactivity of these optically enriched products versus their chlorinated counterparts is exemplified by their utility as intermediates in the synthesis of products of pharmaceutical interest.[2] Additionally, these products are produced in high enantioselectivity (ee) and moderate to good chemical yields.

SCHEME 1. Tandem Catalytic Asymmetric Bromination/ Esterification

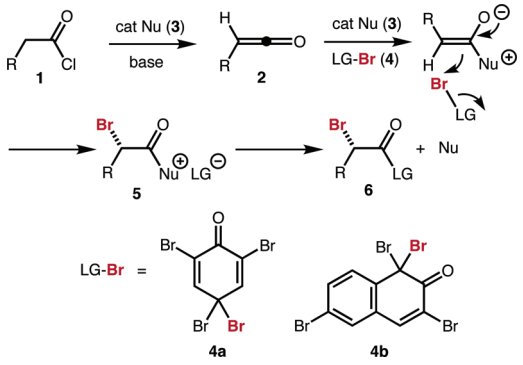
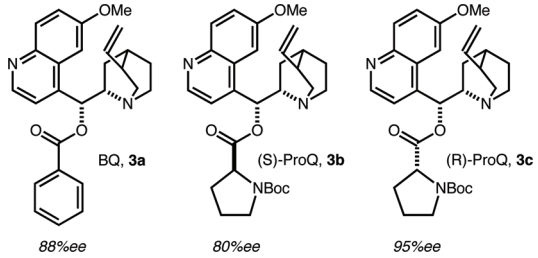


CHART 1. Cinchona Alkaloid Catalysts



Reaction Optimization. A major component of the bromination process is the catalyst system. Although we have successfully used benzoylquinine (BQ, **3a**, Chart 1) as a catalyst in the past,[3] it was clear to us that, in this case, our catalyst system may require further optimization. A standard approach to the problem of catalyst optimization is to systematically modify the existing cinchona alkaloid core[4] with appropriately placed substituents, a task generally accomplished through laborious manual screening.

We turned instead to previous theoretical studies we had done on the correlation of catalyst structure with observed enantioselectivity for reactions involving ketenes.[5] In this earlier work, we discovered that molecular mechanics (MM) calculations

† Current address: DuPont Crop Protection, Stine-Haskell Research Center, 1090 Elkton Road, Newark, DE 19711.

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

(2) For example, see: (a) Qian, X.; Zheng, B.; Burke, B.; Saindane, M. T.; Kronenthal, D. R. *J. Org. Chem.* **2002**, *67*, 3595−3600. (b) Dutton, F. E.; Lee, B. H.; Johnson, S. S.; Coscarelli, E. M.; Lee, P. H. *J. Med. Chem.* **2003**, *46*, 2057−2073.

(3) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6636. Also, see ref 18.

(4) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, *7*, 961−998.

(5) Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002**, *58*, 8351−8356.

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SCHEME 2. Zwitterionic Enolate Complex

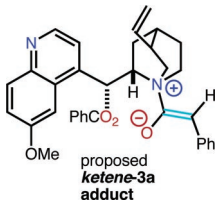
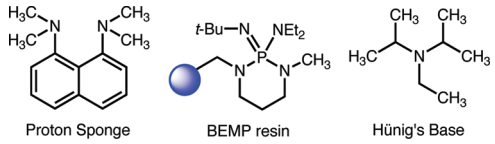


CHART 2. Organic Bases Tested

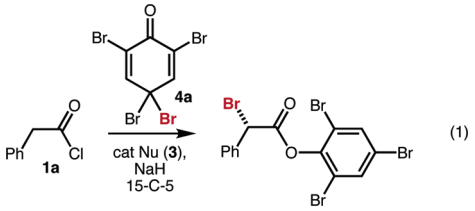


(Macromodel program) are useful for predicting both the sense of induction and the enantioselectivity in our β-lactam forming reaction. Our prototype model for the lactam reaction was found in the complex derived from the reaction of BQ (**3a**) with phenylketene (Scheme 2). We performed a calculation using a modified AMBER force field that showed a preference for approach of the imino ester electrophile to the *re*-face of the ketene enolate, with the *si*-face being 2.64 kcal/mol higher in energy. This value suggested high selectivity in the reaction, a prediction that was borne out in practice, as the (*R*,*R*)-β-lactam was formed in 99% ee.

We used the same MM calculations to guide the design of a substituted cinchona alkaloid derivative that should be even more selective than BQ (**3a**) for the bromination reaction (a de novo catalyst). Amino acids and peptides are classes of substituents that we thought would prove to be suitable for derivatization (Chart 1).[6] For example, when the benzoyl group is replaced by (*S*)-Boc-prolyl (**3b**), our MM protocol predicts a drop in ee from our BQ benchmark of 88% (more precisely, a lessening in the gap between low-energy *re* and *si* face-exposed conformations from BQ's 2.64 to 1.5 kcal/mol). Use of (*R*)-Boc-prolyl (**3c**) is predicted to increase ee based on this model, as the energy gap between *re* and *si* conformations increases to 5.6 kcal/mol instead. Experimentally, this fact is borne out: whereas **3b** gives diminished ee (80%) in a standard bromination involving 3-phenoxypropionyl chloride,[7] **3c** affords enhanced (98%) ee.

Another crucial aspect of the bromination process involves the choice of stoichiometric base. The use of proton sponge (Chart 2) results in the formation of a phenolysis byproduct concomitant with the production of various polyhalogenated proton sponges, a result analogous to that obtained in the chlorination reaction.[8]

The resin-bound phosphazine base BEMP[9] perhaps works best in the reaction overall, but its utility is limited by its expense and the difficulties one experiences in handling it. In this case, ketene precursors are formed by eluting a solution of acid chloride through a jacketed addition funnel packed with BEMP at −78 °C.[10] We have also tried more cost-effective bases such as $NaHCO_3$,[11] NaH,[12] and K_2CO_3.[1] In each case, these bases work very well for a wide variety of aliphatic and aromatic acid chlorides when very small scale reactions are conducted; however, when scale-ups are undertaken, enantioselectivities, especially those obtained when arylacetyl chlorides are employed, drop significantly. For example, using phenylacetyl chloride (**2a**) as substrate, product is obtained in 93% ee with NaH as a stoichiometric base (eq 1, on a 0.05 mM scale). On a 1 mM scale, however, the ee drops to 78%, at best. The bromination reaction itself begins with a ketene "preformation" step, which seems to fail increasingly as the scale of the reaction is increased. In these cases, ketene is not fully formed and leftover NaH remains at the end; it is very possible that solubilized NaH could cause racemization during the course of the reaction. The K_2CO_3-based system also fails for similar reasons upon scale-up. Aliphatic acid chlorides, in contrast, preserve most (if not all) of their enantioselectivity upon scale-up. However, these substrates were overall poorer performers under our original reaction conditions, giving subpar selectivities and yields relative to aromatic substrates at the original scale.[1]



We believe that some racemization may be occurring with aryl-containing substrates (which makes sense when one considers the enhanced acidity of the α-position), especially with the use of stoichiometric bases such as NaH and K_2CO_3 (some quantity of which may still be present in the reaction pot during the actual halogenation step). As mentioned previously, ketene formation with NaH appears to become progressively more inefficient upon reaction scale-up. For example, in many cases we have observed vigorous fizzing of the reaction mixture upon aqueous quench, indicating the presence of lingering NaH. A more telling experiment was our attempt to form ketene using NaH and a cinchona alkaloid derivative on one side of a double barrel flask.[13] When the bromination reaction was performed on the other side of the glass apparatus, virtually no desired product was observed, indicating that ketene formation progressed little, if at all. When analogous reactions were conducted on a very small scale, these problems were not encountered.

Brominating Agent Development. It makes sense that the intermediate most susceptible to the aforementioned racemization is the acylammonium salt (**5**, Scheme 1). We expect that it is slightly longer-lived than its counterpart in the chlorination reaction,[14] perhaps due to the fact that the phenol counterion

(6) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012.

(7) Standard reaction conditions with phenoxypropionyl chloride: 10 mol % cat., NaH as base, 10 mol % 15-crown-5, in THF at −78 °C. Also, see the Supporting Information.

(8) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245−4255.

(9) Polymer-bound BEMP resin (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine) is commercially available from Aldrich Chemical Co.

(10) For a detailed description of a ketene-forming reaction employing BEMP as base, see: Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532.

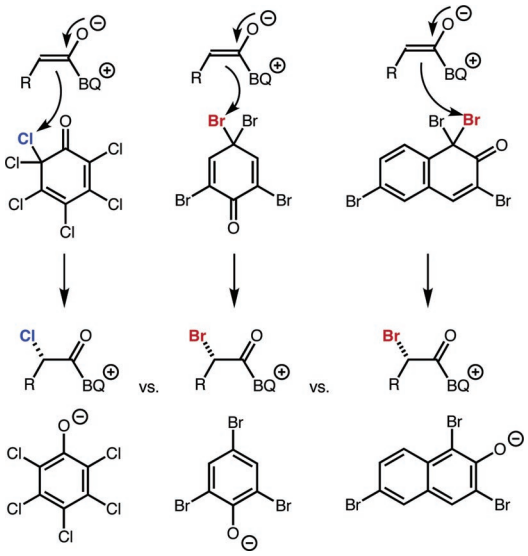
(11) Shah, M. H.; France, S.; Lectka, T. *Synlett* **2003**, *12*, 1937−1939.

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

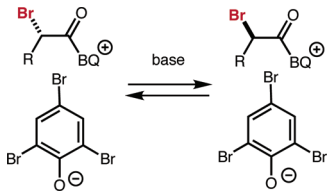
(13) The "double barrel" flask is made up of two reaction flasks separated by a glass frit. See ref 5 for a full description of the flask (commercially available from Chemglass).

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

SCHEME 3. Ortho versus Para Halogenating Agents



SCHEME 4. Enolate Epimerization



must "wheel around" to capture the acylammonium salt, whereas in the chlorination, trapping occurs rapidly by virtue of the ortho positioning of the phenolic oxygen to the site of halogenation (Scheme 3). By virtue of this extended lifetime, the acylammonium salt could racemize to some extent from adventitious bases in the reaction medium (Scheme 4). We theorized that if we used an ortho brominating agent, then the intermediate (**5**) would be less available for racemization because transacylation would occur much faster than with a para brominating agent, assuming the existence of tight ion pairs.[15]

This logic led us to synthesize and test a number of *ortho*-polybromoquinones as halogenating agents, which could solve the problem if our hypothesis is correct (Chart 3). Most brominated quinones are very easy to make; simply treat a phenol with bromine in acetic acid (eq 2).[16] Upon addition of ice water, the product precipitates out. Most of the time, a simple drying is all that is necessary, although the quinones can be recrystallized from toluene, if desired.

Brominating agent **4b**, which is easily prepared from 2-naphthol,[17] showed immediate promise. In a typical reaction on a 0.43 mM (200 mg) scale, phenylacetyl chloride (**1a**) was added to a stirred suspension of NaH and 10 mol % each of 15-crown-5 and catalyst **3c** in THF at −78 °C. A THF solution of **4b** was slowly added, and the reaction was stirred at −78 °C for 5 h before being quenched with methanolic HCl. Workup and column chromatography led to α-bromoester **6a** in 55% yield and 99% ee (Table 1).

(15) Preliminary data support tight ion pairing. Further mechanistic studies are being conducted and will be published in due course.

(16) Calo, V.; Ciminale, F.; Lopez, L.; Todesco, P. *J. Chem. Soc. C* **1971**, *21*, 3652−3653. The brominating reagent **4a** is commercially available from Aldrich. Also, see ref 5 for a synthetic procedure.

(17) (a) Fries, K.; Engel. *Liebigs Ann. Chem.* **1924**, *439*, 237−245. (b) Janney, N. W. *Liebigs Ann. Chem.* **1913**, *398*, 365−372.

CHART 3. Brominating Agents Synthesized

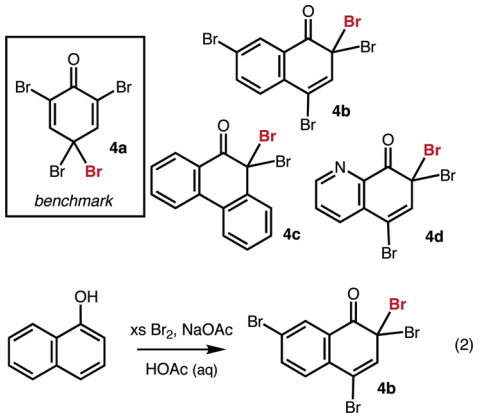
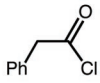
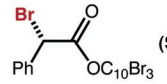
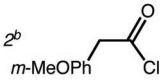
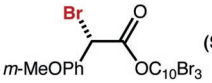
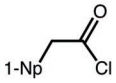
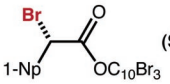
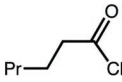
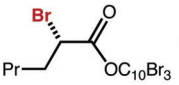
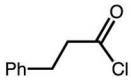
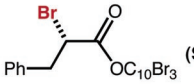
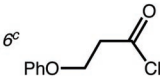
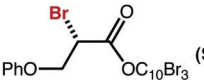


TABLE 1. Catalyzed Asymmetric α-Bromination of Arylacetyl and Aliphatic Acid Chlorides

entry	acid chloride		product		% ee	% yield[a]
1[b]		**1a**		**(S)-6a**	99	55
2[b]		**1b**		**(S)-6b**	96	59
3[b]		**1c**		**(S)-6c**	99	51
4[c]		**1d**		**(S)-6d**	99	41
5[c]		**1e**		**(S)-6e**	99	48
6[c]		**1f**		**(S)-6f**	98	68

[a] Reactions run with 10 mol % catalyst **3c** (0.609 mmol of acid chloride, 0.435 mmol of **4b**) at −78 °C for 5 h in THF. [b] NaH was used as the stoichiometric base. [c] Hünig's base was used as the stoichiometric base. The % yield was based on brominating agent **4b** after chromatography.

A number of other arylacetyl chloride substrates were screened using the same procedure and resulted in similar yields with good to excellent ee's (Table 1). For example, 1-naphthylacetyl chloride (**1c**) gave the corresponding α-bromoester **6c** in 51% yield and 99% ee. Other substituted aryl α-bromoesters were formed in yields ranging from 51% to 59% and ee's from 96% to 99%. The reaction of aliphatic acid chlorides is similar to that of the arylacetyl chlorides. Addition of the acid chloride to a solution of 1 equiv of Hünig's base and 10 mol % catalyst **3c** in THF at −78 °C was followed by the addition of a THF solution of brominating agent **4b**. The reaction was then stirred at −78 °C for 5 h before being quenched with methanolic HCl. Standard workup and column chromatography on Florisil led to α-bromoesters in fair yield and good to excellent ee. For example, dihydrocinnamoyl chloride (**1e**) was subjected to the above conditions to give **6e** in 48% yield and 99% ee. Other aliphatic substrates were also screened, as summarized in Table 1. The listed scale for these reactions is approximately 10 times

greater than those previously reported, and we have performed experiments on up to a 1 g scale without loss of yield or enantioselectivity. We have also done a few preliminary experiments with quinone **4d**, which contains a metal binding site (Chart 3).[18] In the presence of indium, the desired product of a standard reaction involving phenyl acetyl chloride (albeit at small scale) is obtained in 90% ee and 60% yield.

In conclusion, the optimization of a robust and flexible methodology for the catalytic, asymmetric, α-bromination of acid chlorides to produce activated α-bromoesters in moderate to good yields and in excellent enantioselectivity is reported. This new procedure allows for the reaction to be scaled-up without loss in enantioselectivity or yield by employing an easily synthesized ortho brominating agent and commercially available bases, along with a de novo amino acid−cinchona alkaloid conjugate catalyst. Future endeavors will include reactivity, crossover, and ion pairing experiments as well as computational and molecular dynamics studies that will shed further light on the mechanism of this reaction.

Experimental Section

Representative Procedure for Arylacetyl Products: (*S*)-2-Bromo-2-phenylacetic Acid 1,3,6-Tribromo-2-naphthyl Ester (6a). To a stirred suspension of catalyst **3c** (0.044 mmol), 15-crown-5 (0.044 mmol), and sodium hydride (0.522 mmol) in 3 mL of THF at −78 °C was added dropwise a solution of phenylacetyl chloride **1a** (0.609 mmol) in 1 mL of THF. Next, a solution of **4b** (0.435 mmol) in 3 mL of THF was added dropwise over 5 min. The resulting solution was allowed to stir for 5 h at −78 °C. The reaction mixture was then quenched with methanolic HCl (4 drops of HCl in 3 mL of methanol) and extracted three times with Et_2O. The organic layers were combined, dried with $MgSO_4$, and purified by column chromatography (100% hexanes) to yield **6a** in 55% yield. White crystalline solid (analytical sample was recrystallized from hexanes): mp = 114 °C; $[\alpha]_{25} = +45$ (*c* = 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.0−7.9 (m, 3H), 7.7−7.6 (m, 3H), 7.4 (m, 3H), 5.7 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 164.78, 143.52, 134.63, 133.64, 133.64, 131.61, 130.77, 130.26, 129.82, 129.71, 129.21, 129.16, 129.01, 128.93, 122.03, 116.15, 45.77; IR (CH_2Cl_2) 1775 cm^{-1}. Anal. Calcd for $C_{18}H_{10}Br_4O_2$: C, 37.41; H, 1.74; Br, 55.31; O, 5.54. Found: C, 37.38; H, 1.79; Br, 55.28; O, 5.55.

Representative Procedure for Aliphatic Products: (*S*)-2-Bromo-3-phenylpropionic Acid 1,3,6-Tribromo-2-naphthyl Ester (6e). To a stirred solution of catalyst **3c** (0.044 mmol) and Hünig's base (0.435 mmol) in 3 mL of THF at −78 °C was added dropwise a solution of dihydrocinnamoyl chloride **1e** (0.522 mmol) in 1 mL of THF. Next, a solution of **4b** (0.435 mmol) in 3 mL of THF was added dropwise over 5 min. The resulting solution was allowed to stir for 5 h at −78 °C. The reaction mixture was then quenched with methanolic HCl (4 drops of HCl in 3 mL of methanol) and extracted three times with Et_2O. The organic layers were combined, dried with $MgSO_4$, and purified by column chromatography (100% hexanes) to yield **6e** in 48% yield. White crystalline solid (analytical sample was recrystallized from hexanes): mp = 130 °C; $[\alpha]_{25} = -0.56$ (*c* = 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.0 (m, 2H), 7.9 (m, 1H), 7.6 (d, 1H), 7.3 (m, 5H), 4.8 (dd, 1H), 3.7 (dd, 1H), 3.4 (dd, 1H); ^{13}C NMR ($CDCl_3$) δ 166.00, 143.54, 136.32, 133.771, 132.01, 131.60, 130.74, 130.34, 129.73, 129.13, 128.80, 127.53, 122.01, 117.16, 116.21, 43.68, 41.06; IR (CH_2Cl_2) 1776 cm^{-1}. Anal. Calcd for $C_{19}H_{12}Br_4O_2$: C, 38.55; H, 2.04; Br, 54.00; O, 5.41. Found: C, 38.51; H, 2.09; Br, 54.02; O, 5.38.

Acknowledgment. T.L. thanks the NIH (GM064559), the Sloan and Dreyfus Foundations, and Merck & Co. for support. C.D.-I. thanks Mrs. Nathaniel Boggs for a fellowship.

Supporting Information Available: General procedures for the synthesis of catalysts, brominating agents, α-bromoesters, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The synthesis of quinone **4d** is similar to that reported for the related trichloroquinone, see: France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245−4255.