Letter

Synergistic Ammonium (Hypo)Iodite/Imine Catalysis for the Asymmetric α-Hydroxylation of β-Ketoesters

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ABSTRACT: The synergistic use of chiral bifunctional ammonium iodide catalysts in combination with simple catalytically relevant aldimines allows for an unprecedented asymmetric α-hydroxylation reaction of β-ketoesters using H_2O_2. The reaction proceeds via in situ formation of a hypervalent iodine species, which then reacts with the used aldimine to generate an activated electrophilic oxygen transfer reagent.

The use of chiral quaternary ammonium salt ($R_4N^+X^-$) ion pairing catalysts is one of the most versatile approaches to facilitate the noncovalent organocatalytic asymmetric control of prochiral starting materials, and numerous highly enantioselective (and often easily scalable) applications have been reported.[1,2] Although the significance of the chiral quaternary ammonium group R_4N^+ for activation and control of the starting materials/reagents is well-appreciated, the influence of the achiral counteranion X^- is usually less systematically addressed, as most scientists rely on the anion originating from the catalyst synthesis (i.e., Cl^- or Br^- for the commonly used cinchona- and Maruoka-type catalysts[1−4]). It has, however, been well-demonstrated that sometimes different counteranions can have a remarkable influence on catalyst performance and selectivity.[1,5−8] This effect becomes even more relevant when reactions are carried out under oxidative conditions, where anions like Br^- or especially I^- may easily be oxidized to hypervalent halogen species $X(O)_n^-$. The resulting (in situ formed) $R_4N^+X(O)_n^-$ species, such as iodide-based ones (Scheme 1A), show interesting and unique catalytic properties, merging the potential of (asymmetric) quaternary ammonium salt catalysis[1,2] and hypervalent iodine catalysis.[9]

Although this powerful combination is more commonly documented for achiral ammonium iodides (and bromides to a lesser extent),[9,10] the catalytic utilization of in situ formed chiral quaternary ammonium (hypo)iodite or iodate species $R_4N^+I(O)_n^-$ has so far been reported sparingly, with a handful of highly impressive (intramolecular) examples by Ishihara's group mainly (Scheme 1B).[11,12]

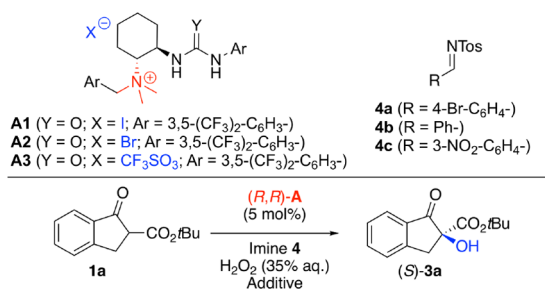Over the past years, our group has had a strong focus on the development and use of asymmetric (bifunctional) ammonium salt catalysts.[8,13] In 2016, we reported the asymmetric bifunctional ammonium iodide **A1**-catalyzed α-hydroxylation of β-ketoesters **1** using oxaziridines **2** as the O-transfer reagents (Scheme 1C).[8] Despite the high selectivities that were obtained hereby, combined with an efficient kinetic resolution of the oxaziridines,[8] we recently looked for strategies avoiding the need for the oxaziridine synthesis. Inspired by results by the Ooi

Scheme 1. Use of Ammonium Iodides under Oxidative Conditions, Recent Studies, and Preliminary Results
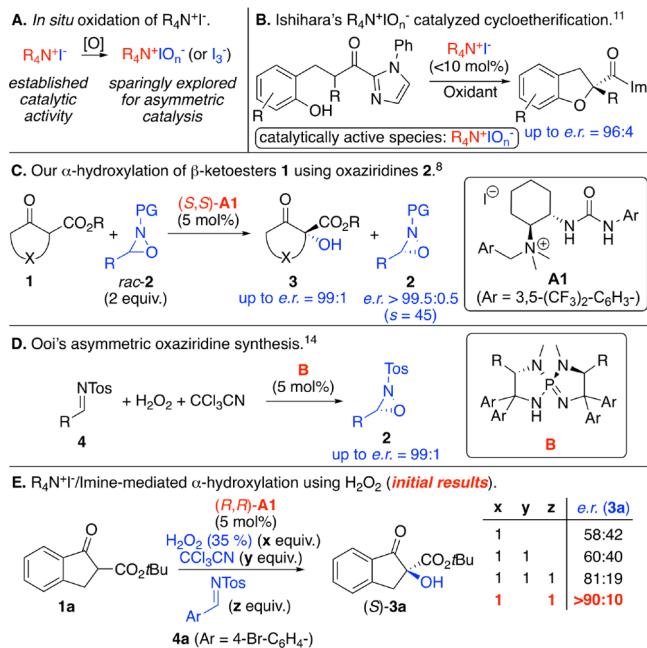
group, who reported the catalytic asymmetric synthesis of enantioenriched oxaziridines from imines **4** via a Payne-type oxidation (Scheme 1D),[14−17] we thought about developing a process where oxaziridines **2** would be generated in situ starting

Table 1. Screening of Reagents and Reaction Conditions[a]

A1 (Y = O; X = I; Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-)
A2 (Y = O; X = Br; Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-)
A3 (Y = O; X = CF$_3$SO$_3$; Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$-)

4a (R = 4-Br-C$_6$H$_4$-)
4b (R = Ph-)
4c (R = 3-NO$_2$-C$_6$H$_4$-)

entry	A	4 (equiv)	H$_2$O$_2$ (equiv)	additive (equiv)	solvent	yield (%)[b]	er[c]
1	A1		1		toluene	22	58:42
2	A1		1	CCl$_3$CN (1)	toluene	34	60:40
3	A1	4a (1)	1	CCl$_3$CN (1)	toluene	47	81:19
4	A1	4a (2)	2	CCl$_3$CN (2)	toluene	72	90:10
5	A1	4a (2)	2		toluene	75	93:7
6	A1	4a (1)	1		toluene	89	94:6
7	A1	4a (0.5)	1		toluene	82	93:7
8	A1	4a (0.2)	1		toluene	57	70:30
9	A1	4b (1)	1		toluene	90	92:8
10	A1	4c (1)	1		toluene	<50[d]	64:36
11	A1	4a (1)	1		CH$_2$Cl$_2$	60	87:13
12	A1	4a (1)	1		MTBE	96	95:5
13[e]	A1	4a (1)	1		MTBE	98/88[f]	96.5:3.5
14	A2	4a (1)	1		MTBE	97	95:5
15	A3	4a (1)	1		MTBE	21	51:49

[a]All reactions were run for 20 h at 0 °C using 0.1 mmol 1a (0.02 M) and 5 mol % of A unless otherwise stated. [b]Isolated yields. [c]Determined by HPLC using a chiral stationary phase. Absolute configuration of the major *S*-enantiomer (with *R,R*-catalysts) was assigned by comparison of retention time and optical rotation as described previously.[8] [d]Limited conversion of 1a because of rapid imine hydrolysis. [e]0.01 M with respect to 1a. [f]Using 1 mmol 1a (er = 96.5:3.5).

from imines 4 and may then be utilized for the α-hydroxylation of 1.[17]

Very interestingly, during our initial experiments, we made some rather unexpected observations (see Scheme 1E for a first summary and Table 1 for more details). Whereas the A1-catalyzed α-hydroxylation of the parent ketoester 1a with H$_2$O$_2$ alone[18] as well as in combination with CCl$_3$CN[19] yielded small amounts of product 3a with low selectivities only (entries 1 and 2), the use of an equimolar mixture of H$_2$O$_2$, CCl$_3$CN, and aldimine 4a had a beneficial effect (giving 3a with er = 81:19; entry 3). This initial result could be improved (er = 90:10) by increasing the excess of the reagents (entry 4) and in this case also the formation of slightly enantioenriched oxaziridine 2 (er = 63:35) was observed. Very surprisingly, however, when carrying out the reaction in the presence of the aldimine 4a and H$_2$O$_2$ only, product 3a was obtained with an even higher enantioselectivity of 93:7 (entry 5).

It is well-known that chiral iminium salts or imines can undergo in situ oxidations to oxaziridinium salts or oxaziridines, which may then be utilized for asymmetric epoxidation or sulfoxidation reactions.[21,22] Quite contrary, however, no oxaziridine formation was observed under our conditions when using ammonium iodide catalyst A1, imine 4a, and H$_2$O$_2$ (this was regularly checked during all further optimization). This observation rules out a mechanism proceeding via (our initially targeted) in situ formation of 2 as the active O-transfer reagent. In addition, these reported iminium-salt-catalyzed oxidations mainly used non-oxidizable counter-anions,[21] which is in sharp contrast to our reaction where the presence of an oxidizable anion is crucial (vide infra).
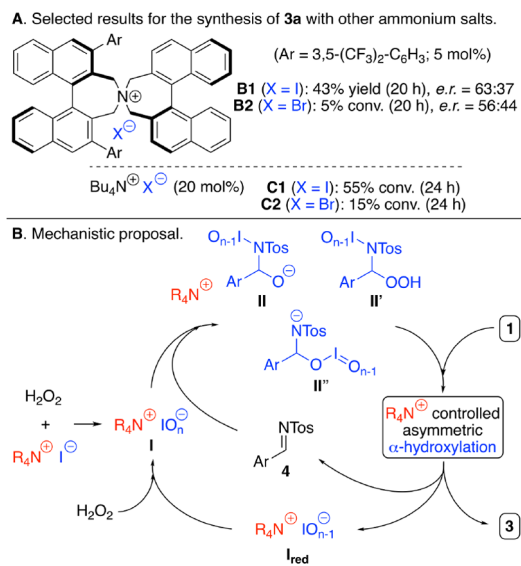
Based on these initial experiments, which suggest a rather unique α-hydroxylation mechanism involving the synergistic combination of chiral ammonium iodides and imines under oxidative conditions, we then investigated this (to the best of our knowledge, unprecedented) catalysis concept further (Table 1 gives an illustrative overview of the most significant results of a detailed screening).[20]

Optimization was carried out with the parent bis-CF$_3$-phenyl-containing bifunctional catalyst system A1,[23] but other (less selective) catalysts were tested, as well.[20] After our first hit (entry 5), we found that a lower imine and H$_2$O$_2$ amount resulted in a slightly more selective and higher-yielding product formation (entry 6; lower yields with excess H$_2$O$_2$ can be explained by faster imine hydrolysis and decarboxylation of 1). Based on the fact that the α-hydroxylation in the presence of imine 4a proceeded much more selectively and higher-yielding than in its absence (entry 1 vs 6) and the observation that we could recover significant quantities of 4a after the reaction (plus the corresponding aldehyde hydrolysis product), we speculated that imine 4a serves as a catalytic shuttle in the enantioselective hydroxylation process. To substantiate this assumption, we lowered the imine content and were glad to see that, even with half an equivalent of imine 4a, the outcome is more or less the same (entry 7). Unfortunately, a further reduction to "truly" catalytic quantities suffered from the notable background hydrolysis of 4a under the reaction conditions (entry 8), but in general, the catalytic role of the imine was confirmed. We next varied the imines 4 (see entries 9 and 10 for two examples and the Supporting Information for further details)[20] and found that the imine nature has a strong impact on the selectivity and thus plays

a fundamental role in the stereodetermining step (again no in situ formed oxaziridines **2** were observed in any of these experiments). Other N-protecting groups turned out to be not well-suited,[20] and we thus used **4a** for our further testing. Among different solvents, dry MTBE was the best (entry 12), and analogously to our previous oxaziridine report,[8] higher dilutions were slightly beneficial (entry 13), which can be rationalized by the aggregation tendency of the catalysts at higher concentrations.[8] We also investigated the influence of catalyst loading and reaction temperature, but no further improvement was possible.[20] The optimized conditions turned out to be rather robust, allowing for the same selectivity and high yield on a 1 mmol **1a** scale, as well (entry 13). Other oxidants were tested, as well, but neither of them matched the performance of H_2O_2.[20] Finally, testing different catalyst counteranions showed that oxidizable anions are absolutely crucial (entries 13−15). Whereas bromide catalyst **A2** performed almost as good as iodide **A1** (entries 13 and 14), non-oxidizable anions did not allow for any noteworthy catalysis (entry 15 shows one example, but others were tested with the same outcome).

As mentioned before, other catalysts were less selective and less active.[20] Especially noteworthy are the results obtained with Maruoka's ammonium salts **B**[4] and achiral PTCs (Scheme 2A).

Scheme 2. Influence of Ammonium Salt Properties and Proposed Mechanistic Scenario

A. Selected results for the synthesis of **3a** with other ammonium salts.

(Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$; 5 mol%)
B1 (X = I): 43% yield (20 h), e.r. = 63:37
B2 (X = Br): 5% conv. (20 h), e.r. = 56:44

Bu$_4$N$^{\oplus}$X$^{\ominus}$ (20 mol%)   **C1** (X = I): 55% conv. (24 h)
                C2 (X = Br): 15% conv. (24 h)

B. Mechanistic proposal.

In contrast to ammonium bromide **A2** (entry 14, Table 1), the commercially available ammonium bromide **B2** was found to be catalytically relatively incompetent, whereas the analogous ammonium iodide **B1** (derivatives thereof were used by Ishihara in their oxidative approaches[11,12]) allowed for some product formation, albeit with low enantioselectivity (Scheme 2A). Using tetrabutylammonium iodide (**C1**, TBAI) or bromide (**C2**, TBAB) as achiral PTCs, the conversion was also measurably slower compared to that with catalysts **A**. This striking difference between catalyst class **A** and ammonium salts **B** or **C** most likely can be attributed to the H-bonding motif of catalysts **A**, but the exact mode of activation remains yet speculative.
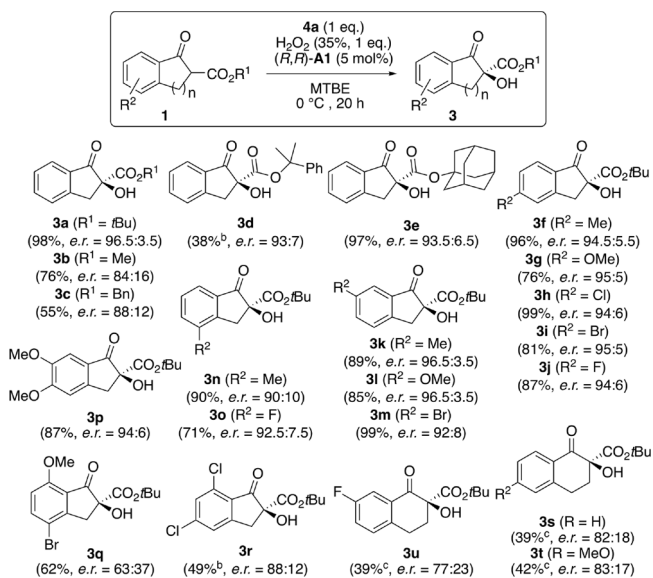
Nevertheless, all of our observations clearly substantiate a mechanism where oxidation of the counteranion (i.e., iodide) and formation of an activated O-transfer agent by reaction of the oxidized halide species with the imine occurs. Control experiments in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or dibutylhydroxytoluene (BHT) point toward a radical-free pathway, as neither of these two additives influenced the reaction. Concerning the oxidation of I^-, higher oxidation states like IO_3^- or even IO_4^- can most likely be ruled out under these neutral conditions.[24] Among the lower oxidation state species (I_2, I_3^-, IO^-, and IO_2^-), our observations suggest that I_2 itself is not the catalytically relevant species, as I_2 in combination with **4a** did not allow for any α-hydroxylation, whereas addition of H_2O_2 to this mixture allowed for product formation. Investigations by Ishihara and others clearly showed that IO^- is most likely the catalytically relevant species for quaternary ammonium iodides under oxidative conditions.[10,11] Formation of hypoiodite may also explain why this reaction proceeds well under base-free oxidative conditions when I^- is present: HIO has a pK_a of 10.4,[25] and thus IO^- may not only be relevant for the oxidation but also can play a role in the deprotonation of β-ketoesters **1**.[26] It should, however, be noted that the formation and catalytic activity of I_3^- or even the unstable IO_2^- cannot yet be perfectly ruled out; for example, some experiments with stoichiometric or catalytic amounts of Bu$_4$NI$_3$ or in situ formed Bu$_4$NIO[11] in the presence of H_2O_2 and **4a** gave formation of racemic **3a**, and in situ formation of IO_2^- may also be possible under these conditions.[27]

Accordingly, a plausible and very general mechanistic scenario is shown in Scheme 2B. H_2O_2 first oxidizes the ammonium iodide to a hypervalent species **I**. This species then reacts with the imine **4** to a yet unknown O-transfer species such as compounds **II** (other options are feasible, as well!). The catalyst then controls the enantioselective reaction of this species, with the β-ketoester **1** giving **3** combined with a release of the imine **4** again. In addition, the reduced catalyst species **I$_{red}$** will be reoxidized with H_2O_2 again, closing the proposed catalytic cycle.

With an optimized procedure for the asymmetric α-hydroxylation of the parent substrate **1a** at hand, we next investigated the application scope of this protocol (Scheme 3). Testing different ester groups first, we noticed that bulky esters

Scheme 3. Application Scope[a]

3a (R^1 = tBu) (98%, e.r. = 96.5:3.5)
3b (R^1 = Me) (76%, e.r. = 84:16)
3c (R^1 = Bn) (55%, e.r. = 88:12)

3d (38%,[b] e.r. = 93:7)

3e (97%, e.r. = 93.5:6.5)

3f (R^2 = Me) (96%, e.r. = 94.5:5.5)
3g (R^2 = OMe) (76%, e.r. = 95:5)
3h (R^2 = Cl) (99%, e.r. = 94:6)
3i (R^2 = Br) (81%, e.r. = 95:5)
3j (R^2 = F) (87%, e.r. = 94:6)

3k (R^2 = Me) (89%, e.r. = 96.5:3.5)
3l (R^2 = OMe) (85%, e.r. = 96.5:3.5)
3m (R^2 = Br) (99%, e.r. = 92:8)

3n (R^2 = Me) (90%, e.r. = 90:10)
3o (R^2 = F) (71%, e.r. = 92.5:7.5)

3p (87%, e.r. = 94:6)

3q (62%, e.r. = 63:37)

3r (49%,[b] e.r. = 88:12)

3u (39%,[c] e.r. = 77:23)

3s (R = H) (39%,[c] e.r. = 82:18)
3t (R = MeO) (42%,[c] e.r. = 83:17)

Reaction scheme: **1** + 4a (1 eq.), H$_2$O$_2$ (35%, 1 eq.), (R,R)-**A1** (5 mol%), MTBE, 0 °C, 20 h → **3**

[a]All reactions were carried out using 0.1 mmol β-ketoester **1**.[20] [b]Fast decarboxylation of the ester under the reaction conditions. [c]Limited conversion of around 50% after 20 h.

(i.e., *t*Bu-based ones) are clearly better suited for high enantioselectivities than Me- or Bn-esters (compare products **3a−e**). Varying the aryl substituents of indanone-based *t*-Bu esters next, we found that a broad variety of groups in the 4-, 5-, or 6-position are equally well-tolerated (see products **3f−p**). In contrast, however, substituents in the 7-position (products **3q** and **3r**) had a detrimental effect on the selectivity. This is in sharp contrast to our recent oxaziridine-mediated protocol where these substrates performed well,[8] demonstrating the obviously different transition state scenarios of these two mechanistically complementary approaches. Finally, tetralone-based β-ketoesters could also be α-hydroxylated under the standard conditions, but unfortunately their reactivity was found to be lower (incomplete conversion after 20 h), and the obtained selectivities were clearly less satisfactory as compared to the indanone-based ones (see products **3s−u**).

Summing our investigations up, we found that the synergistic catalyst combination of chiral bifunctional ammonium iodides with simple aldimines allows for the enantioselective α-hydroxylation of β-ketoesters using H_2O_2. The reaction most presumably proceeds via an in situ generated hypervalent iodine species which then forms the activated O-transfer agent by reaction with the used imine shuttle. Control experiments underline the necessity of iodide as an oxidizable counteranion, and it was also shown that the bifunctional nature of the catalyst is crucial. The protocol tolerates a variety of differently functionalized cyclic β-ketoesters. We are currently working on getting a better mechanistic understanding of this unprecedented synergistic catalysis principle and will hopefully be able to expand this concept to other target reactions soon.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02198.

> Experimental and analytic details (including copies of HPLC traces) as well as further details of the screening and optimization process (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Prof. Karl Grubmayr, who has been an inspiring (and patient) teacher to all of us, on the occasion of his 70th birthday.

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