C–C Cleavage

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# Facile Access to Chiral Ketones through Metal-Free Oxidative C–C Bond Cleavage of Aldehydes by $O_2$**

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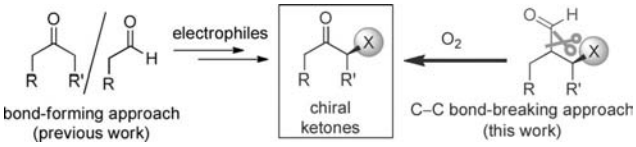
Functionalized chiral ketones, such as α-amino ketones, β-nitro ketones, and their derivatives, are prevalent building blocks and ubiquitous subunits present in natural products and pharmaceutical lead compunds.[1] The synthesis of chiral ketones can be achieved through direct α substitution. For example, the synthesis of α-amino ketones has been developed by Jørgensen and co-workers using an elegant catalytic amination of ketones by diethyl diazenedicarboxylate (DEAD).[2] Despite the success, some drawbacks of this method lie in the unsatisfactory and undesired regioselectivities for unsymmetric ketones, and to a certain extent the demanding reaction conditions required for subsequent N–N bond cleavage. Another approach for chiral ketone synthesis employs N-heterocyclic carbene catalysis.[3] Rovis and co-workers have recently reported excellent asymmetric Stetter reactions of aldehydes to nitroalkenes to afford β-nitro ketones.[4] The aldehyde substrates are restricted to (hetero)-aryl aldehydes and enals as the acyl anion precursors, and usually only aliphatic nitroalkenes can behave as effective Michael acceptors. We envisioned that limitations[5] associated with current new bond-forming reactions for chiral ketone synthesis could be substantially overcome by a less common C–C bond-breaking approach (Scheme 1).




*Scheme 1.*

Reported herein is the C–C bond cleavage of chiral aldehydes by $O_2$ for facile access to optically enriched α-amino ketones, α,α′-diamino ketones, and α-substituted β-nitro ketones. Given the large number of enantioselective methods available for the preparation of chiral aldehydes, especially the recent success with inexpensive amino catalysis,[6] we expect this approach to be applicable for the synthesis of a wide range of useful molecules. Our method may also stimulate new synthetic approaches to building complex molecules.

The C–C bond cleavage holds tremendous potential in synthesis, but has remained underdeveloped in part due to the inherent inert nature of the C–C bonds.[7] The impressive yet still limited studies have mainly relied on transition-metal reagents or catalysts.[8,9] Recently, Yamamoto et al. designed a very efficient metal-free nitrosobenzene-mediated C–C bond cleavage for esters and 1,3-diketo compounds.[10] The C–C bond-cleaving transformation for achiral aldehydes has been studied since the 1950s, and involves the oxidation of the corresponding preformed enamines in the presence of strong metal oxidants or catalysts.[11] However, nearly all the reported reactions for C–C bond cleavage of aldehydes were sluggish and multiple side products (or even large amounts of undesired products) were formed as a result of the nonselective reaction conditions. In addition, these methods have only dealt with achiral and simple aldehydes bearing no useful functional groups.

We first used the Mannich adduct **2a** as a model substrate to develop an oxidative cleavage approach to furnish the α-amino ketone **1a** as the desired product (Table 1). The Mannich adduct was prepared in essentially pure form without column chromatography starting from readily available materials (aldehydes and aryl imines) and the inexpensive proline catalyst using the protocol reported by List and co-workers.[6a] We decided to form enamine intermediates in situ for operational simplicity and to avoid complications in preparing preformed enamines of these chiral aldehydes containing functional groups. An initial survey of cyclic secondary amines [pyrrolidene, piperidine, and morpholine (**A**)] known in the literature[11] for enamine oxidation did not lead to detectable amounts of the ketone product **1a** when using metal-based oxidants or metal catalysts under a range of reaction conditions (Table 1, entries 1–4; also see the Supporting Information). Additional studies revealed that the use of primary amines (**B**–**G**) in the presence of $O_2$ at 50 °C could afford the ketone product **1a** in 12–34 % yield upon isolation, and electron-rich phenyl amines performed better than alkyl amines (Table 1, entries 5–10). We then chose to use the inexpensive *p*-methoxy aniline (**F**) for additional optimization of the reaction. In the presence of one equivalent of the aniline **F** under ten atmospheres of $O_2$ at 50 °C in toluene, the ketone product **1a** could be obtained in 91 % yield and 99 % *ee* (Table 1, entry 12). It was very fortunate to observe

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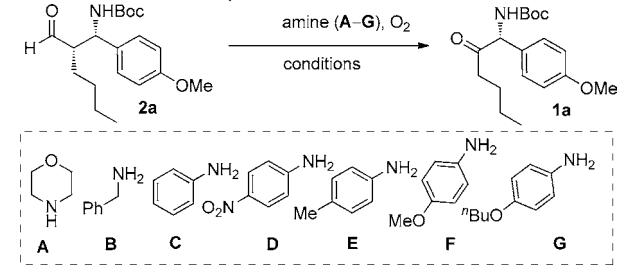
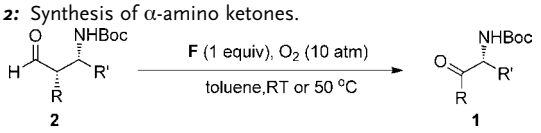
***Table 1:*** Model reaction optimization.[a]




| Entry[b] | Conditions | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|
| 1[e] | **A**, CuCl, 1 atm $O_2$, $CH_3CN$, 70 °C | 0[e] | – |
| 2[e] | **A**, CuI, 1 atm $O_2$, $CH_3CN$, 70 °C | 0[e] | – |
| 3[e] | **A**, $CuCl_2$, 1 atm $O_2$, $CH_3CN$, 70 °C | 0[e] | – |
| 4[e] | **A**, $CuCl_2$, 1 atm $O_2$, toluene, 70 °C | 0[e] | – |
| 5 | **B**, 1 atm $O_2$, toluene, 50 °C | 12 | n.d. |
| 6 | **C**, 1 atm $O_2$, toluene, 50 °C | 15 | n.d. |
| 7 | **D**, 1 atm $O_2$, toluene, 50 °C | 0[e] | – |
| 8 | **E**, 1 atm $O_2$, toluene, 50 °C | 23 | n.d. |
| 9 | **F**, 1 atm $O_2$, toluene, 50 °C | 32 | n.d. |
| 10 | **G**, 1 atm $O_2$, toluene, 50 °C | 34 | n.d. |
| 11 | **F**, 10 atm $O_2$, toluene, RT | 0[f] | – |
| 12 | **F**, 10 atm $O_2$, toluene, 50 °C | 91 | 99 |
| 13[g] | **F**, 10 atm $O_2$, toluene, 50 °C | 88 | 97 |
| 14 | **F**, 10 atm $O_2$, $CH_3CN$, 50 °C | 43 | n.d. |
| 15 | **F**, 10 atm $O_2$, $CH_3Cl$, 50 °C | 12 | n.d. |

[a] Special caution should be taken when using toluene as solvent under $O_2$ especially at elevated temperatures. [b] Reaction conditions: Aldehyde **2a** (0.15 mmol; 99% *ee*, >20:1 d.r.) and amine (0.15 mmol) in solvent (1.5 mL) for 24 h. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] 20 mol% of metal catalyst. [f] Determined by TLC and $^1$H NMR analysis of the crude reaction mixture. [g] 2.0 equiv of amine was used. n.d. = not determined.

***Table 2:*** Synthesis of α-amino ketones.




| Entry[a] | R | R′ | **1** | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1[d] | Me | Ph | **1b** | 1 | 83 | 92 |
| 2[d] | *n*Bu | Ph | **1c** | 4 | 92 | 99 |
| 3 | 7-octenyl | Ph | **1d** | 14 | 89 | 97 |
| 4 | *i*Pr | Ph | **1e** | 36 | 83 | 92 |
| 5 | Bn | Ph | **1f** | 16 | 88 | 99 |
| 6 | *n*Bu | 4-$MOeC_6H_4$ | **1a** | 24 | 91 | 99 |
| 7 | *i*Pr | 4-$MeOC_6H_4$ | **1g** | 36 | 71 | 99 |
| 8 | *n*Bu | 4-$ClC_6H_4$ | **1h** | 48 | 76 | 95 |
| 9 | *i*Pr | 4-$ClC_6H_4$ | **1i** | 48 | 74 | 88 |
| 10 | *n*Bu | 4-$FC_6H_4$ | **1j** | 24 | 81 | 91 |
| 11 | *n*Bu | 4-$BrC_6H_4$ | **1k** | 30 | 86 | 96 |
| 12 | *n*Bu | 2-$MeC_6H_4$ | **1l** | 24 | 87 | 98 |
| 13 | *n*Bu | 3-$MeC_6H_4$ | **1m** | 24 | 91 | 99 |
| 14 | *n*Bu | 4-$MeC_6H_4$ | **1n** | 24 | 94 | 99 |
| 15 | *n*Bu | 2-naphthyl | **1o** | 20 | 81 | 97 |

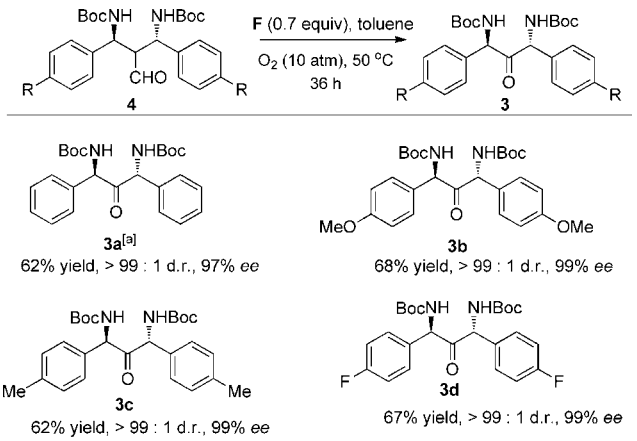
[a] Reaction conditions: **2** (0.15 mmol; *ee* > 97% and d.r. > 20:1), **F** (0.15 mmol), toluene (1.5 mL), $O_2$ (10 atm). [b] Yield of isolated **1**. [c] Determined HPLC analysis using a chiral stationary phase. [d] Reaction at RT. Bn = benzyl.

no apparent erosion on the chiral center of the ketone product **1a**. Increasing the loading of the amine reagent beyond 100 mol% did not show additional improvements (Table 1, entry 13). A brief solvent screening (Table 1, entries 14–15) indicated toluene to be the solvent of choice. Mechanistically, the C–C cleaving reaction likely proceeds through the decomposition of a dioxetane intermediate resulting from oxidation of the enamine by oxygen.[12]

We next examined the scope of the amino aldehydes **2** with various R and R′ substituents (Table 2). When R is a methyl (Table 2, entry 1) or *n*-alkyl group (entry 2) and R′ is a phenyl group, the reactions are complete within 1–4 hours at room temperature and give the corresponding ketone products with excellent yields and optical purities. With other R substituents, such as alkenyl, branched alkyl, or benzyl groups, a longer reaction time (14–36 h) and higher temperature (50 °C) are necessary (Table 2, entries 3–5). The effects of the electronic nature R′ when it is aryl were then studied (Table 2, entries 6–11). The reactions proceeded to completion within 24–48 hours, thus giving products with excellent yields and optical purities; both electron-donating (Table 2, entries 6–7, 12–14) and electron-withdrawing substituents (entries 8–11) were tolerated. When R′ is aryl, the substitution patterns (*ortho*, *meta,* and *para*) showed no observable effects on the outcome of the reaction (Table 2, entries 12–14).

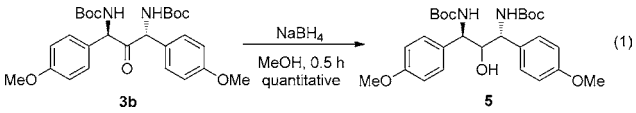
To further demonstrate the simplicity of this method, we combined protocol from List and co-wrokers for the catalytic Mannich reaction[6a] and our oxidative cleavage in a single-pot operation on a gram scale synthesis to yield the ketone product **1a** with 72% overall yield and 96% *ee* (see the Supporting Information).

We then extended this oxidative cleavage approach for the asymmetric synthesis of α,α′-diamino ketones (Scheme 2). The precursor aldehyde **4a** (R = H)[6b] was first subjected to



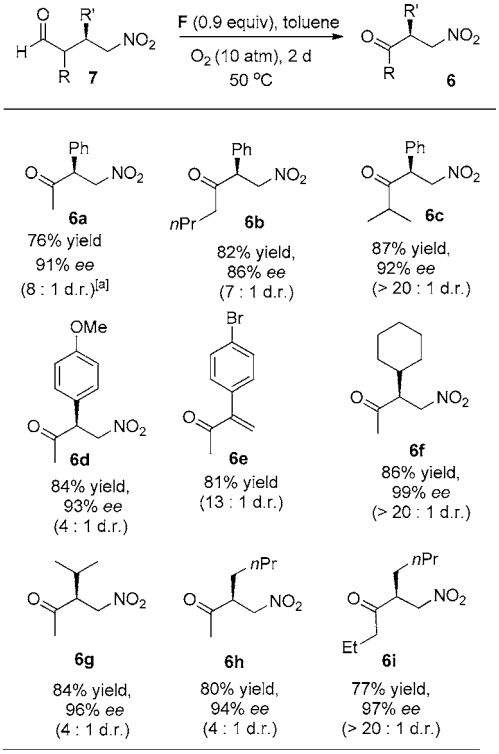

***Scheme 2.*** Synthesis of α,α′-diamino ketones. Reaction conditions: **4** (0.10 mmol; *ee* > 99%; d.r. > 20:1), **F** (0.07 mmol), $O_2$ (10 atm), toluene (1.5 mL). Yields are for the isolated product. The d.r. values were determined by $^1$H NMR spectroscopy and the *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] Reaction time was 16 h.

the standard reaction conditions used in Table 2 (1 equiv **F**, 10 atm $O_2$). To our disappointment, the ketone product **3a** was obtained as a diastereomeric mixture (d.r. ≈ 7:3). Additional studies showed that the residual amine **F** could mediate the epimerization of the ketone product. By lowering the amount of the amine **F** to 0.7 equivalents, the product **3a** could be obtained with acceptable yield and essentially as a single diastereomer with 97% *ee*. The α,α′-diamino ketone products can be easily transformed into optically pure diamino alcohols [Eq. (1)], analogues of which are key fragments in HIV-1 protease inhibitors.[1f]




(1)

To further demonstrate the applicability of our methods in preparing other chiral α-functionalized ketones, we sought to synthesize the β-nitro ketones **6** through C–C bond cleavage of the corresponding and readily available γ-nitro aldehydes[6c] (Scheme 3). The use of metal-based oxidants or catalysts was again not successful (see the Supporting Information). The metal-free conditions, run with molecular $O_2$, used above worked effectively here after a very slight modification (e.g., using 0.9 equivalents of amine **F**, to avoid ketone product racemization). The scope of the reaction was briefly examined (Scheme 3). The aldehydes **7** having R as both *n*-alkyl and branched alkyl substituents could give the products with good *ee* values and yields (**6b** and **6c**). The R′ substituents could be either aryls or alkyls. However with R′ being an electron-deficient aryl substituent, the initial β-nitro ketone product (stable during the C–C cleaving reaction and crude $^1$H NMR analysis) underwent subsequent E2 elimination (**6e**) during $SiO_2$ column chromatography. It is worth noting that the aldehyde substrates **7** having relatively low d.r. values could be used to give the ketone products **6** with high *ee* values.




***Scheme 3.*** Synthesis of β-nitro ketones. Reaction conditions: **7** (0.24 mmol), **F** (0.21 mmol), $O_2$ (10 atm), toluene (1.5 mL). Yields are for the isoalted product. The *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] The d.r. values stated underneath each compound are those of the corresponding aldehyde substrates **7**.

In conclusion, we have developed a metal-free approach using molecular $O_2$ as the sole oxidant for the C–C bond cleavage of chiral aldehydes through in situ formed enamine intermediates. By using this method, α-amino ketones, α-substituted β-nitro ketones, and unprecedented α,α′-diamino ketones with high optical purities can be prepared from readily available substrates. Today's synthetic chemistry has primarily focused on the design of bond-forming strategies. It is expected that the inverse process of chemical bond cleavages will provide unique opportunities for organic syntheses and materials fabrications.

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