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ARTICLE

Desymmetrization of cyclic 1,3-diketones via Ir-catalyzed hydrogenation: an efficient approach to cyclic hydroxy ketones with a chiral quaternary carbon

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We herein report an efficient method to synthesize cyclic hydroxy ketones with a chiral quaternary center. Catalyzed by an Ir/f-ampha complex, cyclic α,α-disubstituted 1,3-diketones were hydrogenated, giving mono-reduced products with both high enantioselectivities and diastereoselectivities. In addition, C=C and C≡C bonds could survive in this catalytic system. This method was applied in the preparation of (+)-estrone. No diols were observed in this chemical transformation. The enantiomeric and diastereomeric induction were achieved as a result of steric hindrance.

Introduction

Desymmetrization reactions have been proved to be an efficient method to generate compounds bearing chiral quaternary carbons[1] which have historically been problematic in synthetic chemistry[2, 3]. A successful example of this strategy is mono-reduction of cyclic α,α-disubstituted 1,3-diketone, which typically gives hydroxy ketones with two vicinal stereogenic center[1]. This product has been demonstrated to be a versatile synthon that attracts synthetic chemists. Many synthetic works were documented to use this 5- or 6-member ring synthon to construct complex molecules with multiple stereogenic centers. Successful examples include coriolin[4], anguidine[5], (+)-crotogoudin[6], (+)-paspaline[7, 8], (+)-estrone[9], cortistatins[10] and aplysiasecosterol A[11].

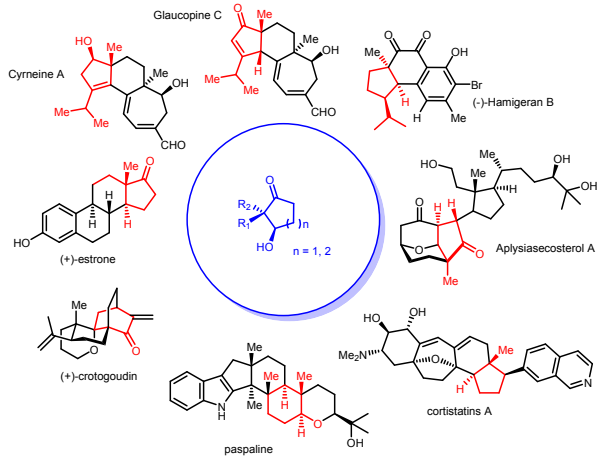
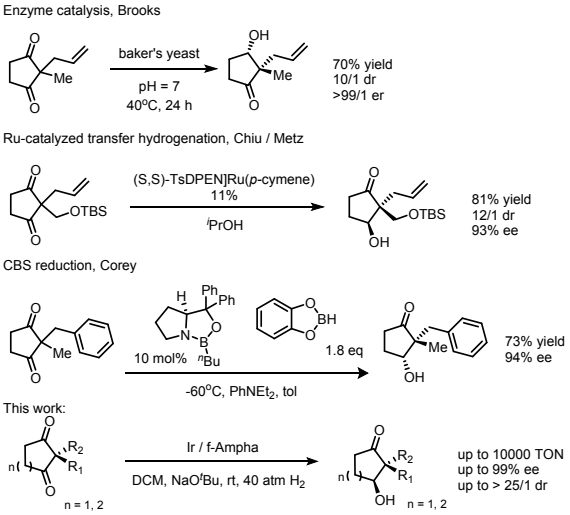


Fig. 1 Chiral cyclic hydroxy ketones in total synthesis.

The construction of this important synthon, however, is limited to enzyme catalyzed reduction[12, 13], Ru-catalyzed transfer hydrogenation[14, 15] and Corey-Bakshi-Shibata[9] reduction with borane. These methods suffer from the drawbacks of narrow substrate scope, moderate selectivity or high catalyst loading. The challenges of mono-reduction of cyclic α,α-disubstituted 1,3-diketone lie in such areas as (1) enantioselectivity and diastereoselectivity being realized in one step and (2) the prevention of over-reduction to diol. In the hydride transfer step, different facial approaches towards the substrate lead to two pairs of diastereomers (marked with blue and red arrows in Fig. 2). Enantioselectivity originates in the differentiation of a quaternary carbon from a methylene group (Fig. 2).



Scheme 1 Methods of mono-reduction of cyclic 1,3-diketone to generate a chiral quaternary carbon.

Our group has been dedicated to transition metal catalyzed ketone reduction during recent two decades and has developed a series of ferrocene-based tridentate ligands for

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iridium catalyzed hydrogenation[16-18]. A variety of simple or functionalized ketones can be hydrogenated to chiral alcohols with remarkably high ee's and turnover numbers (TONs). To the best of knowledge, direct hydrogenation has not been applied in the preparation of the aforementioned synthon. Due to our continuous interest in construction of chiral molecules via transition metal catalyzed asymmetric hydrogenation, we envisioned that this efficient catalytic system could be applied in the mono-reduction of 1,3-diketones.

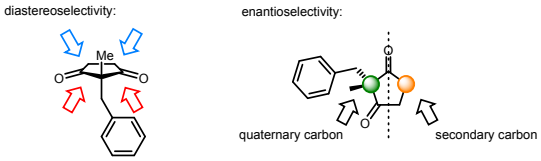
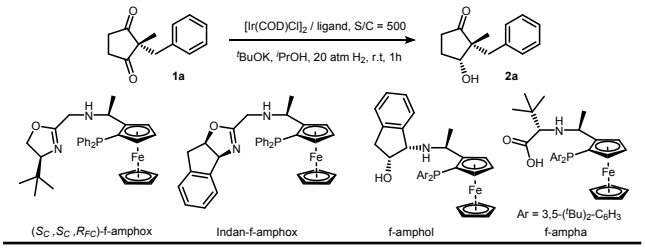


Fig. 2 Origin of stereoselectivities in mono-reduction of 1,3-diketone.

Results and discussion

We initiated our investigation by screening a suitable ligand. Although simple ketones such as acetophenone could be reduced efficiently with all these ligands (f-amphox[16], f-amphol[17] and f-ampha[18]), their performances in functionalized ketones were different. We selected 2-benzyl-2-methylcyclopentane-1,3-dione as the model substrate and conducted hydrogenation with iridium in isopropanol with potassium *tert*-butoxide. To prevent further reduction, less forced conditions (20 atm H_2) and a short reaction time (1 h) were applied. Those ligands performed differently: f-amphox and f-ampha gave promising results in the preliminary assessment (Table 1).

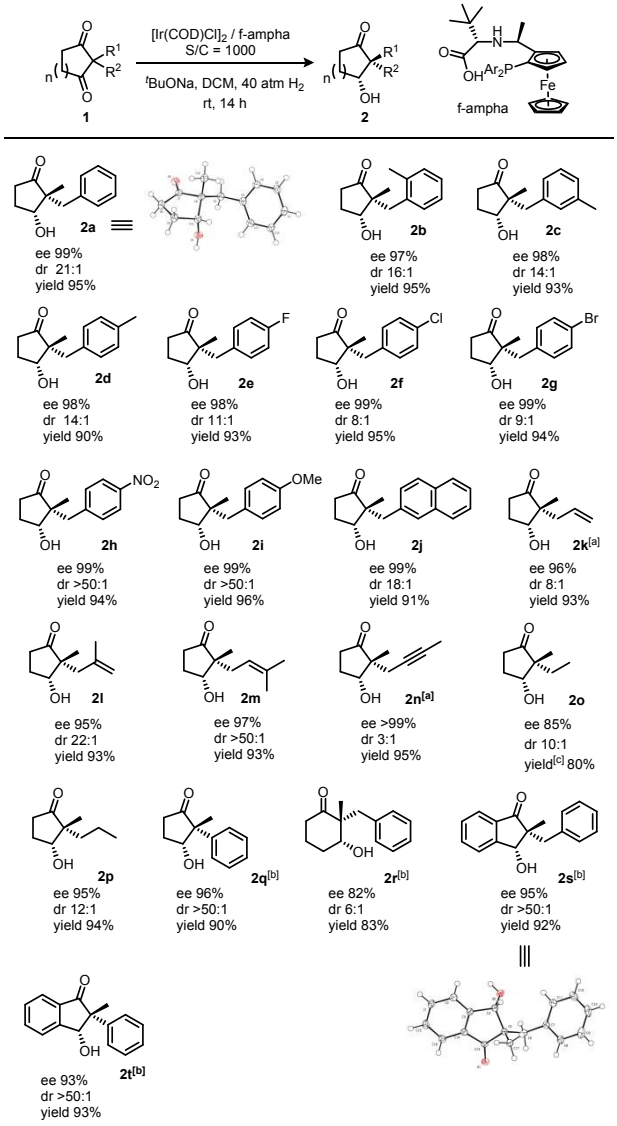
Table 1. Preliminary investigation of ligands in hydrogenation of cyclic 1,3-diketone[a]



entry	ligand	Conversion[b]	dr[c]	ee[c]
1	f-amphox	24%	7.3/1	93%
2	indan-f-amphox	11%	5.4/1	28%
3	f-amphol	50%	4.1/1	37%
4	f-ampha	84%	10.1/1	95%

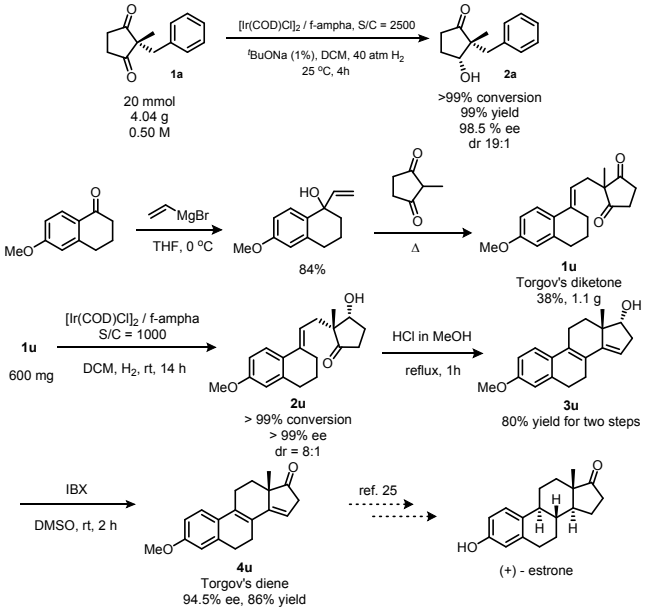
[a] Reaction condition: **1a** (0.1 mmol, 0.1 M), **1a**/[Ir(COD)Cl]$_2$/ligand/base = 500/0.5/1.1/10, 20 atm H_2, rt, 1 h. [b] Conversion was determined by ^{1}H NMR analysis, no by product was observed. [c] dr and ee were determined by HPLC on a chiral stationary phase.

Elongating the reaction time and increasing the hydrogen pressure drove this reaction to a full conversion. Interestingly, no over-reduction product (diol) was observed under harsher conditions. After careful optimization [for detailed condition screening, see supplementary information], we finally obtained a satisfactory condition: catalyzed by an Ir/f-ampha complex (0.1 % loading), the symmetric 1,3-diketone was reduced in dichloromethane in the present of sodium *tert*-butoxide, giving the corresponding chiral hydroxy ketone with 99% ee and 21/1 dr. To our delight, no diol was observed in the crude reaction mixture. The turnover number of this reaction could reach 10000 without obvious erosion of stereoselectivities[19].

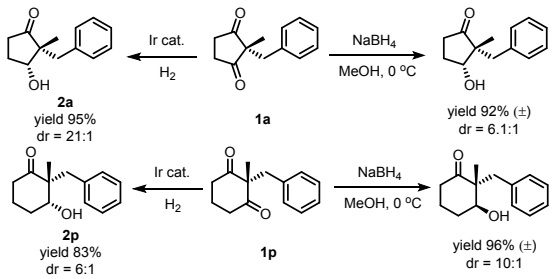


Scheme 2 Reaction scope of desymmetrization of cyclic 1,3-diketones via hydrogenation. Reaction condition: **1** (0.2 mmol, 0.2 M), **1**/[Ir(COD)Cl]$_2$/f-amphox/^{t}BuONa = 1000/0.5/1.1/10, 40 atm H_2, rt, 14 h; isolated yields; dr and ee were determined by HPLC on a chiral stationary phase. [a] Substrate/catalyst/base = 200/1/10, 15 min. [b] Substrate/catalyst/base = 200/1/10, 14 h. [c] Volatile compound, > 99% conversion.

We applied the optimized condition to explore the scope of this method with 0.1% catalyst loading. Various substation groups on the benzene ring, no matter electron-withdrawing or electron-donating groups, did not bring significant changes in both of the stereoselectivity and conversion (**2a** to **2j**). 1,3-Diketones with an allyl group, instead of benzyl, were hydrogenated with high enantioselectivities as well as satisfactory diastereoselectivities (**2k** to **2m**). In addition to alkene, alkynyl group also survives in this chemical transformation (**2n**). The preference of reducing polar C=O bonds demonstrated its chemoselectivity. To our surprise, dialkyl substrate also worked well in this reaction (**2o** and **2p**). This excellent stereoselectivity indicated that this catalytic system could discriminate the two different alkyl groups (methyl vs ethyl and methyl vs propyl). Discrimination between simple alkyl groups has always been a top challenge in asymmetric catalysis, while alkyl and aryl group are easy to differentiate (**2q**). When we expanded the ring size of the substrate from five to six, the performance faded and moderate stereoselectivities were obtained (**2r**). α,α-Disubstituted 1,3-indandiones could also be hydrogenated, giving desired yields and stereoselectivities (**2s** and **2t**).



Scheme 3 Scale-up reaction and application of desymmetrization via hydrogenation in the synthesis of (+)-estrone.



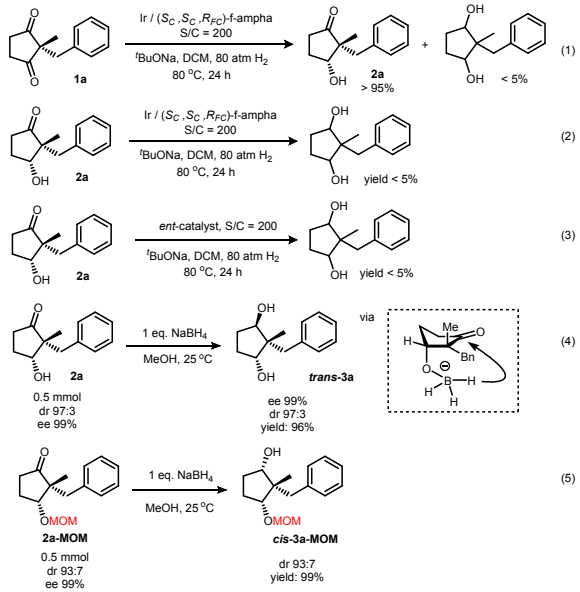
Scheme 4 Attempts of further reduction of the hydroxy ketone.

This reaction could be scaled up smoothly (Scheme 3, top). In order to exploit the potential application of this method in synthetic chemistry, we chose (+)-estrone as a target. This molecule plays a key role in steroidogenesis[20] and chemical synthesis of steroids[7, 21, 22]. We followed Corey's route[9], as well as List's route[23], to synthesize Torgov's 1,3-diketone[24] in a sub-gram scale. Hydrogenation of this diketone under the optimized condition quantitatively give hydroxy ketone with > 99% ee and 8:1 dr. After Prins cyclization/dehydration and oxidation with IBX, Torgov's diene[24] was obtained[25] which could be easily converted to (+)-estrone by a two-step transformation[23].

Our curiosity was drawn by the phenomenon of only one carbonyl group being reduced. When applying a harsh condition, it was also difficult to form diol (Scheme 4, eq. 1). Purified product **2a** could not yield diol under this forced condition as well (eq. 2). Hydrogenation under the same condition with the other enantiomer of the ligand, however, also failed in this transformation (eq. 3). The chiral pocket of both catalyst enantiomers seemed not to be compatible with the hydroxy ketone. Reduction of **2a** with sodium borohydride exclusively gave a chiral *trans*-diol in a quantitative yield. After protecting the hydroxyl group, however, reduction this ketone with sodium borohydride under the same conditions exclusively gave *cis*-diol (Scheme 4, eq. 5). Plausible explanations included an intramolecular hydride transfer after the formation of a boron alkoxide, which could be a result of transesterification of borate[26-28].

Scheme 5 Comparison of Ir-catalyzed hydrogenation and sodium borohydride reduction in desymmetrization of cyclic diketone.

While reduction of five-member-ring cyclic 1,3-diketone by both of sodium borohydride and iridium catalyzed hydrogenation gave the same diastereoselectivity, the reduction of six-member-ring substrate was different. Hydrogenation under the optimized condition gave an alcohol with the -OH *cis* to the larger benzyl group, but mono-reduction with sodium borohydride[29] yielded the other



diastereomer[30] (Scheme 5). These results indicated the same facial preference of iridium catalyzed hydrogenation and sodium borohydride reduction in five-member ring but a different facial preference in six-member ring.

Conclusions

We applied the strategy of transition metal catalyzed hydrogenation in the mono-reduction of cyclic 1,3-diketones. This desymmetrization reaction efficiently gave chiral hydroxy ketones with high stereoselectivities. Gratefully, further reduction that leads to diol was not observed in the hydrogenation step. This catalytic system was highly compatible with C=C and C≡C bonds, therefore making it a practical method to prepare complicated molecules with a chiral quaternary carbon.

Conflicts of interest

There are no conflicts to declare.

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