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Organocatalyzed one-pot sequential deracemization of aromatic ketones bearing a tertiary stereogenic center

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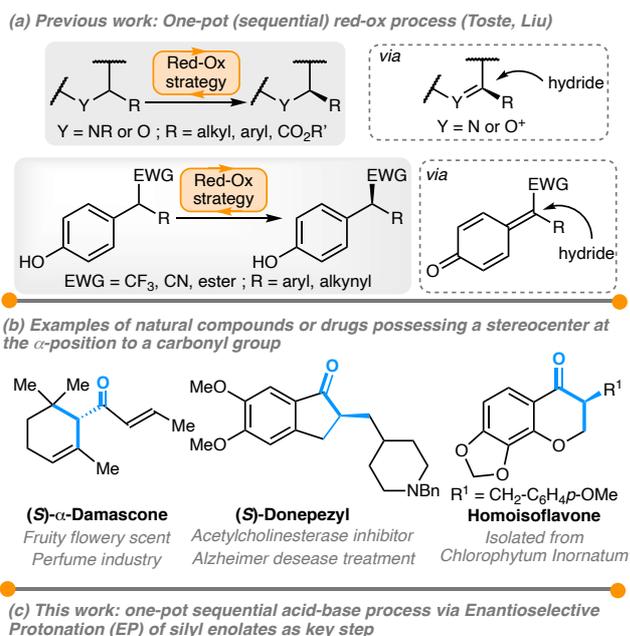


Abstract. An organocatalyzed one-pot sequential deracemization of aromatic ketones bearing a stereogenic center at the α -position was achieved thanks to an acid-base strategy involving an enantioselective protonation reaction as a key step. This simple and efficient protocol yields enantioenriched ketones in up to 89% *ee* without having to isolate sensitive intermediates such as silyl enolates. The key role of water in this process was underlined. This one-pot sequence constitutes a useful extension to previously reported chemically-driven red-ox protocols thus increasing the panel of molecules eligible to a deracemization strategy.

Keywords: Asymmetric catalysis; Ketones; Organocatalysis; Protonation

The synthesis of optically active molecules is an important field of research since both enantiomers of a chiral molecule often exhibit different biological properties. Hence, important efforts were devoted to the development of efficient strategies providing chiral non racemic molecules.^[1] Among them the kinetic resolution^[2] of racemic mixture was generally preferred for the large-scale synthesis due to the ease of implementation. Nevertheless, these approaches suffer from major drawbacks related to the maximal theoretical yield of 50% that could be reached. This limitation can be overcome by implementing a dynamic process giving rise to dynamic kinetic resolution (DKR)^[3] or dynamic kinetic asymmetric transformation (DYKAT)^[4] strategies. In these cases, further chemical transformations are required to transform the enantioenriched product of the reaction into the corresponding enantioenriched starting material, the structure of the product generally differing from the one of the starting materials. A more straightforward deracemization approach, which eventually provides an enantioenriched form of the racemic starting material without modification of its structure, has thus been considered as an attractive alternative.^[5] Keeping in mind the challenging microscopic reversibility issue,^[6] the racemic starting material is generally transformed into an achiral intermediate, which is regenerated to the starting material in an enantioenriched form in the presence of

a chiral catalyst. Metal or enzymatic red-ox conditions turned out to be particularly well-suited and have thus been extensively reported in the literature.^[5] More recently, examples of catalytic enantioselective photochemical reactions that enable deracemization of chiral compounds using a light-driven process in the presence of metal^[7] or organic^[8] photocatalysts were reported. The groups of Toste^[9] and Liu^[10] have tackled the deracemization reaction by using one-pot red-ox conditions involving an enantioselective organocatalytic hydride addition as a key step but the scope of the transformations was mainly limited to amines and ethers until recently (Scheme 1a, upper part). In 2020, Liu *et al.* reported on a one-pot red-ox deracemization sequence of compounds bearing an electron withdrawing group such as trifluoromethyl, cyano or esters (only one example with ester group) at the α -stereocenter (Scheme 1a, lower part).^[11] Due to the inherent limitation of the red-ox strategy, the scope of molecules eligible to a one-pot red-ox deracemization process remains narrow. Thus, there is still a need for the development of other approaches, especially by means of organocatalysis, allowing to widen the field of molecules accessible through a deracemization strategy.



Scheme 1. a) Previously reported: One-pot (sequential) red-ox strategies. b) Molecules of interest encompassing a tertiary carbon stereocenter at the α -position to a carbonyl group. c) This work: Organocatalyzed one-pot acid-base strategy.

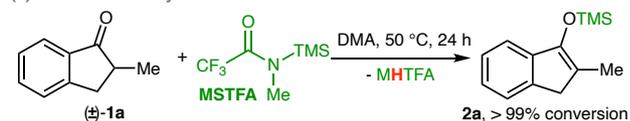
In this context, carbonyl compounds bearing a stereocenter at the α -position, which are widespread in chiral naturally occurring molecules or drugs such as (*S*)- α -Damascone, (*S*)-Donepezil or homoisoflavone derivatives to cite a few, have been considered as substrates of choice (Scheme 1b).^[12] In this article, we are pleased to report on the development of a one-pot deprotonation/enantioselective protonation^[13] sequence starting from carbonyl derived compounds **1** that would provide an unprecedented non-red-ox deracemization process thus opening the scope of this powerful strategy (Scheme 1c). Our approach is based on the use of silylating agent (BTMS) able to both deprotonate and transfer a silyl group under mild and nearly neutral conditions.^[14] We have thus postulated that, in a first step, treatment of racemic carbonyl compound **1** with BTMS would generate *in situ* the corresponding silyl enolate **2** along with the conjugate acid BH as a stoichiometric source of proton. In a second step, the addition of a chiral Brønsted base organocatalyst (Cat*) would activate BH thus enabling both the desilylation and the enantioselective protonation of **2** (Scheme 1c).

At first, we studied separately the two steps, while keeping in mind that experimental conditions for the

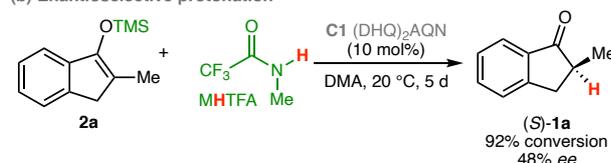
two reactions must be compatible. In order to secure our approach, we first checked that whether 1) the generation of silyl enolate **2** could be achieved by using a silyl probase (Scheme 2a) and 2) the enantioselective protonation step is possible (Scheme 2b). *N*-methyl *N*-(trimethylsilyl)trifluoroacetamide (MSTFA)^[15] and 2-Me indanone **1a** were selected as silyl probase and carbonyl compound respectively.

Preliminary results:

(a) Formation of silyl enolate



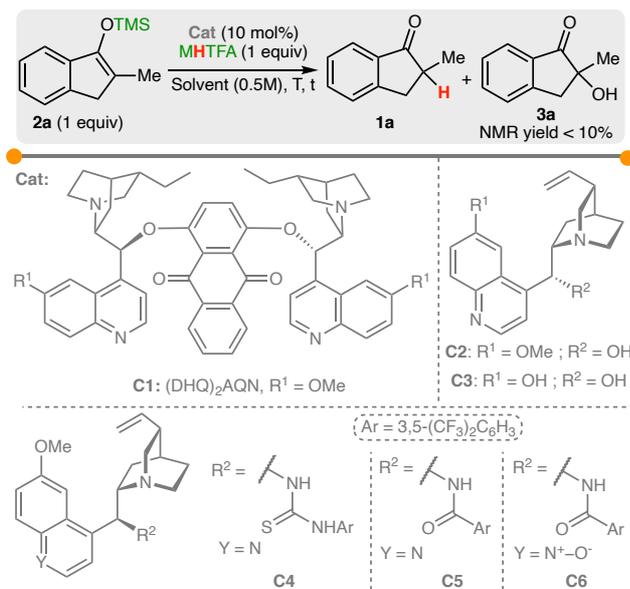
(b) Enantioselective protonation



Scheme 2. Preliminary results: (a) Silyl enolate formation. (b) Enantioselective protonation.

Complete conversion (>99%) of 2-Me indanone **1a** into its corresponding silyl enol ether **2a** was observed after heating at 50 °C in DMA for 24h. Next, the reaction of **2a** in the presence of 1 equivalent of MHTFA and commercially available (DHQ)₂AQN **C1** as catalyst^[12b, 16] yielded the enantioenriched 2-Me indanone (*S*)-**1a** with a promising 48% *ee* and 92% conversion. At this point, we first decided to explore several parameters^[15] of the enantioselective protonation reaction (Table 1).

Table 1. Optimization of the enantioselective protonation step.



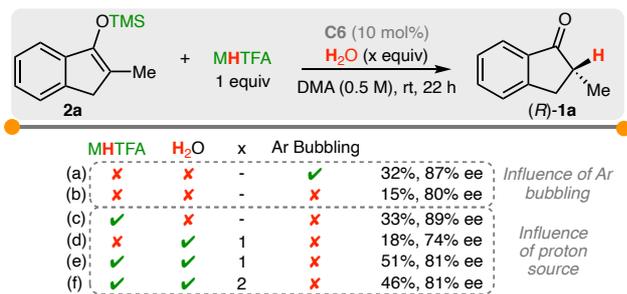
Entry	solvent	T (°C)	t	Cat	Yield (%) ^{a)}	<i>ee</i> (%) ^{b)}
1	DMA ^{c)}	20	5 d	C1	92	48 (<i>S</i>)
2	THF	20	5 d	C1	20	24 (<i>S</i>)

3	DCM	20	5 d	C1	22	20 (<i>S</i>)
4	DMSO	20	5 d	C1	62	46 (<i>S</i>)
5	DMA ^{c)}	20	22 h	C1	97	71 (<i>S</i>)
6	DMA ^{c)}	0	22 h	C1	45 ^{d)}	74 (<i>S</i>)
7	DMA ^{c)}	20	22 h	C2	65	9 (<i>S</i>)
8	DMA ^{c)}	20	22 h	C3	86	22 (<i>R</i>)
9	DMA ^{c)}	20	22 h	C4	27	75 (<i>R</i>)
10	DMA ^{c)}	20	22 h	C5	60	71 (<i>R</i>)
11	DMA ^{c)}	20	22 h	C6	51	79 (<i>R</i>)
12	DMA ^{c)}	20	40 h	C6	78	79 (<i>R</i>)

a) Determined by ¹H NMR analysis using Bn₂O as internal standard. b) Determined by HPLC analysis using a column that contains a chiral stationary phase. The absolute configurations were established by comparison of the experimental data with those reported in the literature^[15] and are given between brackets. c) Argon was bubbled into the solvent prior to the introduction of the reagents. d) The reaction performed at 0° for 3 days instead of 22 h has provided **1a** in 78% yield and 73% *ee*.^[15]

First of all, it has to be noticed that the formation of **1a** from **2a** was always accompanied by small quantities of racemic α -hydroxylated product **3a** (NMR yield < 10%).^[17] Regarding the solvent, the use of less polar solvent resulted in a drastic drop of both NMR yields and *ees* (Table 1, entries 2 and 3). While other polar solvent such as DMSO (Table 1, entries 4) provided almost the same level of stereoselection (46% vs 48% *ee* in DMA), the NMR yield decreased to 62%. The reduction of the reaction time from 5 days to 22 hours in DMA allowed to improve the enantiomeric excess to 71% while maintaining high NMR yield (Table 1, entry 5). This results clearly indicate that a racemization event occurred over time. Eventually, lower temperature of 0 °C benefited to the enantiomeric excess but at the expense of the NMR yield (45% NMR yield, Table 1, entry 6). Changing **C1** catalyst for simple quinine **C2** or cupreine **C3** (Table 1, entries 7 and 8 respectively) gave decent NMR yields (65% and 86% respectively) but poor level of enantioselecton (9% *ee* and 22% *ee* respectively). Then, catalysts with H-bonding donor capabilities were studied (Table 1, entries 9-11). While catalyst **C4** with a thiourea moiety was able to achieve an interesting level of stereoselection (75% *ee*), the NMR yield remains very disappointing (27% yield, Table 1, entry 9). Interestingly, while maintaining high level of enantiomeric excess of 71%, catalyst **C5** bearing an amide moiety allows to improve the NMR yield to 60% (Table 1, entry 10). After an extensive study of Cinchona alkaloid catalysts (see supporting information for full catalysts screening including squaramide catalysts), original catalyst **C6** bearing both an amide function at C-9 position and a *N*-oxide on the quinoline moiety (Table 1, entries 11-12) provided the best compromise between high NMR yield and enantiomeric excess providing that the reaction was performed during 40 h instead of 22 h (78% NMR, yield, 79% *ee* vs 51% NMR yield, 79% *ee*).

Having in hand our optimized protonation conditions, we then performed some control experiments (Scheme 3).

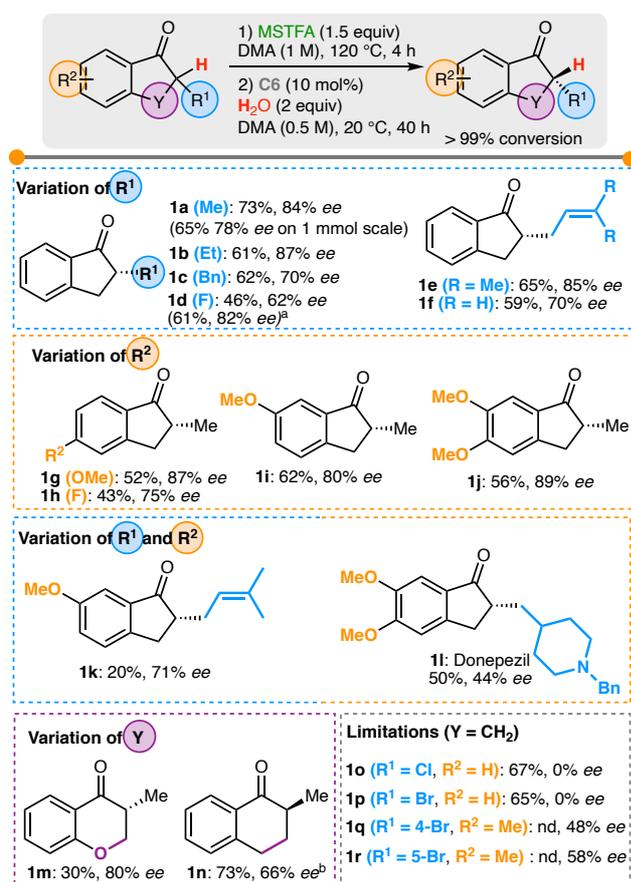


Scheme 3. Influence of the presence of water: control experiment

First, we were surprised to observe that a reaction occurred in the absence of proton source providing (*R*)-**1a** in moderate 32% NMR yield along with an excellent 87% *ee* (Scheme 3a). We thus postulated that water could be introduced within the reaction media during the Ar bubbling implemented in order to prevent the formation the α -hydroxylation product **3**.^[18]

Thus, the NMR yield of the reaction in the absence of proton source was divided by two (15%) by using directly commercial DMA^[19] (no prior Ar bubbling) without observing more than 10% of product **3a** (Scheme 3b). We then turned our attention to the nature of the proton source *e.g.* MHTFA or H₂O^[5f, 20] (Scheme 3c-e). Whereas both reactions with MHTFA or H₂O (1 equivalent each time) provided the compound **1a** with low isolated yield and good level of enantioselection (33%, 89% *ee* and 18%, 74% *ee* respectively), a balanced effect was observed when a mixture of MHTFA and H₂O was used (51%, 81% *ee*). Finally, for practical reasons (precision and reproducibility of the measurement of the water volume), 2 equivalents of water along with 1 equivalent of MHTFA was elected as the optimized conditions for this enantioselective protonation reaction (Scheme 3f).

We then performed the one-pot deracemization sequence after a slight modification of the silylation conditions (120 °C, 4 h instead of 50 °C, 24 h)^[21] in order to reduce the overall duration of the process (Scheme 4).

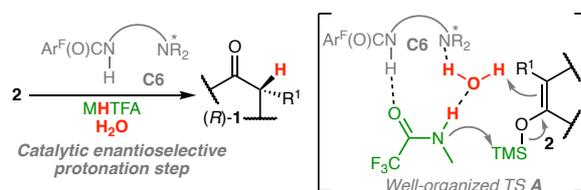


Scheme 4. Scope of the one-pot deracemization sequence.^a 1) silylation 2 h then 2) protonation 4 h. ^b 1) MSTFA (1.5 equiv), DMA (2 M), 16 h, 135 °C then 2) (DHQ)₂AQN (10 mol%), H₂O (2 equiv), 4 d, 20 °C.

Generally speaking, we were pleased to obtain the enantioenriched products **1a-n**, bearing a wide variety of substituent, in isolated yield of around 60%. We first studied the influence of the R¹ group at the α -position of the carbonyl. Product **1a** with a methyl substituent was obtained in high 73% isolated yield and excellent 84% *ee* in a one-pot sequence thus demonstrating the compatibility of both steps. The reaction could be performed on a larger scale (1 mmol) without dramatically affecting both yield and enantiomeric excess (65%, 78% *ee*). Product **1b** with an ethyl group gave almost the same result as for the product **1a** with a slight increase in the enantiomeric excess (87% *ee*) whereas product **1c** with a benzyl substituent resulted in a drop of the enantiomeric excess to 70% while maintaining the isolated yield around 60%. The compound with a fluorine atom **1d** was prone to racemization in the reaction conditions as demonstrated by the rise of the *ee* from 62% to 82% by shortening reaction times for both steps of the sequence (2 h instead of 4 h for the silylation and 4 h instead of 22 h for the protonation step). Products **1e** and **1d** (R¹ = allyl or dimethyl-allyl respectively) were also well-tolerated providing the corresponding enantioenriched product in 70% *ee* and 85% *ee* respectively. We next paid attention to the substituent on the aromatic ring of the indanone scaffold (R²

substituent). Methoxy group at either 5 or 6-position (**1g** and **1i** respectively) gave high level of enantioselectivity (87% *ee* and 80% *ee* respectively), the best result being obtained for 5,6-dimethoxy product **1j** (89% *ee*). Compound **1h** with a fluorine atom at the 6-position can also be obtained with moderate yield and satisfactory 75% *ee*. Then, both R¹ and R² substituents were modified providing product **1k** with low yield but acceptable 71% *ee*. Interestingly, unprotected Donepezil **1l** (a molecule involved in the treatment of Alzheimer's disease for which the *S* enantiomer have a 2.2-fold higher affinity for AchE than the *R* enantiomer)^[22] could be obtained in 50% yield and 44% *ee*. Finally, other sizes and types of rings were surveyed. Among them, 2-Me chromanone **1m** gave high enantiomeric excess of 80% albeit in low 30% yield. 2-Me-tetralone **1n** was also tolerated (73% yield, 66% *ee*) providing that the reaction conditions were slightly modified [1) MSTFA (1.5 equiv), DMA (2 M), 16 h, 135 °C then 2) C1 (10 mol%), H₂O (2 equiv), 4 d, 20 °C]. Nevertheless, some limitations remain. Products **1o** (R¹ = Cl, R² = H) and **1p** (R¹ = Br, R² = H) could be obtained in satisfactory 67% and 65% isolated yields respectively but as a racemate.^[15] In addition, for product **1q** (R¹ = Me, R² = 4-Br) and **1r** (R¹ = Me, R² = 5-Br), no isolated yields could be determined due to purification issue even if moderate enantioselective excesses of 48% and 58% respectively were measured.^[15]

Based upon mechanistic experiments performed by NMR spectrometry^[15] a catalytic cycle was proposed (see supporting information for the complete catalytic cycle) involving a postulated transition state depicted in Scheme 5.



Scheme 5. Postulated transition state for the enantioselective protonation step.

Upon addition of the catalyst **C6** and water to the silyl enolate **2**, the enantioselective protonation occurs through a well-organized transition state **A** thanks likely to a hydrogen bonding network involving the water as the source of proton while the silyl enol ether **2** would be activated by the amide partner. The involvement of the *N*-oxide part of the catalyst in the activation step of the silyl group, even if not observed by NMR experiment,^[15] cannot totally be ruled out.

In conclusion, we have reported on the first chemically-driven one-pot deracemization reaction based on an acid-base strategy. This approach allows to open the panel of compounds eligible to the non-enzymatic deracemization while providing simple and

user-friendly conditions avoiding the manipulation of relatively unstable silyl enolate derivatives **2**. By using original organocatalyst **C6**, enantiomeric excesses of up to 89% could be reached for several indanone **1a-l** and chromanone **1m** derivatives while 2-Me-tetralone **1n** could be obtained in 66% *ee* by moving to commercially available **C1** ((DHQ)₂AQN) as an optimal catalyst. A mechanistic study was undertaken by NMR spectroscopy allowing to propose a plausible catalytic cycle which likely involves water as a proton source.

Experimental Section

General procedure: Organocatalyzed One-pot sequential deracemization of α -substituted ketones **1a-n**

In an oven-dried glass vial were sequentially introduced racemic ketone **1a-n** (1 equiv), DMA (1 M) and MSTFA (1.5 equiv), and the resulting mixture was heated to 120 °C and stirred for 4 h. The reaction mixture was let cool to 20 °C followed by the addition of catalyst **C6** (10 mol%), water (2 equiv) and DMA (0.5 M). The reaction mixture was stirred at 20 °C for 40 h, diluted with Et₂O and quenched with brine/H₂O 1:1. Aqueous layer was extracted three times with Et₂O. Combined organic layers were washed three times with brine, dried over MgSO₄, filtered and concentrated in vacuo. Crude residue was purified by flash chromatography on silica gel to obtain the desired enantio-enriched ketone **1a-n**.

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