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Chiral phosphoric acid catalyzed redox deracemization of triarylmethanes

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Abstract

Described here is the first deracemization of triaryl-substituted carbon stereocenters, which is in contrast to the well-established processes to deracemize monoaryl- and diaryl-substituted ones. This one-pot redox process involves *in situ* generation of a *para*-quinone methide intermediate followed by asymmetric reduction by chiral phosphoric acid catalysis. A wide range of highly enantioenriched triarylmethanes could be generated with high efficiency under mild conditions.

Keywords: Triarylmethanes, deracemization, *para*-quinone methide, chiral phosphoric acid

INTRODUCTION

Deracemization is an attractive strategy to provide access to enantioenriched organic molecules[1-8]. However, direct conversion of the racemic form of a chiral compound to its enantioenriched form is a thermodynamically unfavorable transformation due to the positive Gibbs free energy change as a result of

the increased entropy of the reaction system as well as the principle of microscopic reversibility under thermal conditions[9,10]. To overcome this hurdle, various strategies have been devised to achieve successful deracemization[1-8], including the use of excited states (via photochemical condition)[1,2,11-14], reversal of thermodynamics by extrusion of small gas molecules[15,16], and the design of multistep reaction sequence (e.g., kinetic resolution or dynamic kinetic resolution)[17-21]. However, there are limited examples of successful implementation of these strategies, and more efficient methods for this purpose remain in high demand.

Enantioenriched organic molecules with benzylic chirality show broad applications in various fields, including organic synthesis, medicinal chemistry, and materials science[22,23]. In particular, a stereogenic carbon center attached to multiple aryl groups represents an important substructure widely observed in natural products and biologically active molecules[24-28]. In contrast to the well-documented diverse strategies to construct benzylic stereogenic centers, the exploitation of the deracemization approach for this purpose has been underdeveloped in general. Among these limited examples, the majority have dealt with those bearing one aryl group at the benzylic position [Scheme 1a][29-33]. Instead, only very few deracemization protocols have been developed for access to enantioenriched 1,1-diarylalkanes with a diaryl-substituted stereogenic center[34-36]. More disappointingly, to the best of our knowledge, there has been no demonstration of deracemization of triaryl-substituted stereogenic centers, despite the fact that 1,1,1-triarylalkanes are versatile structures in medicinal chemistry. In this context, here we report the first example of this type employing *para*-quinone methides as the key intermediate.

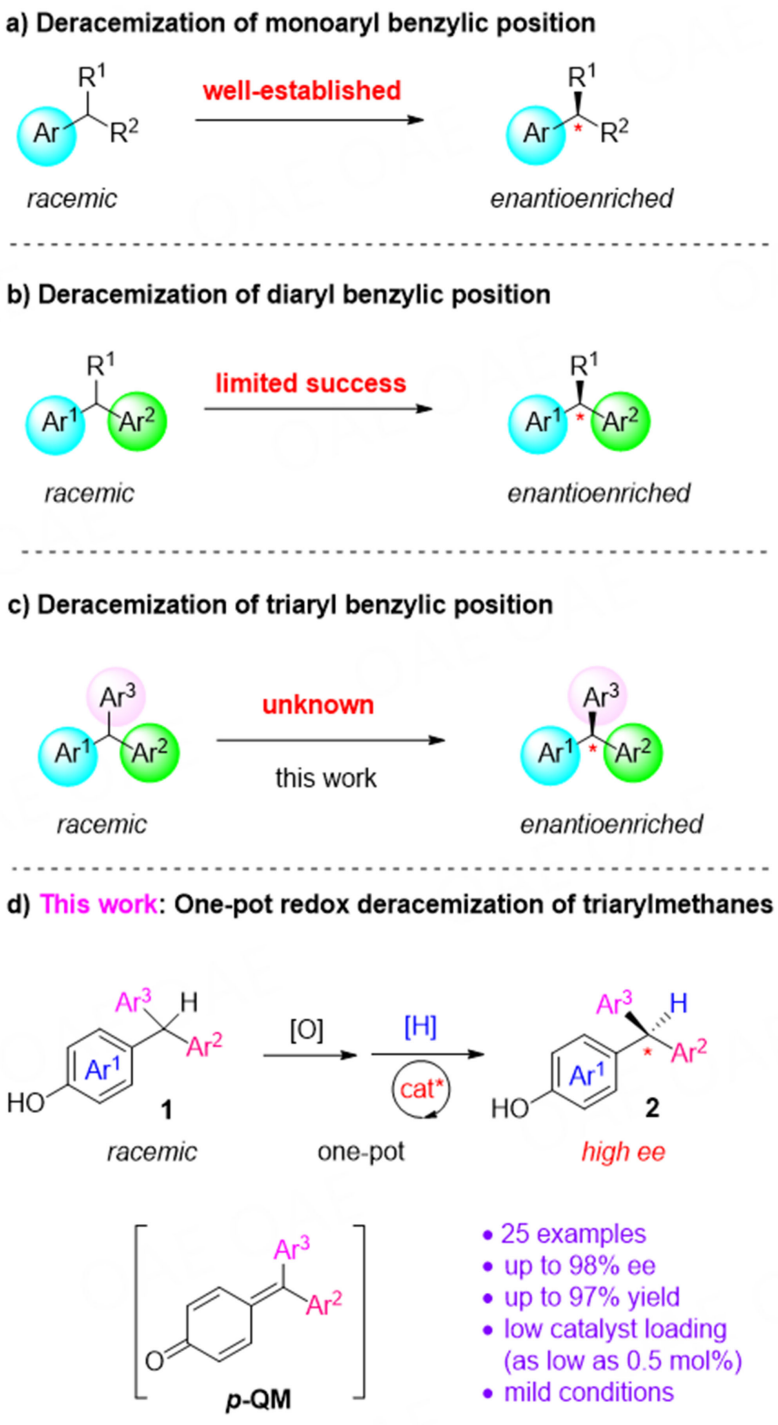
Recently, Liu and co-workers have reported a series of elegant organocatalytic redox racemization examples with outstanding performance for the access to enantioenriched chiral molecules bearing benzylic stereogenic centers[34-39]. Inspired by this strategy as well as our previous efforts in the study of asymmetric processes involving *para*-quinone methides (*p*-QMs)[40-56], we envisioned that the deracemization of triarylmethane 1 could be potentially achieved by a similar strategy. Specifically, initial oxidation is expected to form the *p*-QM intermediate. Next, in the same pot, a reductant, as well as a chiral catalyst, would affect the asymmetric reduction of this key intermediate, thereby representing a formal deracemization [Scheme 1d]. The challenges associated with this strategy include not only stereo control which requires discrimination between two aryl groups (Ar^2 and Ar^3), but also the compatibility of the two steps which involve mutually destructive oxidant and reductant.

EXPERIMENTAL

At room temperature, a solution of the triarylmethane **1** (0.4 mmol) and DDQ (99.0 mg, 0.44 mmol, 1.1 equiv) in $CHCl_3$ (1.44 mL) was charged into an oven dried 4 mL vial. The mixture was stirred for 5 h and then cooled. The catalyst (*R*)-A3 and the hydrogen source (0.6 mmol, 1.5 equiv) were added to a lower temperature as specified in each case. The mixture was stirred for 96 h. Upon completion, as monitored by TLC, it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the desired product 2.

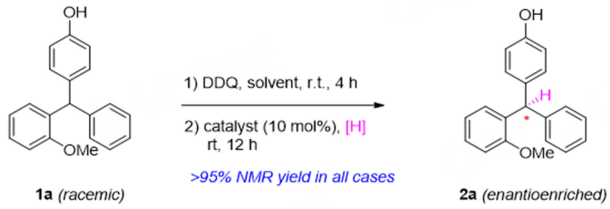
RESULTS AND DISCUSSION

The racemic triarylmethane 1a was chosen as the model substrate for the initial study [Figure 1]. The phenol ring serves as the precursor to the *p*-QM structure. To distinguish the remaining two aryl groups, one of them was substituted with an *ortho*-methoxy group to provide additional interaction with the catalyst[51-56]. DDQ was used as an oxidant for the first step. Based on TLC analysis, this step could be achieved cleanly in DCE at room temperature within 4 h. Notably, other oxidants, including Ag_2O, TEMPO, $Mn(acac)_3$, and O_2, could not work as effectively as DDQ. Next, the search for a suitable reductant and a chiral catalyst



Scheme 1. Introduction and Reaction Design. *p*-QMs: *para*-quinone methides; Ar^2 and Ar^3: two aryl groups.

constituted the key to success. Chiral phosphoric acids were employed as catalysts owing to their well-known performance in such nucleophilic addition reactions[43-66]. Inspired by Akiyama's pioneering study of using benzothiazoline for CPA-catalyzed asymmetric reduction[57,58], the 2-naphthyl-substituted one H1 was initially used as a reductant[65]. To our delight, this one-pot redox process proceeded smoothly to afford the desired enantioenriched product 2a, essentially in quantitative yields in all the cases. Among all the CPAs



1a *(racemic)* **2a** *(enantioenriched)*

Entry	Catalyst	Solvent	[H]	ee%
1	(*R*)-A1	DCE	H1	1
2	(*R*)-A2	DCE	H1	53
3	(*R*)-A3	DCE	H1	96
4	(*R*)-B	DCE	H1	94
5	(*R*)-C	DCE	H1	66
6	(*R*)-A3	DCE	H2	91
7	(*R*)-A3	DCE	H3	0
8	(*R*)-A3	DCE	H4	70
9	(*R*)-A3	$CHCl_3$	H1	97
10	(*R*)-A3	DCM	H1	95
11	(*R*)-A3	CCl_4	H1	86
12[b][c]	(*R*)-A3	$CHCl_3$	H1	96
13[b][d]	(*R*)-A3	$CHCl_3$	H1	98

Figure 1. Optimization of Reaction Conditions[a].

evaluated, the BINOL-derived one bearing two 2,4,6-tricyclohexylphenyl substituents at the 3,3'-positions provided the best enantioselectivity (96% ee, entry 3). Other backbones, such as [H_8]BINOL and spirocyclic bis(indane)-based SPINOL, did not result in better results (entries 4 and 5). Next, we also compared different hydride sources, including 2-phenyl-substituted benzothiazoline H2, catechol borane H3, and Hantzsch ester H4. Unfortunately, they proved inferior in terms of enantioselectivity (entries 6-8). We next screened other solvents, which indicated that chlorinated solvents are in general good for this reaction. Among them, $CHCl_3$ provided the best enantioselectivity (entry 9). Finally, a lower catalyst loading was also evaluated. With only 0.5 mol% of catalyst A3, the reaction efficiency and enantioselectivity remained excellent (entry 12). Furthermore, a scale-up reaction at a lower temperature (-10 °C) provided the best overall outcome (entry 13).

With the optimized conditions [Figure 1, entry 13], we examined the generality of this one-pot deracemization protocol [Figure 2]. Different substituted triarylmethane substrates all participated in this reaction to provide the enantioenriched products with both good yield and excellent enantioselectivity [Scheme 2]. Electron-donating groups and electron-withdrawing groups (e.g., nitro, cyano, halogen, and trifluoromethyl) did not affect the excellent outcome. However, it was found that those electron-poor substrates typically required a higher catalyst loading and/or higher temperature for the reaction to go completion. Thiophene-substituted triarylmethanes [2m and 2o] were also obtained in high enantiomeric

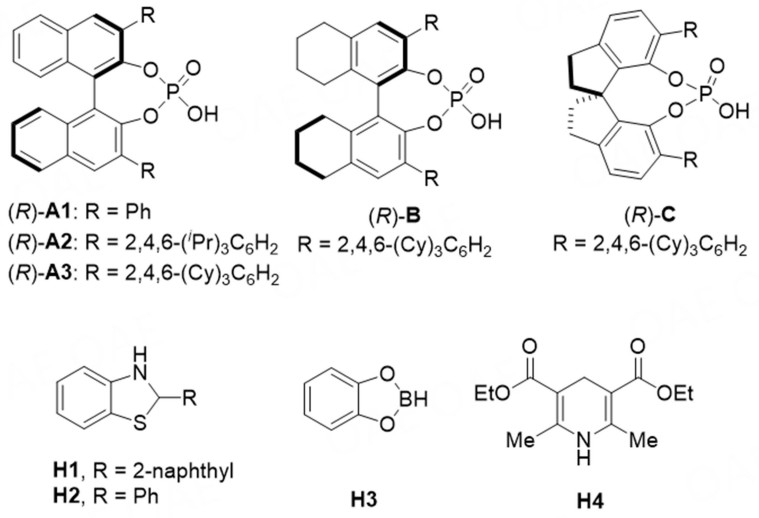


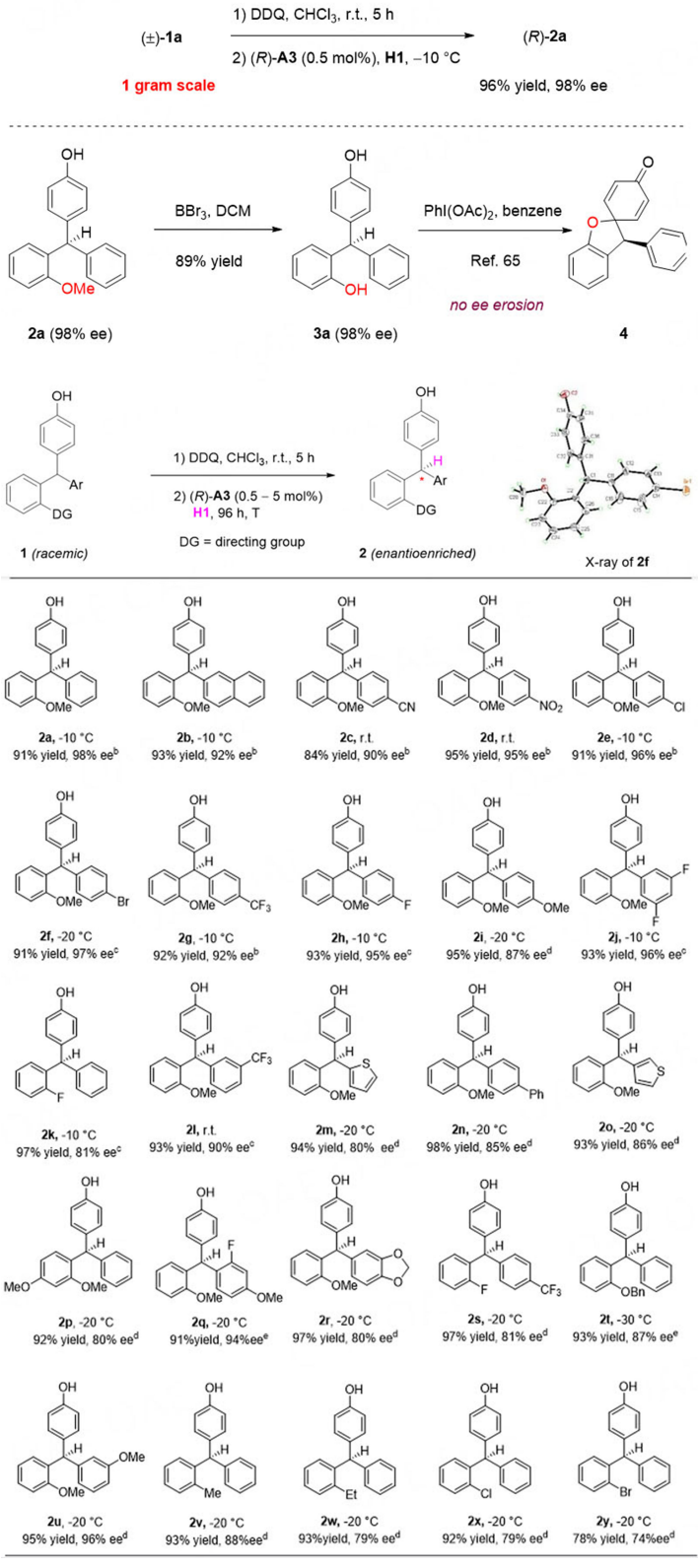
Figure 2. Reaction Scope[a]. [a] Reaction conditions:1a (0.05 mmol), DDQ (0.55 mmol), H1 (0.075 mmol), catalyst (10 mol%), solvent (1.0 mL). The yield was determined to be > 95% in all the cases by ^{1}H NMR and TLC analyses of the crude reaction mixture; ee value was determined by chiral HPLC analysis. [b] Run with 0.5 mol% of catalyst. Solvent (0.18 mL, c = 0.28 M). [c] Run for 36 h. [d] Run at -10 °C, 1a (0.4 mmol), DDQ (0.44 mmol), H1 (0.6 mmol), solvent (1.44 mL), 96 h.

excess, demonstrating the compatibility of this mild protocol to heterocycles. In these examples, an *ortho*-methoxy group was present in one of the aryl rings to provide differentiation between the other arene. It is worth noting that other directing groups, such as fluorine and benzyl ether, could also serve the same purpose[55]. More drastically, discrimination of these two arenes by steric hindrance is also possible. For example, a methyl or ethyl group at the *ortho*-position also led to good enantioselectivity. *Ortho*-halogen (Cl or Br) also provided good levels of differentiation. This is noteworthy since these halide groups can be easily converted to many other functionalities. Interestingly, if both *ortho*-OMe and *ortho*-F are present in the two arenes, effective discrimination was also observed. Notably, the absolute stereochemistry of product 2f was confirmed by X-ray crystallography.

To further demonstrate the robustness of this process, we carried out a gram-scale reaction of 1a. Under the standard conditions, the desired deracemization product was obtained in 96% yield and 98% ee [Scheme 2]. The *ortho*-methoxy group in product 2a could also be deprotected to form a free hydroxyl group without erosion in enantiomeric excess. Based on our previous work[65], this bis(phenol) 3a could be further converted to spirocyclic dienone 4 in the presence of $PhI(OAc)_2$ without erosion in its ee value.

CONCLUSIONS

In summary, we have developed the first deracemization approach for efficient access to enantioenriched triarylmethanes, a type of useful structure in medicinal chemistry. In contrast to the well-established deracemization processes for monoaryl- and diaryl-substituted carbon stereogenic centers, limited success has been achieved previously for triaryl-substituted ones. Specifically, herein a redox strategy involving the initial oxidation of racemic triarylmethanes followed by asymmetric reduction has been achieved in a one-pot fashion. With suitable substitution on the arenes, this process proceeds through the key *para*-quinone methide intermediate. Chiral phosphoric acids have shown excellent capability in catalyzing this process. The reaction features mild conditions and low catalyst loading. This process provided a diverse set of highly enantioenriched triarylmethanes with high efficiency and excellent enantioselectivity. Notably, diverse *ortho*



Scheme 2. Gram-scale Reaction and Product Derivatization. [a] Reaction conditions:1 (0.4 mmol), DDQ (0.44 mmol), H1 (0.6 mmol). Ee was determined by chiral HPLC analysis. Isolated yield. The specified temperature for each example is for the second step (reduction). [b] Run with 0.5 mol% of catalyst. [c] Run with 1 mol% of catalyst. [d] Run with 2 mol% of catalyst. [e] Run with 5 mol% of catalyst.

-substituents on one of the arenes have been demonstrated to be powerful for providing asymmetric discrimination. Further extension of this strategy for more broad applications is expected.

DECLARATIONS

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Authors' contributions

Designing the experiments, writing the manuscript, and being responsible for the whole work: Sun JW, Li PF

Performing the experiments and synthesizing the substrates: Liu C, Li ZY

Availability of data and materials

Detailed experimental procedures and spectroscopic data were published as Supplementary Materials in the journal.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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