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Construction of Multiple-Substituted Chiral Cyclohexanes through Hydrogenative Desymmetrization of 2,2,5-Trisubstituted 1,3-Cyclohexanediones

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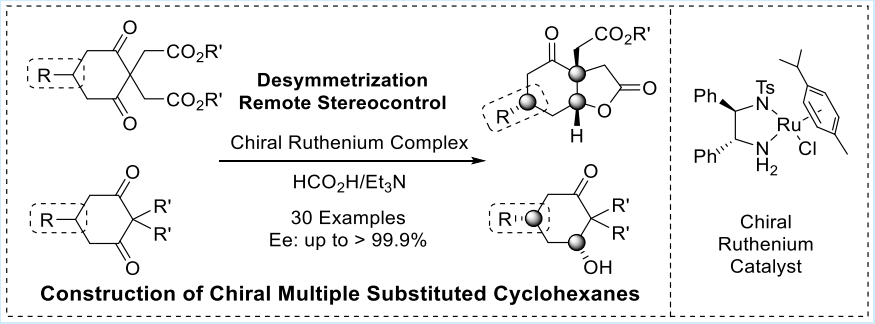
Supporting Information



ABSTRACT: The construction of chiral multiple-substituted cyclohexanes motifs is a challenging topic in organic synthesis. By the combination of desymmetrization and remote stereocontrol, a ruthenium-catalyzed transfer hydrogenative desymmetrization of 2,2,5-trisubstituted 1,3-cyclohexanediones has been successfully developed for the construction of chiral multiple-substituted cyclohexanes with high enantioselectivity and diastereoselectivity. When an ester group was introduced to the two-position, a hydrogenative desymmetrization/transesterification cascade occurred, affording the bicyclic lactones bearing three stereocenters, including two discrete stereocenters and one quaternary stereogenic center, with high enantioselectivity. The products are the multiple-substituted chiral cyclohexanes bearing the hydroxyl and carbonyl functional groups, which provide a new opportunity for further precise elaboration.

Multiple-substituted chiral cyclohexanes are highly valuable structural motifs in natural products and biologically active molecules (Figure 1).[1] For example,

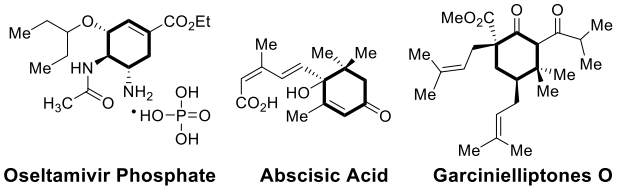


Figure 1. Bioactive molecules containing chiral cyclohexane motifs.

oseltamivir phosphate is an anti-influenza drug with potency for the H5N1 avian flu virus.[2] Abscisic acid demonstrated a hierarchical order of toxicity that was able to suppress the most coleoptile elongation.[3] Garcinielliptone O has potential anti-inflammatory effects.[4] Considering the importance of multifunctionalized chiral six-membered ring moieties, the development of efficient catalytic methods to access these motifs in a stereoselective fashion has thus been the focus of substantial studies. In addition to enzymatic reactions,[5] the concerted pericyclic reactions[6] provide another solution due to the cyclic transition state and the concerted reaction pathway. Aminocatalysis[7] also achieved the stereochemical control by either steric shielding or the hydrogen-bond-directing principle. Despite this remarkable progress, it remains indispensable to find new effective approaches to prepare structurally diverse chiral multiple-substituted cyclohexane derivatives.

The asymmetric (transfer) hydrogenation of α-substituted ketones has been established as one of the most direct approaches to chiral secondary alcohols with two[8] or three[9] continuous stereocenters through dynamic kinetic resolution. Despite the potential for the generation of useful functionalized cyclic building blocks, to our knowledge, the construction of chiral multiple-substituted cyclohexanes with discrete stereogenic centers through hydrogenation has not been reported. In view of the precedent work on the desymmetrization of 1,3-diketones,[10] we considered the combined hydrogenation desymmetrization and remote

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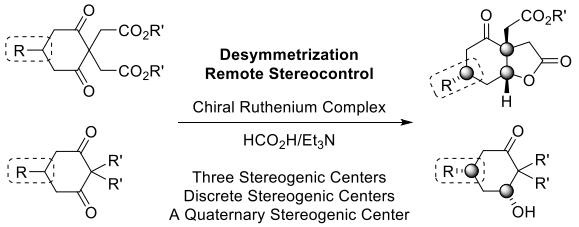
control of five-substituted 1,3-cyclohexanediones to build polysubstituted cyclohexane skeletons.[11] Some challenges remained, namely, the over-reduction[12] and the control of the enantioselectivity and the diastereoselectivity[13] in one step. Herein we report the construction of multiple-substituted chiral cyclohexane skeletons through a ruthenium-catalyzed hydrogenative desymmetrization of 2,2,5-trisubstituted 1,3-cyclohexanediones by the mono-reduction of 1,3-diketones and the control of the remote chirality simultaneously, affording the chiral five-substituted 3-hydroxycyclohexanones bearing two discrete stereogenic centers (Scheme 1). When an ester group was introduced to the two-position, a hydrogenative desymmetrization/transesterification cascade occurred, affording the chiral bicyclic lactones bearing three stereogenic centers including two discrete stereocenters and one quaternary stereocenter with high enantio- and diastereoselectivities. The products are the chiral multiple-substituted cyclohexanes bearing the hydroxyl and carbonyl functional groups, which provide a new opportunity for further precise elaboration.

Scheme 1. Construction of Multiple-Substituted Chiral Cyclohexanes through Hydrogenative Desymmetrization

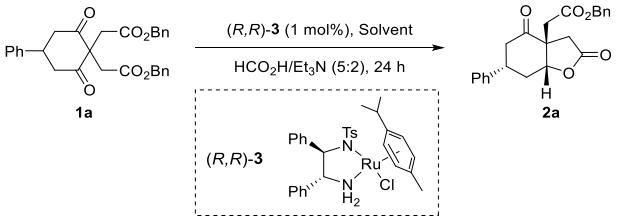


To begin the studies, substrate **1a** bearing two esters on the two-position was chosen as the model substrate considering the easy intramolecular transesterification of the desymmetrization product. This substrate would allow us to address the challenge of the construction of quaternary carbon centers with a densely substituted bicyclo[*m*,*n*,0] frame. First, the reaction was conducted with ruthenium catalyst (*R*,*R*)-**3** and an azeotrope of formic acid and triethylamine. 58% conversion and excellent enantio- and diastereoselectivity were obtained. The moderate conversion may be rationalized as a result of the poor solubility of **1a** (Table 1, entry 1). Hence, the solvent effect was investigated; aprotic solvents gave high ee values with 75−97% conversion (entries 2−5). Poor yield was obtained with the protic solvent (entries 6 and 7). A full conversion was obtained when the catalyst loading was increased to 2 mol % (entry 8). So, the optimal conditions were established as (*R*,*R*)-**3** (2.0 mol %), HCO_2H/Et_3N (0.50 mL), EtOAc (1.0 mL), 25 °C, and 24 h.

With the optimized reaction conditions in hand, a number of 2,2,5-trisubstituted 1,3-cyclohexanediones bearing diverse five-position substituents (Scheme 2) were tested. In general, alkyl- or aryl-substituted 1,3-cyclohexanediones smoothly underwent the hydrogenative desymmetrization/transesterification cascade, giving the chiral bicyclic lactones products in 98 → 99.9% ee. In all cases, an over-reduction product was not observed. The reaction was relatively insensitive to the electronic or steric properties of the aryl substituents: The presence of ortho, meta, and para substituents has negligible influence on the reactivity and enantioselectivity (**2a**−**g**). The variation of alkyl substituents was investigated and proved to have a marginal effect on the yield and enantioselectivity (**2h**, **2i**). Intriguingly, 1,3-cyclohexanediones (**1j**−**l**) containing an ethyl ester functional group were also suitable substrates with high reactivity and enantioselectivity.

Switching the substituent at the two-position to methyl (Scheme 3), the scope of this desymmetrization reaction was further examined. Both electron-donating and -withdrawing

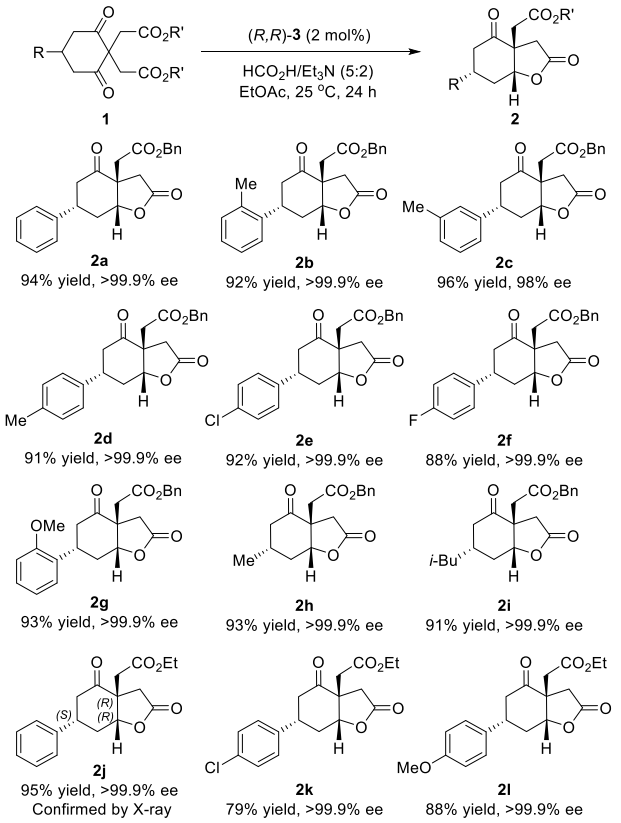
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	conv. (%)[b]	ee (%)[c]
1		58	99.6
2	THF	80	99.6
3	DMF	93	>99.9
4	DCM	75	99.5
5	EtOAc	97	99.6
6	EtOH	27	98.5
7	*i*-PrOH	13	98.8
8[d]	EtOAc	>95(94)	>99.9

[a]Conditions: **1a** (0.2 mmol), (*R*,*R*)-**3** (1.0 mol %), HCO_2H/Et_3N (0.5 mL), solvent (1.0 mL), 25 °C, 24 h, dr >20:1. [b]Determined by ^1H NMR. [c]Determined by HPLC. [d]2.0 mol % (*R*,*R*)-**3** was used. [e]Isolated yields.

Scheme 2. Tandem Transfer Hydrogenative Desymmetrization/Transesterification



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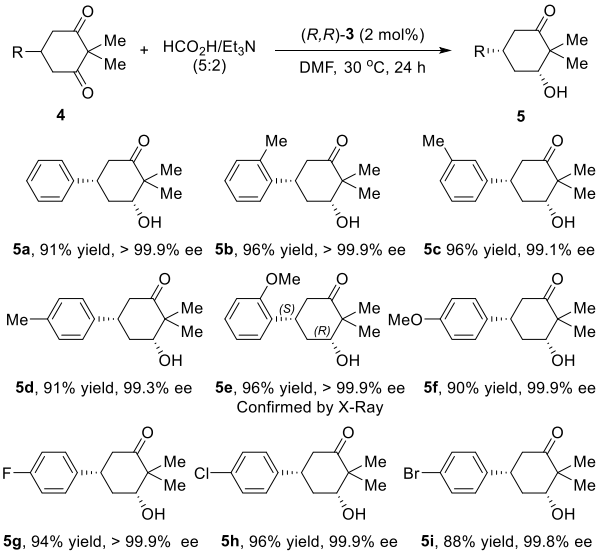
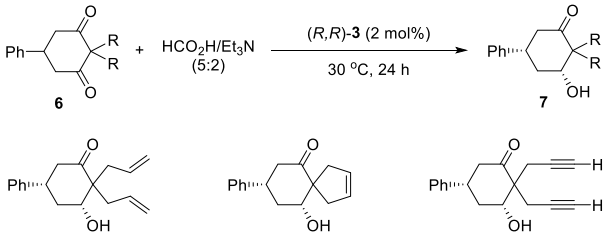
Scheme 3. Substrate Scope: 2,2-Dimethyl-5-Substituted 1,3-Cyclohexanediones



substituents on the phenyl ring were successfully employed, giving excellent enantioselectivity and diastereoselectivity. Once more, the steric effect was also evaluated; 2-substituents on the phenyl ring did not hinder the efficient transfer hydrogenation (**5b**, **5e**). In other cases, the halogen substituents are also well tolerated (**5g**–**i**).

It is of note that the functional groups at the two-position including the carbon−carbon double bond (**6a**, **6b**) and the carbon−carbon triple bond (**6c**) were conserved under hydrogenation conditions (Scheme 4), providing the potential reactive point for the further application.

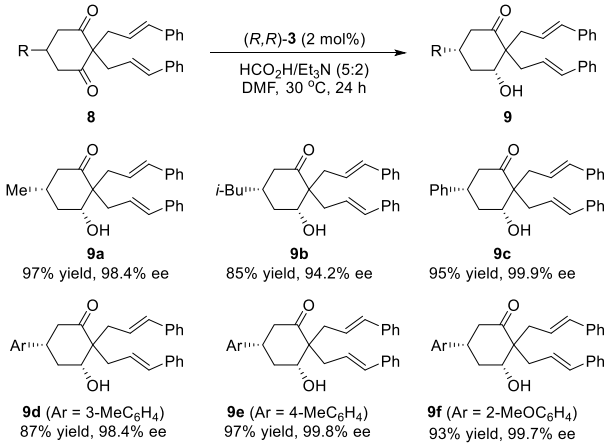
Scheme 4. Substrate Scope: 5-Phenyl-2-Substituted 1,3-Cyclohexanediones



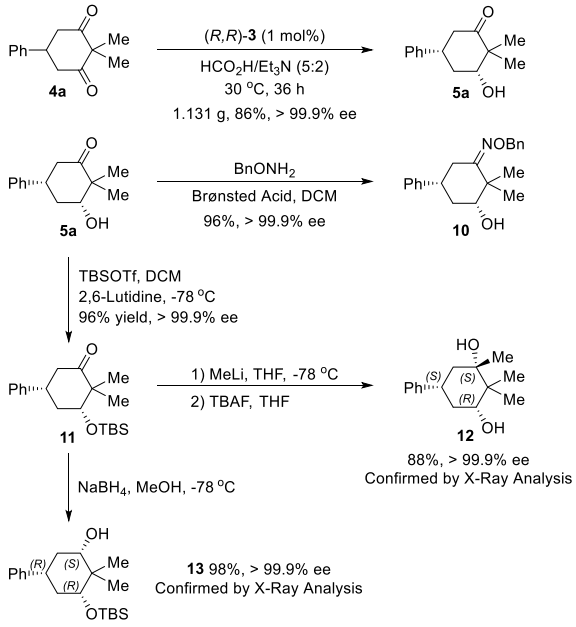
Next, we turned our attention to 2,2-dicinnamyl-1,3-cyclohexanediones bearing diverse five-position substituents **8a**–**f** (Scheme 5). In general, 5-alkyl- or aryl-substituted 1,3-cyclohexanediones underwent desymmetrization to deliver the desirable chiral products with 94–99.9% ee.

To demonstrate the synthetic utility of this method, the reaction on the gram scale was performed (Scheme 6), and the yield and enantioselectivity were maintained. Meanwhile, the remaining carbonyl is an attractive functional group for further transformations. For example, oxime ether **10** was obtained through the condensation with *O*-benzylhydroxylamine. After the hydroxyl protection with TBSOTf, nucleophilic addition with methyl lithium and the removal of TBS gave the chiral diol **12** with high diastereoselectivity. Monoprotected diol **13** with three stereogenic centers could

Scheme 5. Substrate Scope: 2,2-Dicinnamyl-5-Substituted 1,3-Cyclohexanediones



Scheme 6. Experiment on a Gram Scale and Elaborations



be synthesized through TBS protection and reduction with sodium borohydride. Notably, for the above transformations, no loss of optical purity was observed.

In summary, by a combination of desymmetrization and remote stereocontrol, a ruthenium-catalyzed hydrogenative desymmetrization of 2,2,5-trisubstituted 1,3-cyclohexanediones has been successfully developed for the construction of multiple-substituted chiral cyclohexanes. When an ester group was introduced to the two-position, a hydrogenative desymmetrization/transesterification cascade occurred, affording the chiral bicyclic lactones bearing three stereocenters, including two discrete stereocenters and one quaternary stereocenter, with high enantio- and diastereoselectivities and a broad substrate scope and a wide tolerance of functional groups. The above methodology provides facile and efficient access to the chiral multiple-substituted cyclohexane skeletons.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03622.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1552745, 1819215, 1840025, and 1855654 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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