Asymmetric Catalysis

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Asymmetric Intramolecular Oxa-Michael Reactions of Cyclohexadienones Catalyzed by a Primary Amine Salt**

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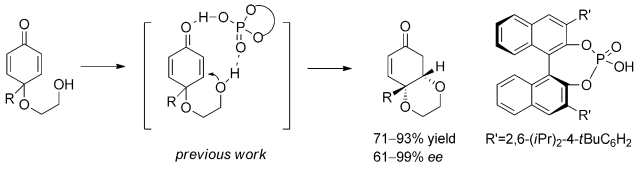
Since the first example of oxa-Michael addition of an alcohol to a conjugate acceptor was reported by Loydl in 1878,[1] oxa-Michael reactions have been the subject of increasing interest from synthetic organic chemists as one of the most efficient and directed methods for carbon–oxygen bond formation.[2] Generally, the nucleophiles involved in the reactions are alcohols, phenols, oximes, and hydrogen peroxide. Compared with other more reactive nucleophiles, oxa-Michael reactions involving alcohols still remain challenging owing to a reversible addition step and the poor nucleophilicity of alcohols.[2b,c] Tandem oxa-Michael reactions, where the reversible intermediates are immediately transformed into the final products, are effective in solving the first problem.[3] Whereas, the main strategies used to overcome the poor nucleophilicity of oxygen atoms are: 1) Deprotonation by strong bases to enhance their nucleophilicity.[4] 2) Activation of the conjugate acceptor by Lewis acids, transition metal complexes, or amines to lower the LUMO level.[5] 3) A bifunctional activation pathway is employed, using a chiral phosphoric acid or a tertiary amine thiourea as catalyst.[8a–c]

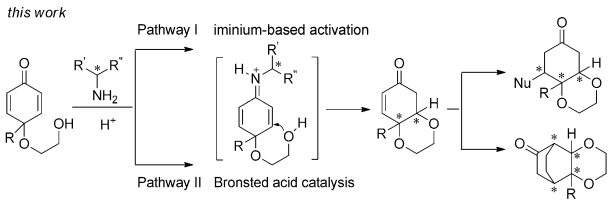
As a key reaction step, oxa-Michael reactions were frequently applied in the total synthesis of complex natural products.[6] Thus far, few organocatalytic enantioselective oxa-Michael reactions have been reported.[7] The first organocatalytic intramolecular oxa-conjugate addition of an alcohol to a chiral α,β-unsaturated ketone was accomplished by Hong et al. in the total synthesis of psymberin.[6k] Despite this, only a few organocatalytic asymmetric oxa-Michael reactions of α,β-unsaturated ketones have been reported.[8]

Because of their wide range of biological activity, oxygen-containing heterocycles such as tetrahydropyrans, benzopyran, xanthones, γ-butyrolactones, and 1,4-dioxanes, which can be synthesized from alcohols through oxa-Michael reactions, can often be found in natural products.[9] As a practical synthon, 1,4-dioxanes could be easily synthesized through the desymmetrization of cyclohexadienones.[10] Until very recently, only a few examples of the asymmetric desymmetrization of cyclohexadienones had been reported.[11] In 2010, You and co-workers reported the Brønsted acid-catalyzed desymmetrization of cyclohexadienones by intramolecular oxa-Michael reaction through bifunctional activation,[8b] which leads to highly enantioenriched addition products in excellent yield (Scheme 1).



Scheme 1. Brønsted acid-catalyzed enantioselective intramolecular oxa-Michael reaction.

Intrigued by these elegant reports, we envisaged that the intramolecular oxa-Michael reaction of cyclohexadienones might be realized through iminium-based activation (Scheme 2, pathway I).[12] Simultaneously, a background reaction could proceed when Brønsted acids were employed as



Scheme 2. General reaction design.

additives (pathway II). Herein, we report a highly enantioselective intramolecular oxa-Michael reaction catalyzed by an inexpensive and easily prepared chiral primary amine salt. Moreover, the gentle reaction conditions are more compatible with the functional or protecting groups of the substrates and can avoid potential side reactions, which could expand its range of applications in total synthesis.

Choosing compound **7a**, with the smallest group (methyl) in the 4 position, as a model substrate with which to optimize the reaction conditions, we focused our initial studies on a series of easily prepared chiral primary amines. No oxa-Michael products were obtained when the reaction was catalyzed only by a primary amine (Table 1, entry 3). Using the benzoic acid salts of either (*R*,*R*)-1,2-cyclohexanediamine or 9-amino(9-deoxy)epi-quinine, led to the desired product in

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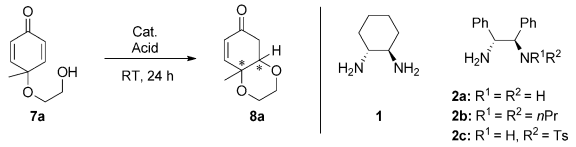
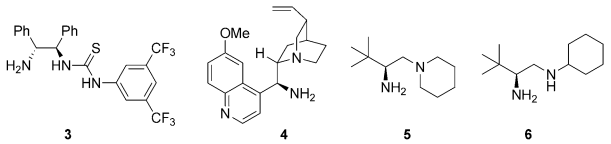
Table 1: Screening of chiral amine catalysts and acidic additives.[a]



Entry	Cat.	Solvent	Acid	Conv. [%][b]	*ee* [%][c]
1	**1**	CH_2Cl_2	$PhCO_2H$	82	50
2	**2a**	CH_2Cl_2	$PhCO_2H$	78	60
3	**2a**	CH_2Cl_2	none	<5	n.d.
4	**2b**	CH_2Cl_2	$PhCO_2H$	54	0
5	**2c**	CH_2Cl_2	$PhCO_2H$	62	0
6	**3**	CH_2Cl_2	$PhCO_2H$	50	18
7	**4**	CH_2Cl_2	$PhCO_2H$	60	−44
8[d]	**5**	CH_2Cl_2	$PhCO_2H$	58	−33
9[d]	**6**	CH_2Cl_2	N-Boc-L-Phe	98	−94
10	**2a**	CH_2Cl_2	N-Boc-L-Pro	82	72
11[e]	**2a**	CH_2Cl_2	N-Boc-L-Pro	80	85
12[e]	**2a**	CH_2Cl_2	N-Boc-D-Pro	80	84
13	none	CH_2Cl_2	N-Boc-L-Pro	0	n.d.
14[e]	**2a**	toluene	N-Boc-L-Pro	>99	82
15[e,f]	**2a**	toluene	N-Boc-L-Pro	60	95
16[g]	**2a**	toluene	N-Boc-L-Pro	95	95
17[g]	(±)-**2a**	toluene	N-Boc-L-Pro	95	4

[a] Reaction conditions: catalyst (10 mol%) and acid (20 mol%) in CH_2Cl_2 (0.5 M) at room temperature for 24 h. [b] Determined by GC analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Catalyst (20 mol%) and acid (20 mol%). [e] Catalyst (10 mol%) and acid (10 mol%). [f] Reaction at 0°C for 72 h. [g] Catalyst (15 mol%) and acid (15 mol%) at 0°C for 96 h.

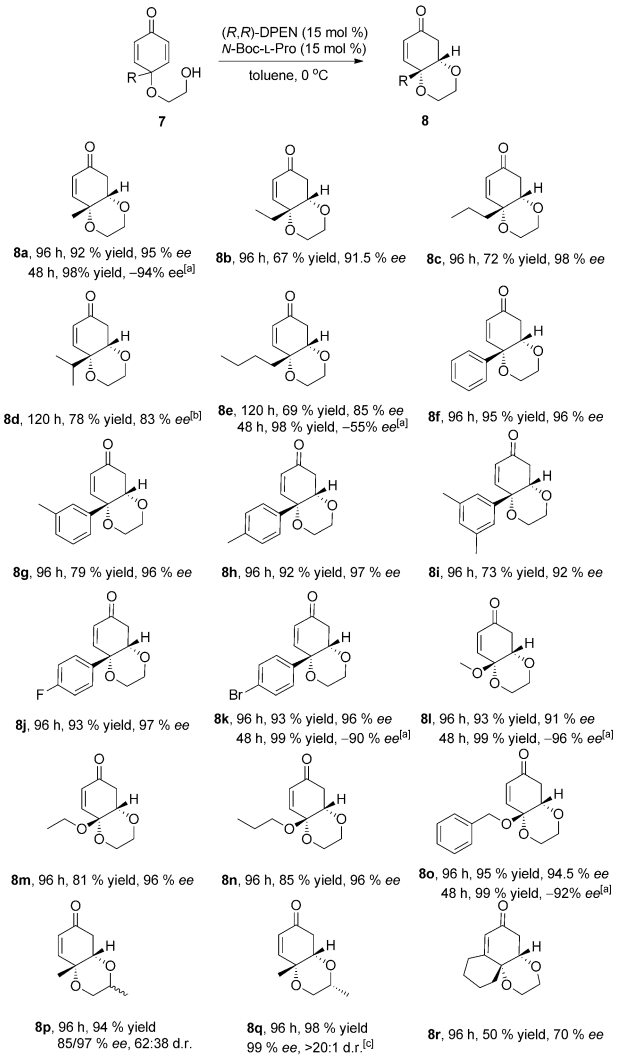


good conversion and moderate *ee* (entries 1 and 7). When the reaction was catalyzed by the benzoic acid salt of (1*R*,2*R*)-diphenylethylenediamine (DPEN), 60% *ee* was obtained. The enantioselectivity dropped significantly when the reaction was catalyzed by catalysts derived from (*R*,*R*)-DPEN: primary/tertiary amine catalyst **2b**, primary amine/hydrogen bonding catalyst **2c** and catalyst **3** (entries 4–6). With these moderate results in hand, we introduced a tert-butyl group into the catalyst scaffold,[13] and the resulting catalyst **6** showed excellent stereocontrolling ability in regulating the enantioselectivity (−94% *ee*).

With the intention of using inexpensive and simple catalysts to improve the reaction efficiency, a series of weakly acidic organic additives were screened for coordination with (*R*,*R*)-DPEN to improve the *ee* while simultaneously avoiding the background reaction. The results showed that the reaction was sensitive to different acidic additives (for details, see the Supporting Information). When *N*-Boc-L-proline (Boc = *tert*-butoxycarbonyl) was employed, the *ee* increased to 72% (entry 10). After varying the quantity of acidic additives, 85% *ee* and 80% conversion (entry 11) were achieved without a detectable background reaction (entry 13).

After slight modification of the reaction parameters (for details, see the Supporting Information), including changing the solvent, lowering the reaction temperature, increasing the catalytic salt loading, and prolonging the reaction time, 95% conversion and 95% *ee* were finally achieved (entries 14–16). Entries 11, 12, 16, and 17 indicate that the chiral amine is essential for stereoinduction in the products.

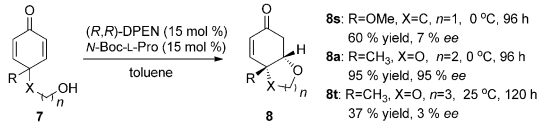
After the optimized conditions had been established, the substrate scope was investigated. To make this method more practical, we used chiral DPEN, which was commercially available in both enantiomeric forms for most of our work. As summarized in Scheme 3, the reaction was tolerant of alkyl, alkoxy, electron-withdrawing, or electron-donating substituents on the aromatic groups in the 4 position of cyclohex-



Scheme 3. Organocatalytic enantioselective intramolecular oxa-Michael reaction. Reaction conditions: (*R*,*R*)-DPEN (15 mol%) and N-Boc-L-Pro (15 mol%) in toluene (0.5 M) at 0°C for 96–120 h. [a] Catalyst **6** (20 mol%) and N-Boc-L-Phe (20 mol%) in CH_2Cl_2 (0.5 M) at room temperature for 48 h. [b] *o*-fluorobenzoic acid was used. [c] **7p** was prepared from (*R*)-1,2-propylene glycol. Yields shown are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

adienone. It has been reported that the alkyl group at the 4 position of the cyclohexadienone has a great influence on the enantioselectivity (Me, 94% *ee*; Et, 78% ee; *i*Pr, 61% *ee*).[8b] Herein, the enantioselectivities were greatly improved and the alkyl-substituted substrates (**8a**–**8e**) were expanded: R = Me, 95% *ee*; Et, 91.5% *ee*; *n*Pr, 98% *ee*; *i*Pr, 83% *ee*; *n*Bu, 85% *ee*. Different aromatic-substituted substrates were suitable for the intramolecular oxa-Michael reaction, and lead to the desired products in 73–95% yield and 92–97% *ee* (**8f**–**8k**). The reaction of the substrates with alkoxy substituents in the 4 position of cyclohexadienone proceeded quite well, with 81–95% yield and 91–96% *ee* (**8l**–**8o**), which has not previously been reported. The *ee* of product **8p**, with the introduction of one methyl group in the 3 position, decreased slightly to 62:38 d.r. When the chiral center at C3 possessed an *R* configuration, **8r** was obtained in 99% *ee* and >20:1 d.r. Product **8s**, with a triple-ring structure, was synthesized with 50% yield and 70% *ee*. When the reaction was carried out on a larger (1.008 g) scale, the desired product **8a** was obtained in high yield and high enantioselectivity. Some experiments were conducted using **6** and N-Boc-L-phenylalanine as catalysts; the products were obtained in excellent yields and moderate to good enantioselectivities: R = Me, −94% *ee*; *n*Bu, −55% *ee*; 4-Br-C_6H_4, −90% *ee*; MeO, −96% *ee*; BnO, −92% *ee*. Crystals of bromide product **8k** were obtained for single-crystal X-ray analysis, and the result revealed a 4a*S*,8a*S* configuration (see the Supporting Information).[17]

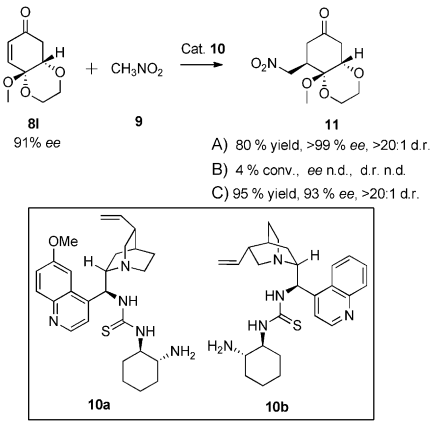
Subsequently, we tried to apply the above catalytic system to synthesize intramolecular oxa-Michael reaction products with various ring sizes. A significant drop in chemical yields and enantioselectivities was observed in the synthesis of five and seven-membered ring products **8s** and **8t** in preliminary studies (Scheme 4).



Scheme 4. Ring sizes of the oxa-Michael reaction products.

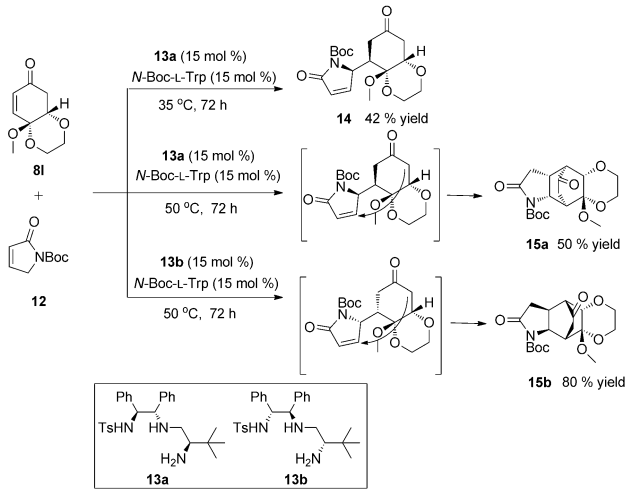
As a Michael acceptor, 1,4-dioxane derivative **8l** was applied in a conjugate addition with nitromethane for the synthesis of ketones with three chiral centers.[14] The reaction was catalyzed by **10a** and its diastereomer **10b**, which gave entirely different results (Scheme 5). Interestingly, the *ee* remained high when potassium carbonate was used as a catalyst. The results indicate that the addition step is highly sensitive to steric effects in the γ-position. Single-crystal X-ray analysis of **11** revealed a 4a*S*,8*R*,8a*S* configuration (see the Supporting Information).[17]

There are few examples where organocatalytic diastereoselective synthesis was attained by changing reaction conditions, including catalysts, ligands, and additives, as well as by modifying substrates.[15] Herein, we have realized the diastereoselective synthesis of tetracyclic compounds with strong structural rigidity, starting from the same chiral molecule. In keeping with our previous vinylogous Michael addition of



Scheme 5. Application of the oxa-Michael reaction product. A) Catalyst **10a** (10 mol%) in EtOAc (0.5 M) at room temperature for 72 h. B) Catalyst **10b** (10 mol%). C) Potassium carbonate (10 mol%) in EtOAc/MeOH = 1:1 (0.5 M) at room temperature for 24 h.

5-substituted 3-pyrrolidin-2-ones to α,β-unsaturated ketones,[13g] we used 15 mol% each of **13a** and N-Boc-L-Trp as catalysts and kept the temperature at 35 °C for 3 days, whereupon the desired single-step addition product (42% yield) was detected (Scheme 6); however, almost no product



Scheme 6. Diastereoselective synthesis of tetracyclic compounds containing a bicyclo[2.2.2]octan-2-one backbone.

was generated when the reaction was catalyzed by **13b**. When the temperature was elevated to 50 °C, diastereomeric tandem Michael–Michael reaction products were acquired when catalyzed by **13a** and its diastereomer **13b** (Scheme 6).[16] X-ray analyses of products **15a** and **15b** are shown in the Supporting Information.[17] This result is particularly noteworthy, as it provides concise and stereoselective access to stereodiverse, complex tetracyclic compounds with multiple chiral centers, which could be useful in the total synthesis of complex natural products.

In summary, we have disclosed a primary-amine-salt-catalyzed asymmetric intramolecular oxa-Michael reaction

through iminium-based activation, which provides enantioenriched 1,4-dioxane derivatives with excellent results (up to 99% yield and 98% *ee*). Further exploration provided a useful, concise, and stereoselective access to stereodiverse, complex tetracyclic compounds containing bicyclo-[2.2.2]octan-2-one backbone with multiple chiral centers.

Experimental Section

Catalyst **2a** (0.15 mmol, 0.15 equiv) and N-Boc-L-Pro (0.15 mmol, 0.15 equiv) were added to a solution of **7** (1.0 mmol, 1.0 equiv) in toluene (2.0 mL). The reaction mixture was stirred at 0°C for 4–5 days and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired product.

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