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Construction of Bicyclo[3.2.1]octanes with Four Stereogenic Centers by Organocatalytic Domino Michael/Aldol Reaction

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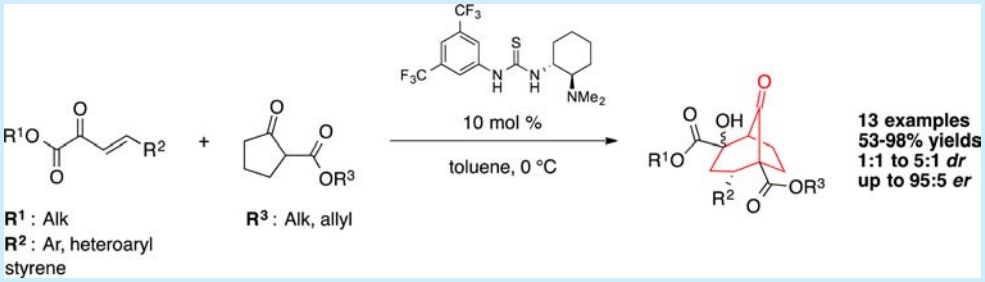
Supporting Information



ABSTRACT: An enantio- and diastereoselective organocatalytic domino Michael/Aldol reaction for the direct preparation of synthetically and medicinally relevant bicyclo[3.2.1]octane derivatives with four stereogenic centers, including two quaternary carbons, has been described. The reaction tolerates a large variety of substituents on β,γ-unsaturated 1,2-ketoesters and cyclic 1,3-ketoesters. It allows for the formation of various bicyclo[3.2.1]octanes in good yields (53−98%), diastereoselectivities (1:1 to 5:1 *dr*), and enantioselectivities (up to 95:5 *ee*).

Bicyclo[3.2.1]octanes are ubiquitous skeletons in many families of biologically active natural compounds[1] such as Enaimeone A,[2] Lilifliodione,[3] and Ialibinone A (Figure 1). For

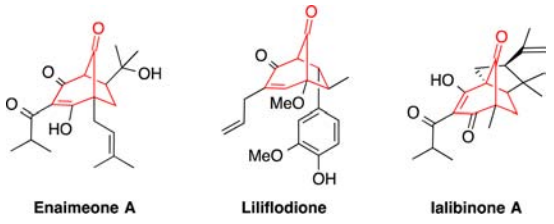


Figure 1. Natural products with bicyclo[3.2.1]octane core.

example, Ialibinone A, which was isolated from *Hypericum papuanum*, presents antibacterial activities.[4] In 2010, Simpkins[5] and George[6] simultaneously described an efficient total synthesis of this compound in racemic form. More generally, several stereoselective synthetic methods toward a bicyclo[3.2.1]octane system were developed during the past decade.[7] However, approaches using chiral pools or multistep syntheses have been the most studied.[8] Moreover, functionalized bicyclo[3.2.1]octanes have proved to be useful reactive intermediates in several stereoselective transformations.[9] These characteristics make them useful building blocks with a crucial impact in modern chemistry. It will, therefore, be relevant to develop a new methodology allowing the direct construction of chiral bicyclo[3.2.1]octanes.

Domino or cascade reactions are a powerful tool for the rapid and efficient synthesis of complex molecules with several stereogenic centers with minimized waste production.[10] Organocatalytic domino processes enable the formation of chiral polysubstituted molecules with environmental friendliness and operational simplicity.[11,12] Although efforts have been made in organocatalytic domino sequences,[13,14] the synthesis of bicyclo[3.2.1]octane cores are still evasive. Moreover, the development of new methodologies for the construction of molecules with several stereogenic centers including quaternary carbons in a cascade manner remains an important challenge in modern synthetic chemistry.[15]

β,γ-Unsaturated 1,2-dicarbonyl compounds are attractive synthetic scaffolds due to their dense number of reactive centers and their ambident reactivity.[16,17] Due to the presence of another adjacent carbonyl group, these compounds have the specific advantage to be coordinated to a Lewis or Brønsted acid. This coordination increases their reactivity, and the use of an organocatalyst would induce enantioselectivity in the reaction. Thanks to these characteristics, β,γ-unsaturated 1,2-dicarbonyl compounds, in particular α-ketoesters,[18] have known widespread utilization in organocatalytic domino reactions forming polysubstituted chiral molecules.[16,17] In 2007, the Tang group reported an asymmetric organocatalytic [3 + 3]-annulation of six-membered cyclic enones onto β,γ-unsaturated 1,2-ketoesters forming chiral bicyclo[3.3.1]octanes.[13a] They extended their methodology to cyclopentanone as a nucleophile giving the formation of bicyclo[3.2.1]octane in high yield but with moderate enantioselectivity. Herein, we describe a direct construction of chiral polysubstituted bicyclo[3.2.1]octanes by

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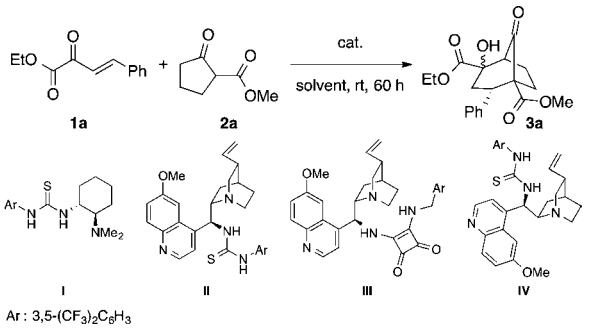
an organocatalytic domino reaction from achiral precursors such as β,γ-unsaturated 1,2-ketoesters and cyclic 1,3-ketoesters. These bicyclic compounds are highly substituted with four stereogenic centers including two quaternary carbons.

Several research groups have recently described readily accessible chiral molecules bearing a thiourea and tertiary amine moiety, such as cinchona alkaloid derivatives.[19] These molecules have been identified as efficient bifunctional organocatalysts in many asymmetric processes, such as Michael reactions,[20] aldol reactions,[21] and domino Michael/aldol reactions.[22] We began therefore our investigations by examinating the feasibility of employing bifunctional Brønsted acid/base catalysts in the organocatalytic domino Michael/aldol reaction of ethyl (*E*)-2-oxo-4-phenylbut-3-enoate **1a** with methylcyclopentanonecarboxylate **2a** (Figure 1). With 20 mol % of the Takemoto catalyst **I**, the expected bicyclic compound **3a** with four stereogenic centers was obtained with moderate diastereoselectivity (1.1:1 *dr*) and enantiomeric ratios (78:22/75:25 *er*) (entry 1, Table 1). Gratifyingly, only two

Table 1. Optimization of the Reactive Conditions



entry[a]	cat.	solvent	*dr*[b]	*er* (dia1/dia2)[c]	conv (%)[d]
1	**I** (20 mol %)	CH_2Cl_2	1.1:1	78:22/75:25	86
2	**II** (20 mol %)	CH_2Cl_2	1:1	19:81/46:54	95
3	**III** (20 mol %)	CH_2Cl_2	1.1:1	22:78/27:73	93
4	**IV** (20 mol %)	CH_2Cl_2	1.1:1	72:28/rac	81
5	**I** (20 mol %)	toluene	3:1	82:18/69:31	full
6	**I** (20 mol %)	EtOAc	1.1:1	76:24/70:30	full
7	**I** (20 mol %)	MeCN	2:1	73:27/70:30	full
8	**I** (20 mol %)	DMF	1.4:1	69:31/60:40	30
9	**I** (10 mol %)	toluene	1.7:1	83:17/76:24	full
10[e]	**I** (10 mol %)	toluene	1.1:1	93:7/89:11	full [41][f]
11[e,g]	**I (10 mol %)**	**toluene**	**1.2:1**	**87:13/82:18**	**full [89]**[f]

[a]Reaction was performed with β,γ-unsaturated 1,2-ketoester (0.1 mmol), cyclic 1,3-ketoester (0.15 mmol) in solvent (0.5 mL). [b]Determined by ^{1}H NMR on the crude reactive mixture. [c]Determined by chiral SFC. [d]Determined by ^{1}H NMR on the crude reactive mixture. [e]The reaction was carried out at 0 °C during 7 days. [f]Isolated yield. [g]Dried toluene was used as solvent.

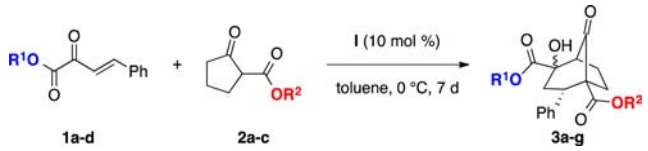
diastereomers of product **3a** over four theoretical possibilities were identified. These diastereomers can be separated by flash chromatography if necessary.

Various bifunctional catalysts derived from cinchona alkaloids were then screened. With 20 mol % of the catalyst **II**, the compound **3a** was synthesized in an excellent conversion with the same level of diastereoselectivity, but without improved enantioselectivities (entry 2, Table 1). The same observations were noticed with catalyst **III** bearing a squaramide moiety (entry 3, Table 1). With the pseudoenantiomer of the catalyst **II**, opposite enantiomers were obtained with lower values (entry 4, Table 1). Other bifunctional catalysts and secondary amines were tested giving no improvements in the reactivity and selectivity (see Supporting Information (SI)).

Various solvents were then screened in order to increase the enantioselectivity of our process. With a less polar solvent, such as toluene, the reactivity in favor of the bicyclic product **3a** was enhanced (entry 5, Table 1). The diastereo- and enantioselectivity for one diastereomer were increased. The other enantiomeric ratio is still moderate. With other polar solvents, the enantioselectivity of each diastereoisomer was decreased (entries 6–8, Table 1). Protic solvent, such as methanol, completely inhibited the reaction (see SI). A lower catalyst loading (10 mol %) furnished also product **3a** in an excellent conversion. A slight decrease in the diastereoselectivity was observed (1.7:1 *dr*) but with enhanced enantioselectivities for each diastereomer (83:17/76:24 *er*) (entry 9, Table 1). Gratifyingly, both enantiomeric ratios were improved at 0 °C, but a moderate isolated yield was obtained (41%) (entry 10, Table1). Finally, bicyclo[3.2.1]octane **3a** was synthesized in higher isolated yield (89%), with the same level of diastereoselectivity and good enantioselectivities for both diastereomers (87:13/82:18) in dried toluene at 0 °C (entry 11, Table 1).

Under these optimized reaction conditions, the generality of the organocatalytic domino Michael/aldol reaction using various β,γ-unsaturated 1,2-ketoesters and cyclic 1,3-ketoesters was investigated. First various β,γ-unsaturated 1,2-ketoesters with different ester moieties were tested (Table 2). Gratifyingly, methyl and *i*-propyl esters showed the same reactivity in the domino process (entries 2–3, Table 2).

Table 2. Organocatalytic Domino Michael/Aldol Reaction of Cyclic 1,3-Ketoesters onto β,γ-Unsaturated 1,2-Ketoesters Catalyzed by I



entry[a]	R^1	R^2	**3**	*dr*[b]	*er* (dia1/dia2)[c]	yield (%)[d]
1	Et	Me	**3a**	1.2:1	87:13/82:18	89
2	Me	Me	**3b**	1.3:1	83:17/81:19	95
3	*i*-Pr	Me	**3c**	1.1:1	87:13/85:15	97
4[e]	H	Me	**3d**	–	–	–
5	Et	Et	**3e**	1:1	86:14/84:16	55
6	Et	allyl	**3f**	1.4:1	88:12/87:13	78

[a]Reaction was performed with β,γ-unsaturated 1,2-ketoester (0.1 mmol), cyclic 1,3-ketoester (0.15 mmol) and catalyst **I** (10 mol %) in toluene (0.5 mL). [b]Determined by ^{1}H NMR on the crude reactive mixture. [c]Determined by chiral SFC. [d]Isolated yield. [e]No reaction occurred.

Polysubstituted bicyclo[3.2.1]octanes with four stereogenic centers were obtained in increased yields (95–97%), with moderate diastereoselectivities (1.2:1 *dr*) and good enantioselectivities (up to 87:13 *er*). Interestingly, a carboxylic acid group inhibited the reaction (entry 4, Table 2). The relative configuration of the two diastereomers was determined by analogy with the previous study on β,γ-unsaturated 1,2-ketoamides.[23]

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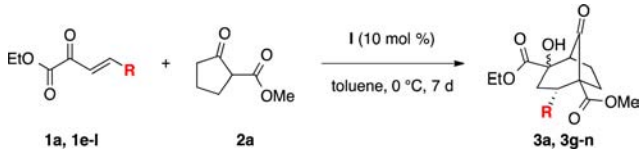
Various cyclic 1,3-ketoesters were then tested. Again, other ester groups were well tolerated by the reaction (entries 5−6, Table 2). Ethyl and allyl esters gave an access to chiral bicyclo[3.2.1]octanes maintaining moderate yields, diastereoselectivities, and good enantioselectivities. Interestingly, compound **3f** with an allyl ester moiety would enable further derivatizations such as Pd-catalyzed decarboxylative allylic alkylation leading to the formation of a bicyclic compound with a new stereogenic quaternary center.[24]

In order to broaden the scope of our methodology, we decided to evaluate the same optimized reaction conditions to various *β,γ*-unsaturated 1,2-ketoesters with different electron-donating and -withdrawing substituents. We were pleased to observe again the general characteristic of our methodology. Indeed, the reaction tolerates electron-donating and -withdrawing substituents in *para* and *meta* positions (entries 2−4, Table 3). *β,γ*-unsaturated 1,2-ketoesters with methyl, bromo, and fluoro substituents in the *para* position provided polysubstituted bicyclo[3.2.1]octanes in high yields (97%), with moderate diastereoselectivities (up to 2:1 *dr*) and good enantioselectivities (up to 88:12 *er*). With a nitro group in the *meta* position, bicyclic compound **3j** was also synthesized in a good yield, with a higher diastereoselectivity and a good enantioselectivity.

Table 3. Organocatalytic Domino Michael/Aldol Reaction of Methylcyclopentanonecarboxylate onto *β,γ*-Unsaturated 1,2-Ketoesters Catalyzed by I



1a, 1e-l 2a 3a, 3g-n

entry[a]	R	3	*dr*[b]	*er* (dia1/dia2)[c]	yield (%)[d]
1	Ph	**3a**	1.2:1	87:13/82:18	89
2	*p*-MeC_6H_4	**3g**	2:1	86:14/75:25	97
3	*p*-BrC_6H_4	**3h**	1:1.1	85:15/88:12	97
4	*p*-FC_6H_4	**3i**	1:1	88:12/80:20	97
5	*m*-$NO_2C_6H_4$	**3j**	1:5	76:24/88:12	96
6	*o*-$NO_2C_6H_4$	**3k**	1:3.4	83:17/90:10	53
7	*o*-$MeOC_6H_4$	**3l**	1:1.6	90:10/95:5	54
8	2-thienyl	**3m**	1:1	82:18/80:20	98
9	PhCH=CH	**3n**	1:4	91:9/94:6	96

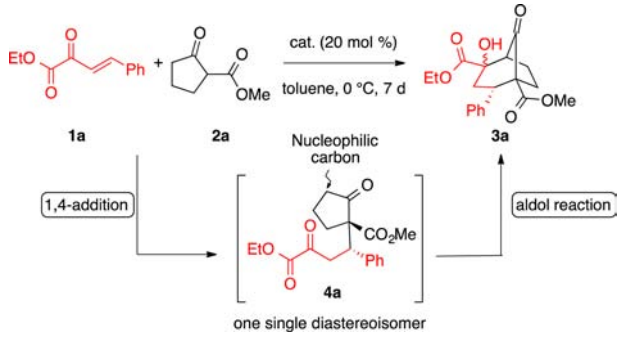
[a]Reaction was performed with *β,γ*-unsaturated 1,2-ketoester (0.1 mmol), cyclic 1,3-ketoester (0.15 mmol) and catalyst **I** (10 mol %) in toluene (0.5 mL). [b]Determined by ^1H NMR on the crude reactive mixture. [c]Determined by chiral SFC for product **4a**. [d]Isolated yield.

Interestingly, with a substituent in the *ortho* position such as a nitro or methoxy moiety, the corresponding bicyclic structures were obtained in lower yields but with higher diastereo- and enantioselectivities (up to 95:5 *er*) (entries 6−7, Table 3).

Not only aromatic but also heteroaromatic groups such as 2-thienyl could be successfully employed to afford the expected bicyclic structure **3m** with a high yield, moderate diastereoselectivity, and good enantioselectivity (entry 8, Table 3). A styryl substituent was also tolerated in the reaction. Bicyclo[3.2.1]-octane **3n** was synthesized with a high yield (96%), high enantioselectivities (94:7/91:9 *er*), and better diastereoselectivity (4:1 *dr*) (entry 9, Table 3). This is really important as the styrene moiety could undergo further derivatization such as an oxidative cleavage leading to an easily functionalizable bicyclic structure.[25]

Afterward, mechanistic investigations were carried out in order to obtain a better understanding of our catalytic system. Product **4a** was isolated after 1 day at 0 °C (see SI) (Scheme 1). It corresponds with the intermediate of the domino reaction forming after the 1,4-addition.

Scheme 1. First Mechanistic Insight



This Michael adduct **4a** was obtained with excellent diastereoselectivity (>20:1 *dr*) and good enantioselectivity (90:10 *er*). As the nucleophilic carbon of the intramolecular aldol reaction is on the same rigid five-membered cycle as one stereogenic center previously formed after 1,4-addition, its stereochemistry will depend on and be fixed by it. Only the configuration of the alkoxy ester will be determined according to the attack face of the dicarbonyl group. From these observations, we conclude that the second step determines the diastereoselectivity of the domino process, the first step being totally diastereoselective.

In conclusion, we have developed a general and direct diastereo- and enantioselective organocatalyzed domino Michael/aldol reaction to form polysubstituted chiral bicyclo[3.2.1]octanes. Several *β,γ*-unsaturated 1,2-ketoesters and cyclic 1,3-ketoesters were used providing an access to the corresponding bicyclic compounds in good to excellent yields with good diastereo- and enantioselectivities. Given the mechanistic insights (Scheme 1), robustness of the developed methodology (Tables 2−3), and possibilities for derivatizations (see **3f**, **3n**),[23,24] further investigations into its applications in the synthesis of natural products are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and complete characterizations (NMR spectra, GC traces, and HRMS) are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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