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Base catalyzed synthesis of bicyclo[3.2.1]octane scaffolds

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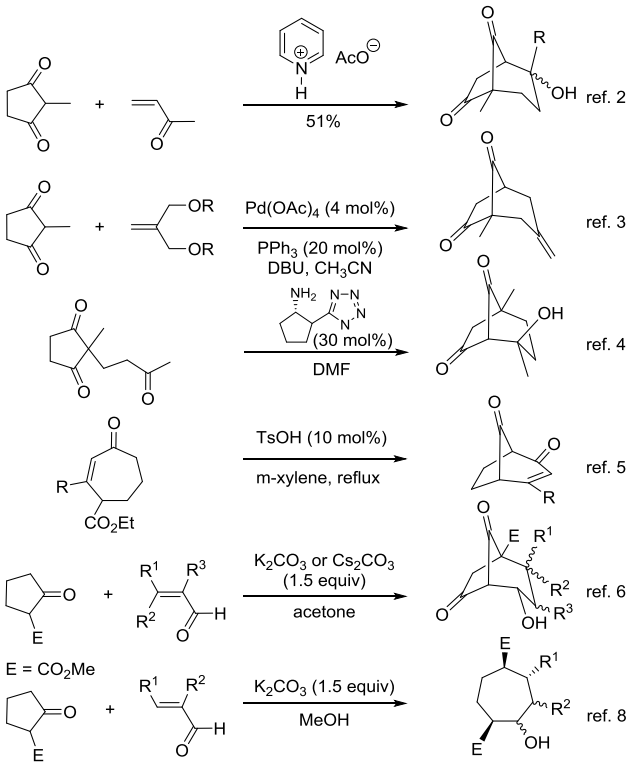
The base-catalyzed reaction of achiral 1,3-cyclopentanediones tethered to activated olefins afforded in high yields bicyclo[3.2.1]octane-6,8-dione or bicyclo[3.2.1]octane-6-carboxylate derivatives bearing respectively three or five stereogenic centers. The course of the reaction is closely related to the reaction time and to the base involved in the reaction.

The bicyclo[3.2.1]octane ring system represents not only the core structure of numerous natural bioactive compounds but also the precursor of polyfunctionalized ring systems through selective fragmentation or specific skeletal rearrangements. Therefore access to this type of skeleton is of importance, as reported by Rodriguez et al..[1] Among the numerous known methods that afford such ring systems, there are only a few reports using cycloalkane-1,3-diones (or derivatives) as starting material. Thus, Hajos et al. reported that the addition of acrolein or methyl vinyl ketone to methyl-2-cyclopentane-1,3-dione gave the corresponding bicyclo[3.2.1]octanedione derivatives in moderate yield.[2] Buono et al. set up a palladium-catalyzed *C,C*-dialkylative cyclization starting from methyl-2-cyclopentane-1,3-dione and an allylic diacetate or dicarbonate.[3] Davies et al. disclosed an organocatalyzed regioselective aldolization to afford the corresponding racemic bicyclo[3.2.1]octane derivative.[4] It was also reported that an acid-catalyzed Dieckmann-type reaction starting from cycloheptanone derivatives, afforded functionalized bicyclo[3.2.1]octanediones.[5] On the other hand, β-ketoesters were often used as starting material. For example, the intermolecular addition of cyclic β-ketoesters to α,β-unsaturated aldehydes promoted by potassium or cesium carbonate (1.5 equiv) in acetone readily afforded bicyclo[3.2.1]octane derivatives.[6] More recently, enantioselective approaches to bicyclo[3.2.1]octane scaffolds were also reported.[7] Nevertheless, when the reaction was carried out in methanol, the formation of cycloheptanols took place with the latter resulting from a Michael-Aldol-Retro-Dieckmann (MARDi) cascade (Scheme 1).[8]



Scheme 1 Syntheses of bicyclo[3.2.1]octane scaffolds and cycloheptanols

However, to the best of our knowledge, there are no reports dealing with the intramolecular reactivity of cycloalkanediones tethered to electrophilic olefins in the presence of different bases, except the reactivity of these compounds with *n*-Bu_3P.[9] Thus, we decided to investigate the base-catalyzed reaction of 1,3-cyclopentanediones tethered to activated olefins. The outcome of the reaction was unexpected. Depending on the reaction conditions, it was possible to obtain in the presence of a catalytic amount of base, either bicyclo[3.2.1]octane 6,8-dione derivatives or

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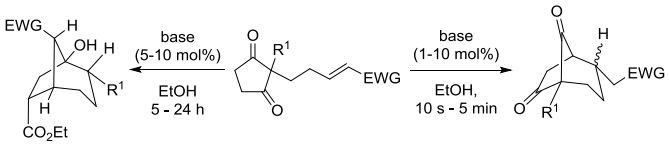
bicyclo[3.2.1]octane-6-carboxylate derivatives in high yields and good diastereoselectivity (Scheme 2).

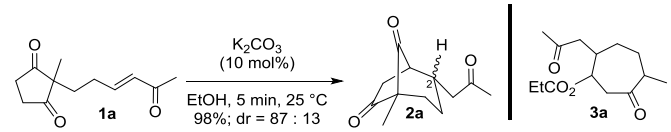


EWG: electron-withdrawing group

Scheme 2 Syntheses of bicyclo[3.2.1]octane scaffolds

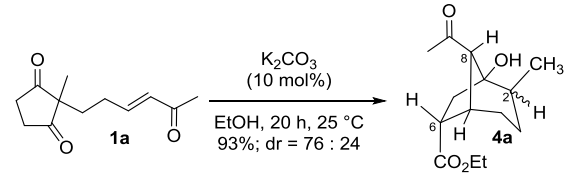
Our interest in the formation of bicyclo[3.2.1]octane derivatives was motivated by our recently reported intramolecular *n*-Bu_3P organocatalyzed reaction starting from cycloalkanediones tethered to activated olefins to give readily bicyclo[3.2.1]octane derivatives.[9] However, under our reaction conditions, no retro-Dieckmann fragmentation took place to generate the corresponding cycloheptane derivatives. Therefore, the formation of the latter was investigated using different bases and ethanol as solvent.

To start our study, triketone **1a** was treated with one equivalent of K_2CO_3 in ethanol at room temperature (rt). After 5 min of stirring, a TLC analysis of the crude reaction mixture indicated the completion of the reaction. The bicyclo [3.2.1] octane-6,8-dione **2a** was isolated in high yield with good diastereoselectivity (98%; dr = 6.7:1), the main isomer bearing an axial hydrogen at position 2. A lower catalyst loading (10 mol %) also gave product **2a** in an excellent yield. The formation of the expected cycloheptane derivative **3a** did not take place, although Rodriguez et al. had observed such products for related bicyclo[3.2.1]octane derivatives (Scheme 3).[6, 8]



Scheme 3 Formation of bicyclo[3.2.1]octane-6.8-dione **2a**

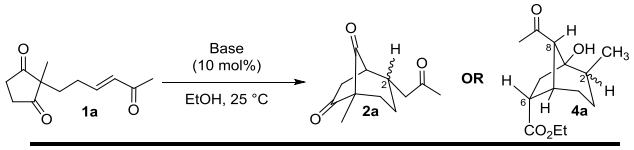
To obtain the cycloheptanone derivative **3a**, the reaction was carried out under the same conditions (10 mol % K_2CO_3, EtOH, rt) but the reaction mixture was stirred for 20 h at rt instead of 5 min. The formation of a new product which was identified as the bicyclo[3.2.1]octane-6-carboxylate derivative **4a** (93%, dr = 3.2:1) was observed, the main isomer bearing the 2-methyl group in the equatorial position. It is noteworthy that this simple reaction allows the introduction of five new stereogenic centers starting from an achiral compound. Nevertheless, the expected cycloheptane derivative **3a** could not be isolated (Scheme 4).



Scheme 4 Formation of bicyclo[3.2.1]octane-6-carboxylate derivative **4a**

To better understand the course of our reactions, the influence of the alkali metal carbonate and the reaction time were investigated. Two sets of experiments were carried out in EtOH at rt using a 10 mol % catalyst loading, and a short (10 s - 5 min) or long (20 h) reaction time. For a short reaction time, the bicyclo[3.2.1]octane **2a** was always obtained in high yield and good diastereoselectivity (entries 3, 4, 6, 8) except in the presence of lithium or sodium carbonate (entries 1, 2). It has to be emphasized that the formation of compound **2a** also readily took place in the presence of only 1 mol % Cs_2CO_3 or sodium ethoxide (entries 5, 7). When the reaction was carried out for 20 h, the bicyclo[3.2.1]octane-6-carboxylate **4a** was always obtained in high yield (entries 11-14) except in the presence of lithium or sodium carbonate where compound **2a** was exclusively obtained (entries 9, 10). This was also true when DBU was utilized as a base (entry 15); however, in the presence of DABCO, no reaction took place and the starting material was fully recovered (entry 16). It is worthy to note that under these reaction conditions, we never obtained a mixture of compounds **2a** and **4a**. Cesium carbonate was the most efficient base for these transformations, this being partly due to the higher solubility of the latter in ethanol compared to the solubility of the other alkali metal carbonates (Table 1).[10, 11]

Table 1 Reaction optimization for the formation of bicyclo[3.2.1]octane derivatives **2a** and **4a**



	Catalyst (10 mol%)	Time	Product (yield, dr)
	Short reaction time		
1	Li_2CO_3	5 min	**2a** (traces)
2	Na_2CO_3	5 min	**2a** (traces)
3	K_2CO_3	5 min	**2a** (98%, 6.7:1)
4	Cs_2CO_3	10 s	**2a** (97%, 6.7:1)
5	Cs_2CO_3[a]	15 min	**2a** (97%; 6.7:1)
6	EtONa	10 s	**2a** (99%; 5.2:1)
7	EtONa[a]	10 s	**2a** (62%; 5.7:1)
8	NaOH	10 s	**2a** (95%, 4.8:1)
	Long reaction time		
9	Li_2CO_3	20 h	**2a** (96%, 6.1:1)
10	Na_2CO_3	20 h	**2a** (99%, 6.7:1)
11	K_2CO_3	20 h	**4a** (93%, 3.2:1)
12	Cs_2CO_3	5 h	**4a** (95%, 5.2:1)
13	EtONa	20 h	**4a** (91%, 3.5:1)
14	NaOH	20 h	**4a** (96%, 3.7:1)
15	DBU	20 h	**2a** (76%, 9:1)
16	DABCO	20 h	no reaction

[a] catalyst loading: 1 mol%

Under these optimized reaction conditions, the reactivity of various cyclopentanediones tethered to activated olefins **1b-h** was investigated (Figure 1).

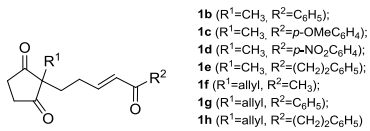
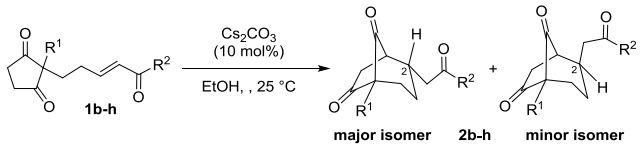


Figure 1 Cyclopentadiones **1b-h** as starting material

First of all, a short reaction time (10 s<length<1 h) in the presence of 10 mol % Cs_2CO_3 was investigated, the reaction being carried out in ethanol. Gratifyingly, the bicyclo[3.2.1]octane-6,8-dione derivatives **2b-h** were always generated in high yields and good diastereoselectivities; the major isomer bears the 2-substituent in the equatorial position (Table 2).

Table 2 Formation of bicyclo[3.2.1]octane-6.8-dione derivatives

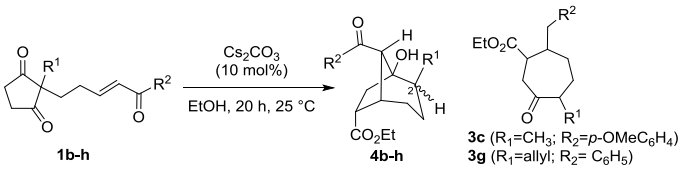


	Starting material	Time	R^1	R^2	Product (yield, dr)
1	**1b**	30 s	CH_3	C_6H_5	**2b** (95%; 2.8:1)
2	**1c**	30 s	CH_3	*p*-$OCH_3C_6H_4$	**2c** (90%; 3.8:1)
3	**1d**	25 min	CH_3	*p*-$NO_2C_6H_4$	**2d** (96%; 5.2:1)
4	**1e**	2 min	CH_3	$(CH_2)_2C_6H_5$	**2e** (71%; 10:1)
5	**1f**	10 min	allyl	CH_3	**2f** (78%; 9:1)
6	**1g**	20 s	allyl	C_6H_5	**2g** (87%; 4.5:1)[a]
7	**1h**	1 min	allyl	$(CH_2)_2C_6H_5$	**2h** (quant; 9:1)

[a] the structure of compound **2g major** was secured by X-ray analysis.[12]

Thereafter, the Cs_2CO_3 catalyzed reaction was carried out for 20 h leading to the formation of bicyclo[3.2.1]octane-6-carboxylate derivatives **4b-h**. The latter were generally isolated in good yields except for compound **4d** bearing a nitro group on the aromatic ring. The diastereoselectivities were lower than those obtained when the reaction was carried out for shorter time. For the first time, seven-membered rings **3c** and **3g** (25% yield, mixture of isomers) were formed along with the bicyclo[3.2.1]octane-6-carboxylate derivatives **4c** and **4g** (Table 3).

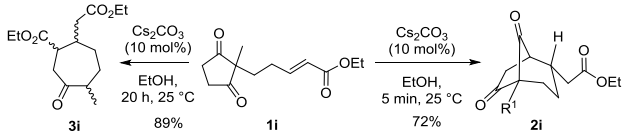
Table 3 Formation of bicyclo[3.2.1]octane-6-carboxylate derivatives



	Starting material	Time	R^1	R^2	Product (yield, dr)
1	**1b**	20 h	CH_3	C_6H_5	**4b** (86%; 1.8:1)
2	**1c**	20 h	CH_3	*p*-$OCH_3C_6H_4$	**4c** (68%; 2.7:1)[a]
3	**1d**	20 h	CH_3	*p*-$NO_2C_6H_4$	**4d** (14%; nd)
4	**1e**	20 h	CH_3	$(CH_2)_2C_6H_5$	**4e** (70%; 1.6:1)
5	**1f**	20 h	allyl	CH_3	**4f** (82%; 1.4:1)
6	**1g**	20 h	allyl	C_6H_5	**4g** (52%; 1.5:1)[a], [b]
7	**1h**	20 h	allyl	$(CH_2)_2C_6H_5$	**4h** (95%; 1.5:1)[b]

[a] the formation of **4c** and **4g** took place along with the seven-membered ring derivatives **3c** and **3g** as a mixture of isomers (yield: 25%; dr = nd); [b] the structure of the main isomer **4g** was secured by X-ray analysis.[13]

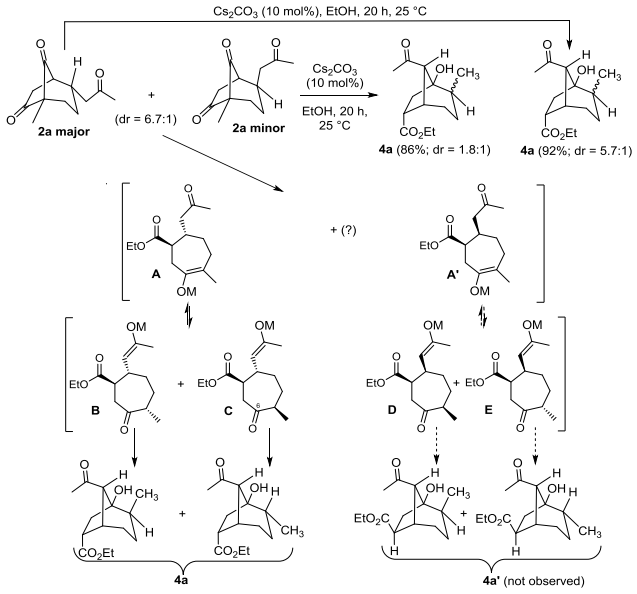
On the other hand, the addition of 10 mol % Cs_2CO_3 to compound **1i** bearing an α,β-unsaturated carbethoxy group afforded the bicyclo[3.2.1]octane-6,8-dione **2i** as a single isomer (short reaction time: 5 min)[14] and the cycloheptane derivative **3i** as a mixture of isomers (long reaction time: 20 h). This observation clearly suggested that the presence of a more potent electron-withdrawing group was absolutely necessary to promote the formation of bicyclo[3.2.1]octane-6-carboxylate derivatives. In other words, the higher pKa of the ester group probably prevented efficient enolization and intramolecular aldol reaction (Scheme 5).



Scheme 5 Formation of bicyclo[3.2.1]octane derivative **2i** and seven-membered ring **3i**

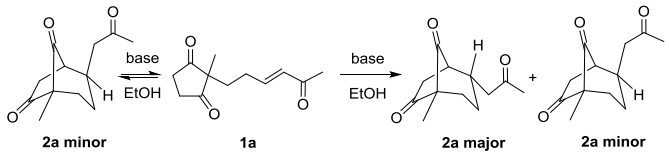
We have also shown that the treatment of the bicyclo[3.2.1]octane-6,8-dione **2a** with 10 mol % Cs_2CO_3 readily afforded the corresponding bicyclo[3.2.1]octane-6-carboxylate derivative **4a** (86% yield, dr = 1.8.1). The diastereomeric ratio **2a** *vs* **4a** was not preserved. Under the same reaction conditions, the **2a major** isomer afforded the bicyclo[3.2.1]octane-6-carboxylate derivative **4a** as a mixture of isomers (92% yield; dr = 5.7:1). However, we were never able to run this reaction starting from **2a minor** isomer because the latter was always contaminated by the **2a major** isomer. To explain our results, we propose that successive reactions probably took place with the first being an intramolecular Michael addition (formation of **2a-h**) and the second a base-induced cascade reaction (formation of **4a-h**). We argue *a priori* that the key intermediate of our cascade reaction are the seven-membered rings **A/A'** which undergo a prototropy to deliver the four isomers **B-E**. The latter should

evolve toward the bicyclo[3.2.1]octane-6-carboxylate isomers **4a** and **4a'**. However, we never observed the formation of isomer **4a'**, probably because the **2a minor** isomer might be poorly reactive in the fragmentation reaction due either to a strong interaction with the approaching nucleophile or to the development of a 1,3-diaxial interaction depending on the facial approach of the nucleophile. Moreover, a steric congestion is noticeable for the seven-membered rings intermediates **D** and **E** (Scheme 6).



Scheme 6 Formation of bicyclo[3.2.1]octane-6-carboxylate **4a** starting from bicyclo[3.2.1]octane-6,8-dione **2a**

Therefore, it is reasonable to postulate that under our reaction conditions, **2a minor** undergoes a retro-Michael reaction affording compound **1a** that evolves by Michael cyclization to give a mixture of **2a** isomers, the major isomer bearing an equatorial substituent at position 2 (Scheme 7).



Scheme 7 Retro-Michael and Michael reactions starting from **2a minor**

Conclusions

In summary, we have developed a very efficient base-catalyzed synthesis affording either bicyclo[3.2.1]octane-6,8-dione or bicyclo[3.2.1]octane-6-carboxylate scaffolds. The latter can be prepared in high yields with good diastereoselectivies and a selectivity that is controlled by the reaction time. Starting from an achiral compound, it was possible to generate bicyclo[3.2.1]octane derivatives bearing either three or five stereogenic centers. Studies of synthetic applications as well as an asymmetric version of our cascade reaction will be reported in due course.

Notes and references

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12 CCDC 1026406 (compound **2g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

13 CCDC 1026312 (compound **4g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

14 CCDC 957679 (compound **2i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif