

Atom- and Step-Economical Pathway to Chiral Benzobicyclo[2.2.2]octenones through Carbon–Carbon Bond Cleavage**

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It has become an imperative issue to improve the step^[1] as well as atom economy^[2] of organic synthesis. A highly atom-economical method to construct carbon frameworks could arise if an unsaturated organic functionality is directly inserted into a carbon–carbon single bond.^[3] Such an insertion reaction also dispenses with functional group manipulations to significantly reduce the steps required for construction of a particular organic skeleton.

A class of benzobicyclo[2.2.2]octene derivatives (**1–3**; Figure 1)) is known to possess a variety of biological activities.^[4] For example, benzobicyclo[2.2.2]octenols **1** act

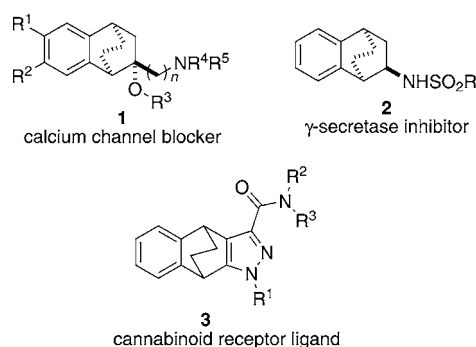
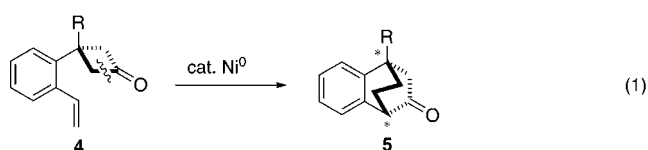


Figure 1. Biologically active benzobicyclo[2.2.2]octene derivatives.

as calcium channel blockers in the treatment or prevention of angina pectoris, ischemia, arrhythmias, high blood pressure, and cardiac insufficiency. In their synthesis, benzobicyclo[2.2.2]octenones serve as the key intermediate with the carbonyl group providing a cornerstone for further derivatization. The reported method to synthesize the key intermediate requires five steps starting from 1,4-benzoquinone and 1,3-cyclohexadiene; four of the steps are used for functional-group manipulation. After all, it affords only

a racemic mixture that additionally necessitates a resolution process.^[5] There has been no report on the straightforward enantioselective synthesis from an achiral precursor.

We have developed a nickel-catalyzed reaction of cyclobutanones **4** in which an alkene undergoes intramolecular insertion into a carbon–carbon single bond to produce benzobicyclo[2.2.2]octenones **5** [Eq. (1)].^[6] The starting cyclo-



butanone can be prepared from 1,2-divinylbenzene through [2+2] cycloaddition with dichloroketene and subsequent reductive dechlorination. Thus, it would provide a more step-economical access to benzobicyclo[2.2.2]octene derivatives in an enantiomerically enriched form if the alkenyl group is inserted into one of the enantiotopic carbon–carbon single bonds of the symmetrical cyclobutanone. Herein we describe a nickel-catalyzed asymmetric intramolecular alkene insertion reaction of 3-(2-styryl)cyclobutanones, a reaction that significantly reduces the steps required for the synthesis of chiral benzobicyclo[2.2.2]octenones.

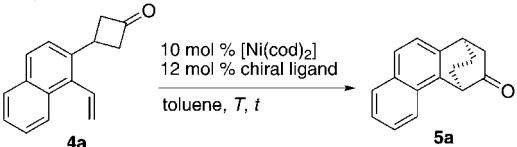
Initially, various types of chiral ligands for nickel were examined in the reaction of the cyclobutanone **4a** (Table 1). Whereas typical bidentate diphosphine ligands like BINAP and DuPhos showed no catalytic activity, monodentate phosphine ligands exhibited the potential to promote the insertion reaction. In particular, phosphoramidite ligands derived from binol^[7] afforded promising results in terms of both the yield and the enantioselectivity. When phosphoramidite **6** was used, the reaction proceeded at 100 °C and **5a** was obtained in 25% yield with 5% *ee* (entry 1). The phosphoramidite ligand **7**, which is combined with chiral 1-phenylethylamine, gave a better result both in the yield and the enantioselectivity (entry 2), both of which were improved to 66% yield and 75% *ee* when **8**, having a more sterically demanding 1-(1-naphthyl)ethylamine group, was used as the amine moiety (entry 3). The diastereomer **9**, incorporating the antipode of the chiral amine of **8**, gave an inferior result (entry 4). Notably, both phosphoramidite ligands **8** and **9** afforded the same enantiomer as the major product, thus suggesting that the axial chirality of the binol skeleton dominated in chirality induction over the amine moieties. Introduction of two *tert*-butyl groups at the 6-positions of the binol skeleton increased the solubility of the nickel complex in hydrocarbon solvents, thereby enhancing the catalyst

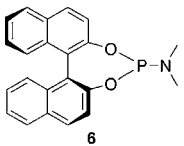
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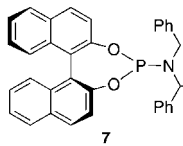
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Table 1: Optimization of the reaction conditions.^[a]

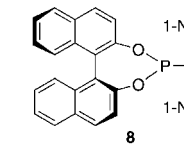




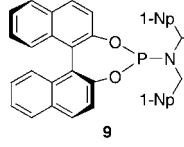
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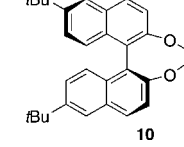
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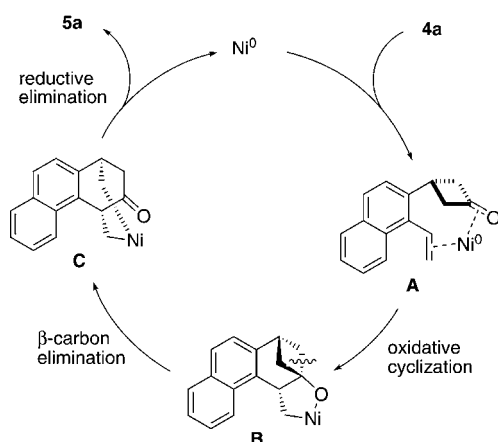
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Entry	Ligand	T [°C]	t [h]	Yield [%] ^[b]	ee [%] ^[c]
1	6	100	2	25	5
2	7	100	2	39	13
3	8	100	2	66	75
4	9	100	2	35	50
5	10	100	2	95	78
6	10	RT	4	85	86
7 ^[d]	10	RT	4	80	91

[a] Reaction conditions: **4a** (0.10 mmol; 1.0 equiv), [Ni(cod)₂] (10 mol %), chiral ligand (12 mol %), toluene (1.0 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] In *n*-hexane.

activity (entry 5).^[8] As a result, the insertion reaction proceeded at room temperature to afford **5a** in 85 % yield with 86 % *ee* (entry 6). Finally, 91 % *ee* was attained when *n*-hexane was used instead of toluene as the solvent (80 % yield, entry 7).

Mechanistically, the nickel-catalyzed reaction is initiated by intramolecular oxidative cyclization between the vinyl group and the cyclobutanone carbonyl group on nickel(0) (Scheme 1).^[9,10] This elementary step determines the stereochemistry of the insertion reaction. Among the two enantiofaces of the carbon–carbon double bond, the chiral phosphor-

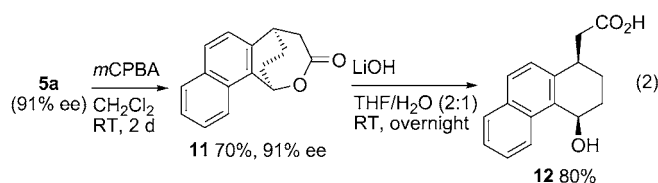


Scheme 1. Plausible mechanisms.

amidite ligand **10** favors the *Re* face over the *Si* face for coordination to nickel, and thus, enantioselectivity is induced at the sp³-carbon atom that is formed upon oxidative cyclization.^[11] The resulting tricyclic oxanickelacyclopentane **B** is no longer symmetrical. In **B**, there are two diastereotopic carbon–carbon bonds which are amenable to cleavage by β -carbon elimination. The one located *cis* to the nickelamethyl substituent is selectively cleaved because of the geometric constraints, thus giving the bicyclic nickelacycle **C**. Reductive elimination furnishes benzobicyclo[2.2.2]octenone **5a** with regeneration of the nickel(0) catalyst.

Various 3-(2-styryl)cyclobutanones were subjected to the alkene insertion reaction (Table 2). *o*-Phenylene-type linkers were allowed in place of a naphthylene linker to give benzobicyclo[2.2.2]octenones **5d–j** with enantioselectivities ranging from 80 to 93 % *ee* (entries 3–9). Both methoxy (entries 1 and 4) and fluoro (entries 5, 6, and 8) groups were tolerated on the aryl rings. In addition, the reaction of the 3,3-disubstituted cyclobutanone **4j** afforded the bicyclic ketone **5j** bearing an all-carbon quaternary chiral center at the benzylic position in 96 % yield with 82 % *ee* (entry 9). In contrast, the insertion reaction failed to occur when substituted alkenyl groups were put on the phenyl ring in place of a simple ethenyl group, probably because of steric reasons.

The obtained benzobicyclo[2.2.2]octenones would serve as useful intermediates for the synthesis of the biologically active molecules,^[4] as mentioned above. Another demonstration of the synthetic utility of the products was given by the Baeyer–Villiger oxidation reaction [Eq. (2)]. When **5a**



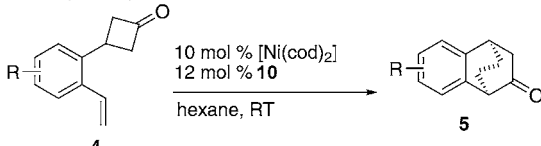
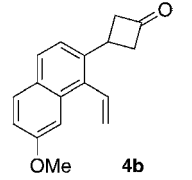
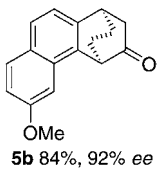
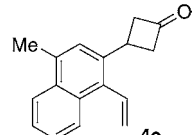
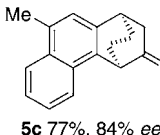
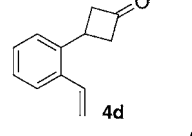
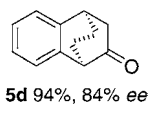
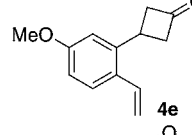
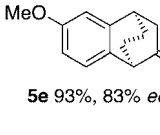
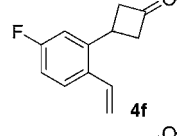
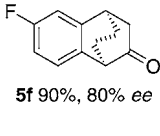
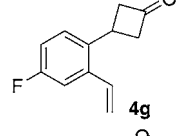
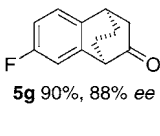
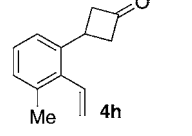
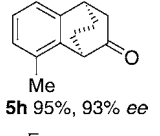
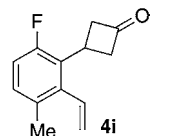
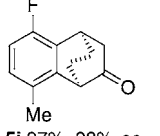
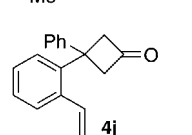
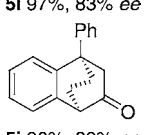
(91 % *ee*) was treated with 5 equivalents of *m*CPBA at room temperature, the secondary carbon atom selectively underwent oxidative migration with retention of the stereochemistry to furnish the lactone **11** in 70 % yield. Subsequent hydrolysis of **11** afforded the *cis*-substituted hydroxycarboxylic acid **12** in 80 % yield [Eq. (2)].

In conclusion, we have developed the asymmetric intramolecular alkene insertion reaction of 3-(2-styryl)cyclobutanones catalyzed by a nickel complex bearing a binol-derived phosphoramidite ligand. The reaction provides a unique and straightforward access to enantiomerically enriched benzobicyclo[2.2.2]octenones. It will significantly improve the step as well as atom economy in the asymmetric synthesis of a class of potent biologically active compounds derived from benzobicyclo[2.2.2]octenones.

Experimental Section

A general procedure for the nickel-catalyzed reaction of **4a**: In an N₂-filled glove-box, [Ni(cod)₂] (2.75 mg, 0.010 mmol) and *n*-hexane

Table 2: Scope of cyclobutanones.^[a]

			
Entry	4	T [°C]	5
1		RT	 5b 84%, 92% ee
2		RT	 5c 77%, 84% ee
3		50	 5d 94%, 84% ee
4		50	 5e 93%, 83% ee
5		50	 5f 90%, 80% ee
6		50	 5g 90%, 88% ee
7		50	 5h 95%, 93% ee
8		50	 5i 97%, 83% ee
9		50	 5j 96%, 82% ee

[a] Reaction conditions: cyclobutanone **4** (0.10 mmol, 1.0 equiv), [Ni(cod)₂] (10 mol %), **10** (12 mol %), *n*-hexane (1.0 mL), 6 h. [b] Yield of isolated product. [c] Determined by HPLC analyses. The stereochemistry of **5d** was assigned by measurement of the optical rotation. The stereochemistry of others was assigned by analogy.

(0.5 mL) were added to an oven-dried screw-cap vial containing a stirrer bar. Then chiral phosphoramidite ligand **10** (9.0 mg, 0.012 mmol) in *n*-hexane (0.5 mL) was added dropwise with stirring. After 5 min, **4a** (22.2 mg, 0.10 mmol) was added in one portion. After being stirred at room temperature for 4 h, the reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) to afford the product **5a** (17.8 mg, 0.80 mmol, 80 %): ¹H NMR: δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.40–7.57 (m, 3H), 4.47 (t, *J* = 2.4 Hz, 1H), 3.60 (quint, *J* = 2.4 Hz, 1H), 2.41 (dd, *J* = 18.6, 2.4 Hz, 1H) 2.16–2.31 (m, 2H), 1.97–2.10 (m, 1H), 1.65–1.82 ppm (m, 2H), [α]_D²⁵ = +183 (*c* = 0.15 in CHCl₃). [(Daicel Chiralcel OD-H, hexane/*i*PrOH = 95/5, flow rate = 1.0 mL min^{−1}, λ = 254 nm): *t*₁ = 11.7 min (major), *t*₂ = 25.3 min (minor) *ee* = 91 %].

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