Diastereoselective Ni(0)-catalyzed carbocyclization to chiral vinylic sulfoxide

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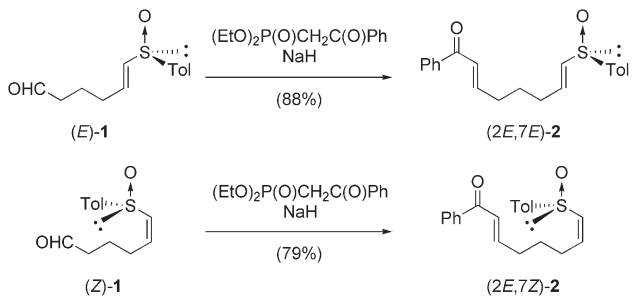
Diastereoselective Ni(0)-catalyzed carbocyclization of enone to chiral vinylic sulfoxide has been accomplished, wherein two stereogenic centers were constructed simultaneously to give *cis*- and *trans*-disubstituted cyclopentanes from (*E*)- and (*Z*)-vinylic sulfoxides, respectively.

Vinylic sulfoxides are known as an attractive chiral controller due to its differentiating ability of the diastereoface and a variety of transformations. However, examples for the application of chiral vinylic sulfoxide to transition metal-catalyzed reactions are limited.[1] Nickel-catalyzed reductive cyclization is a rapidly developing field of organic chemistry.[2] It allows construction of multi-functionalized complex molecules under mild conditions. The reaction was also applied to diastereoselective carbocyclization.[3] During the course of our study concerning new asymmetric reactions using a chiral vinylic sulfoxide, we were interested in the application of the chiral sulfoxide to asymmetric Ni(0)-catalyzed carbocyclization, which has not been reported, to the best of our knowledge. As a result, we found that the Ni(0)-catalyzed carbocyclization between enone and vinylic sulfoxide proceeds with high diastereoselectivity, wherein *cis*- and *trans*-isomers can be synthesized by changing the geometry of the vinylic sulfoxide. The resulting disubstituted cyclopentane derivatives are useful chiral building blocks since the sulfinyl group can be converted into diverse functional groups.[4]

Herein, we describe the first example of Ni(0)-catalyzed enone–vinylic sulfoxide carbocyclization.

Enones (2*E*,7*E*)-**2** and (2*E*,7*Z*)-**2** bearing a vinylic sulfoxide moiety at the end were synthesized by Horner–Wadsworth–Emmons reaction of known aldehydes (*E*)- and (*Z*)-**1**[5] with β-ketophosphonate anion (Scheme 1).



Scheme 1

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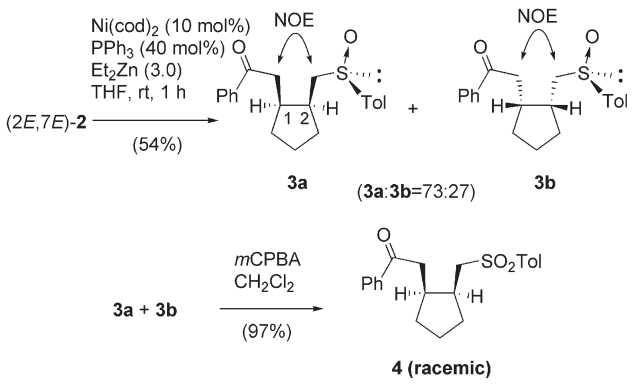
Then, Ni(0)-catalyzed cyclization of the vinylic sulfoxide (2*E*,7*E*)-**2** was carried out according to Montgomery's conditions.[6] Treatment with $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) (10 mol%) and PPh_3 (40 mol%) in the presence of Et_2Zn (3.0 equiv.) in THF at rt afforded two types of cyclized products, **3a** and **3b**, in 54% combined yield with moderate diastereoselectivity (**3a**:**3b** = 73:27).

cis-Stereochemistry of **3a** and **3b** was assigned by NOE experiments. Furthermore, *m*CPBA oxidation led a mixture of **3a** and **3b** to racemic sulfone **4** in 97% yield (Scheme 2). The results indicate the relative stereochemistry of the two carbon stereogenic centers in **3a** and **3b** is the same, and the results are consistent with the NOE experiments. The high *cis*-selectivity is in sharp contrast in as much as no selectivity was observed in the reaction of bis-enone unless alkylzinc halide was prepared *in situ* from alkyllithium and $ZnCl_2$.[6a]

The absolute configuration of **3a** and **3b** was assigned as 1*S*,2*S* and 1*R*,2*R*, respectively, by the PGME (phenylglycine methyl ester) method[7] after conversion of the sulfoxide into the corresponding PGME amides by sequential reactions: (1) Pummerer reaction, (2) $NaClO_2$ oxidation into carboxylic acid, (3) condensation with PGME.

Although carbocyclization was accomplished, the yield of the reaction considerably depends on the lot of the purchased $Ni(cod)_2$ catalyst. To obtain reproducible results, we examined *in situ* generation of the Ni(0) species from $Ni(acac)_2$, the use of which is advantageous due to lower cost and air stability. The results are shown in Table 1.

DIBAL-H was employed as a reductant of the Ni(II)-catalyst.[8] As expected, the reaction proceeded smoothly with almost the same diastereoselectivity as that with the Ni(0)-catalyst (entry 1). The reaction is reproducible and the yield was improved to 68%. We found that the diastereoselectivity was improved with



Scheme 2

Table 1 Ni-Catalyzed carbocyclization of (*E*)-vinylic sulfoxide (2*E*,7*E*)-**2**[a]

Entry	Solvent	Time/h	Yield (%)	dr[b] **3a**:**3b**
1	THF	1	68	70:30
2	Et_2O	1.5	58	73:27
3	Toluene	1	62	82:18
4	Hexane–toluene (1:1)	1.5	39	80:20
5[c]	Toluene	2	59[d]	73:27
6	MeCN	0.5	69	41:59
7	Toluene–MeCN (3 equiv.)	0.5	66	90:10
8[c]	Toluene–MeCN (3 equiv.)	0.5	73	92:8

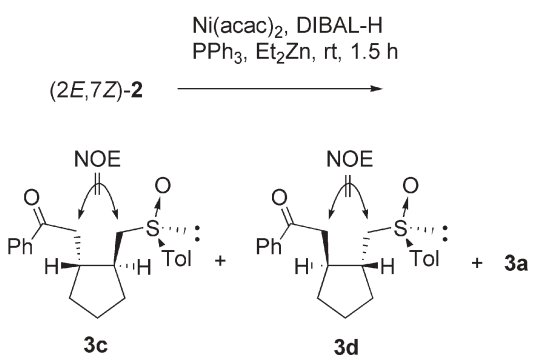
[a] All reactions were carried out using (2*E*,7*E*)-**2** (0.14 mmol), $Ni(acac)_2$ (12 mol%), DIBAL-H (0.24 equiv.), PPh_3 (0.48 equiv.), Et_2Zn (3.0 equiv.) in solvent (0.7 mL) at rt. [b] Determined by HPLC analysis. [c] Without DIBAL-H. [d] Including 10% of impurities.

decreasing polarity of the solvent [ether (73:27), toluene (82:18)] (entries 2 and 3).

However, the use of hexane–toluene (1:1) did not improve the diastereoselectivity, rather making the reaction sluggish due to low solubility of the substrate and PPh_3 (entry 4). Et_2Zn is known to work as a reductant for the Ni(II)-catalyst.[2a] Therefore, the reaction without DIBAL-H was examined, but the reaction became slow and did not complete (entry 5). Interestingly, when MeCN was employed as a solvent, the reaction was completed within 0.5 h and formation of undefined by-products was reduced (entry 6). However, the diastereoselectivity was lost. Since MeCN was effective to improve the yield, we investigated the minimum amount of MeCN so as not to affect the diastereoselectivity using toluene as a solvent. As a result, we found that only three equivalents of MeCN was enough to enhance the reactivity (entry 7). Interestingly, the addition of DIBAL-H was not necessary even in toluene (entry 8). Presumably, MeCN promotes the generation of the Ni(0)-catalyst from $Ni(acac)_2$ by the reductants such as Et_2Zn.

Little attention has been paid to the relationship of *cis*/*trans*-selectivity and the geometry of the substrate in the carbocyclization of bis-enones. We examined the effect of the geometry of vinylic sulfoxide on the stereochemistry. The results are shown in Scheme 3 and Table 2.

(*Z*)-Vinylic sulfoxide (2*E*,7*Z*)-**2** was treated with Ni(0)-catalyst generated from $Ni(acac)_2$ and DIBAL-H to give two *trans*-isomers **3c** and **3d** accompanied by a small amount of **3a**. Even in the reaction of (2*E*,7*Z*)-**2**, the ratio of the major product was decreased



Scheme 3

Table 2 Ni-Catalyzed carbocyclization of (*Z*)-vinylic sulfoxide (2*E*,7*Z*)-**2**[a]

Entry	Solvent	Yield (%)	dr[b] **3a**:**3c**:**3d**
1	Toluene	51	–:25[c]:75
2	MeCN	73	9:34:57
3[d]	Toluene–MeCN (3 equiv.)	75	2:12:86

[a] All reactions were carried out using (2*E*,7*Z*)-**2** (0.14 mmol), $Ni(acac)_2$ (12 mol%), DIBAL-H (0.24 equiv.), PPh_3 (0.48 equiv.), Et_2Zn (3.0 equiv.) in solvent (0.7 mL) at rt for 1 h. [b] The ratio of (**3a** + **3c**) and **3d** was determined by HPLC analysis. After separation from **3d**, the ratio of **3a** and **3c** was determined by ^1H NMR spectral data. [c] The content of **3a** was not determined. [d] Without DIBAL-H.

in MeCN compared to that in toluene (entries 1 and 2). The use of toluene in the presence of three equivalents of MeCN improved both the yield and selectivity (entry 3).†

The ^{13}C NMR spectra of **3c** and **3d** shows considerable difference from those of **3a** and **3b**, especially around two substituents on the cyclopentane ring (Table 3). The upfield chemical shifts for *cis*-isomers due to steric effect compared with the *trans*-isomers support the assignment of stereochemistry. This is the first example that *cis*/*trans*-selectivity was highly controlled by the geometry of the vinylic sulfoxide.‡

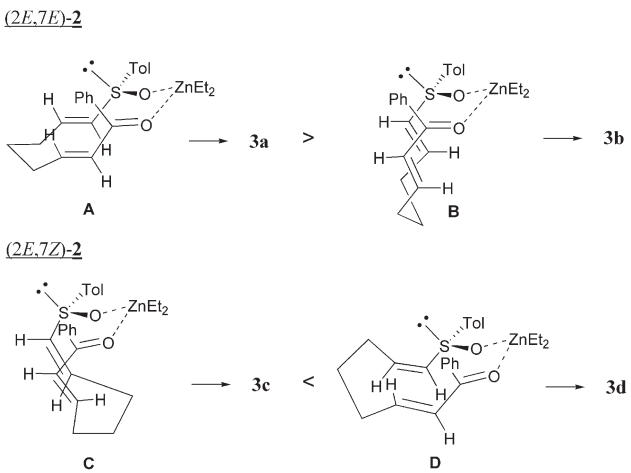
While details of the reaction mechanism are not clear at the present time, we speculate on the stereoselectivity as follows.[9]

Montgomery and co-workers suggested that alkylzinc halide plays an important role in leading to high *cis*-selectivity by substrate preorganization in the bis-enone carbocyclization.[6a] Therefore, we speculate that Et_2Zn preorganizes two alkenes by coordination to the sulfoxide and the ketone. Since a polar solvent such as MeCN breaks the chelation by solvation, the observed loss of the selectivity in MeCN supports the speculation. In the chelation intermediate, Et_2Zn would coordinate between the carbonyl group and the sulfinyl oxygen, wherein the enone would be situated opposite to the large tolyl group in the vinylic sulfoxide (Scheme 4). The intermediates **A** and **D** seem to be more stable than **B** and **C**, respectively, since conformation of the vinylic sulfoxide moiety is more favorable owing to the small $A^{(1,3)}$-strain.[10] The Ni(0)-catalyst would form metallacycle stereoselectively *via* bis π complex with diene,[9] giving **3a** and **3d** from (2*E*,7*E*)-**2** and (2*E*,7*Z*)-**2**, respectively.

In conclusion, we have developed a novel Ni(0)-catalyzed enone–vinylic sulfoxide carbocyclization, which afforded *cis*- and *trans*-disubstituted cyclopentanes with high diastereoselectivity. Since the precedent examples are chiral induction from the endocyclic stereogenic center, the present reaction is a rare example that high diastereoselectivity was accomplished using an internal stereogenic center on the exocyclic substituent. Further study to examine the scope and limitations of this methodology is under way.

Table 3 Selected chemical shifts for ^{13}C NMR spectra of compounds **3a–d**

Compound	α-C(O)	α-S(O)	β-C(O)	β-S(O)
3a	39.1	60.3	38.5	37.4
3b	39.0	59.7	38.3	37.3
3c	43.2	64.1	41.4	40.6
3d	43.7	63.6	41.4	40.3



Scheme 4

Notes and references

† The *trans*-stereochemistry of **3c** and **3d** was assigned by NOE experiments as shown in Scheme 3. The absolute configuration of **3c** and **3d** was confirmed by the PGME method in a similar manner to that described for compounds **3a** and **3b**.

‡ *General procedure* of Ni(0)-catalyzed carbocyclization. *With DIBAL-H*: DIBAL-H (0.24 equiv.) was added to a mixture of $Ni(acac)_2$ (12 mol%) and PPh_3 (0.48 equiv.) in toluene (0.3 mL) with stirring at 0 °C under Ar. After stirring at the temperature for 15 min, Et_2Zn (3.0 equiv.) was added to the mixture, a solution of enone (0.14 mmol, 1 equiv.) in toluene (0.4 mL) was successively added to the mixture. The whole was stirred at room temperature for 1 h. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc and the extract was washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexane–EtOAc (3:2). *Without DIBAL-H*: Et_2Zn (3.0 equiv.) was added to a mixture of $Ni(acac)_2$ (12 mol%), PPh_3 (0.48 equiv.), MeCN (3.0 equiv.) in toluene (0.3 mL) with stirring at 0 °C under Ar. A solution of enone (0.14 mmol, 1.0 equiv.) in toluene (0.4 mL) was successively added to the mixture. The whole was stirred at room temperature for 30 min. The work-up and purification were same as described above.

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