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Catalytic enantioselective intermolecular [2 + 2 + 2] cycloaddition of an alkene and two alkynes†

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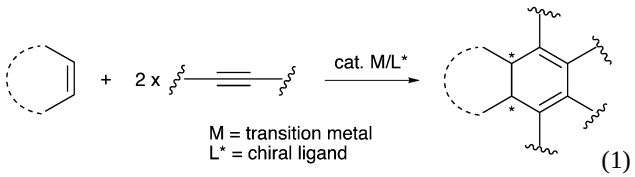
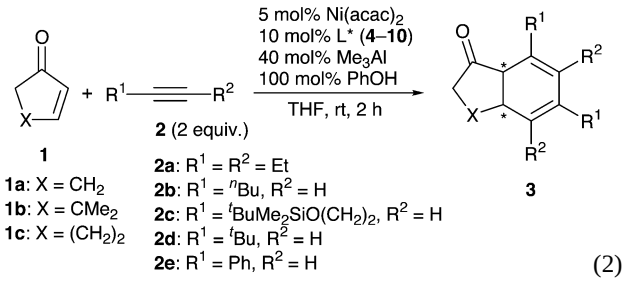
A catalytic enantioselective intermolecular [2 + 2 + 2] cycloaddition of one molecule of alkene (enone) and two molecules of alkyne was developed in the presence of a nickel complex modified by chiral monodentate oxazoline ligands, which have not previously been used as chiral ligands for transition metals in asymmetric catalysts, and an aluminium phenoxide.

[2 + 2 + 2] Cycloadditions are attractive transformations in organic synthesis, since they lead to six-membered cyclic compounds with the formation of three new carbon–carbon bonds in a single operation. Several transition metal complexes promote these reactions as catalysts or stoichiometric reagents.[1,2] Recently, a few examples of asymmetric intramolecular cycloadditions have been reported, that is, a chiral cyclopentadienyl cobalt(I) complex-mediated reaction of endiynes,[3] the cobalt(I)-mediated reaction with chiral auxiliary-substituted endiynes,[4] and a nickel(0)-catalyzed reaction of diynes with acetylene have been realized based on a strategy that involves a new enantiotopic group selective formation of a metallacycle.[5] We have envisaged the development of a new asymmetric cycloaddition of one molecule of alkene and two molecules of alkyne in the presence of transition metal catalysts (M) modified by chiral ligands (L*) [eqn. (1)].



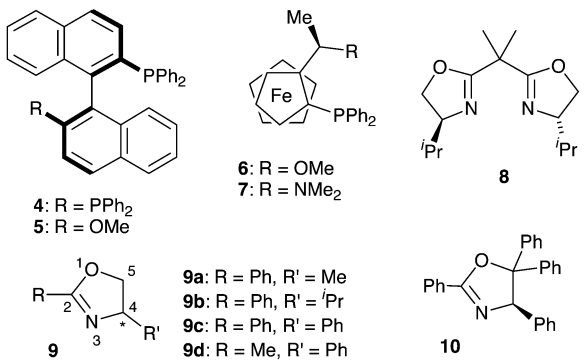
(1)

In the course of our studies on nickel-catalyzed intermolecular domino coupling of enones **1**, alkynes **2**, and organometallics,[6] we found that a binary metal system of nickel and an aluminium species catalyzed the regioselective [2 + 2 + 2] cycloaddition of **1** and **2**.[7] A precatalyst, $Ni(acac)_2$, reacts with some of the added Me_3Al to be converted into an active Ni(0) species. The residual Me_3Al functions as a Lewis acid and activates **1**. When phenol (PhOH) is added to the reaction medium, a more acidic aluminium phenoxide species ($Me_nAl(OPh)_{3-n}$ (n = 0–2)) is generated from the reaction with Me_3Al *in situ*. In this paper, we describe the enantioselective [2 + 2 + 2] cycloaddition of **1** with **2**, catalyzed by a nickel complex modified by chiral monooxazoline ligands such as **9** and **10** and an aluminium species [eqn. (2)].



(2)

Initially, we screened various chiral ligands, which would coordinate to the Ni(0) catalyst and cause asymmetric induction, in the reaction using **1a** and **2a**. The results are summarized in Table 1.‡ Some reputed chiral phosphine ligands like **4**,[8] **5**,[9] **6**,[10] and **7**[10] and a bidentate bisoxazoline ligand **8**[11] gave no or



only low enantioselectivity (runs 1–5). On the other hand, when the reaction was performed with a monodentate oxazoline like **9**,[12] asymmetric induction occurred to give optically active **3aa**. Better results were obtained with 2-phenyl derivatives like **9a**–**9c** (R = Ph) (runs 6–8), compared with a 2-methyl derivative **9d** (R = Me) (run 9). Although the differences in asymmetric induction according to the substituent R′ at the 4-position (stereogenic center) of **9** were slight, the introduction of two phenyl groups to the 5-position of **9** led to an interesting result. Thus, when the reaction was carried out with a 2,4,5,5-tetraphenyl derivative **10**, the enantioselectivity of **3aa** increased to 45% (run 10).

The absolute stereochemistry of (−)-**3aa** was determined to be (3a*R*, 7a*S*) based on an examination of the ^1H NMR spectra

Table 1 Asymmetric induction in Ni/Al-catalyzed cycloaddition of **1a** with **2a** in the presence of some chiral ligands L*[a]

Run	L*	Isolate yield of **3aa** (%)	Enantioselectivity[b] (sign of [α])
1	**4**	15	0% ee
2	**5**	27	10% ee (+)
3	**6**	28	18% ee (+)
4	**7**	0	—
5	**8**	0	—
6	(*S*)-**9a**	67	23% ee (+)
7	(*S*)-**9b**	66	28% ee (+)
8	(*R*)-**9c**	77	34% ee (−)
9	(*R*)-**9d**	28	2% ee (−)
10	**10**	22	45% ee (−)

[a] The reaction was carried out in THF at room temperature for 2 h; molar ratio: [**1a**]:[**2a**]:[$Ni(acac)_2$]:[L*]:[Me_3Al]:[PhOH] = 1:2.2:0.05:0.1:0.4:1. [b] Determined by chiral HPLC.

† Electronic supplementary information (ESI) available: experimental and spectroscopic data. See http://www.rsc.org/suppdata/cc/b2/b208313b/

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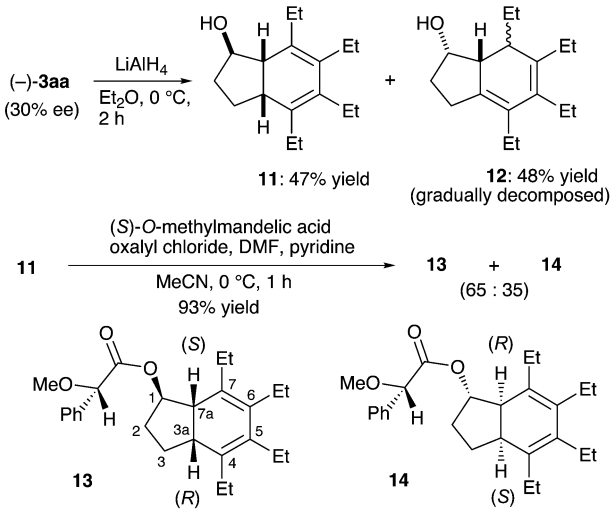
Table 2 Ni/Al-catalyzed enantioselective [2 + 2 + 2] cycloaddition of **1** with **2** in the presence of **9c** or **10**[a]

Entry	1	2	9c or 10	3	Yield of 3[b] (%)	Enantioselectivity
1	**1a**	**2b**	(*R*)-**9c**	**3ab**	93[c]	25% ee[d]
2			**10**		66[c]	48% ee[d]
3	**1a**	**2c**	(*R*)-**9c**	**3ac**	67	33% ee[e]
4			**10**		77	62% ee[e]
5	**1a**	**2d**	(*R*)-**9c**	**3ad**	93	22% ee[d]
6			**10**		72	58% ee[de]
7	**1a**	**2e**	(*R*)-**9c**	**3ae**	47	20% ee[e]
8			**10**		65	55% ee[e]
9	**1b**	**2a**	(*R*)-**9c**	**3ba**	74	53% ee[f]
10			**10**		21	44% ee[f]
11	**1b**	**2d**	(*R*)-**9c**	**3bd**	95	10% ee[e]
12			**10**		25	40% ee[e]
13	**1c**	**2b**	(*R*)-**9c**	**3cb**	92	4% ee[e]
14			**10**		65	4% ee[e]

[a] The reaction was carried out in THF at room temperature for 2 h; molar ratio: [**1**]:[**2**]:[$Ni(acac)_2$]:[**9c** or **10**]:[Me_3Al]:[PhOH] = 1:2.2:0.05:0.1:0.4:1. [b] Isolated yield. [c] Regioselectivity: 95%. [d] Determined by chiral GC. [e] Determined from ^1H NMR spectra using a chiral shift reagent ($Eu(hfc)_3$). [f] Determined by chiral HPLC.



Scheme 1

of diastereomeric (*S*)-*O*-methylmandelates[13] **13** and **14**, which were derived from **11** (Scheme 1).§

The chiral monodentate oxazoline ligands **9c** and **10** were applied to the enantioselective cycloaddition of **1** with **2** (Table 2). These reactions, except the reaction using **2b** (entries 1 and 2), occurred with perfect regioselection. While the higher enantioselection was shown in the reactions using ligand **10**, the yields of **3ba** and **3bd** decreased to 21 and 25%, respectively, and the enantiomeric excess (ee) of **3bd** also did not improve (entries 9–12). The reaction of a cyclohexenone **1c** with **2b** gave **3cb** in lower enantioselectivity (entries 13 and 14), compared with the reactions using cyclopentenones **1a** and **1b**.

In summary, we have described the first example of catalytic enantioselective intermolecular [2 + 2 + 2] cycloaddition of one molecule of alkene and two molecules of alkyne. The reaction described here was accomplished using a binary metal catalytic system consisting of a nickel complex modified by monodentate oxazolines like **11** and **12**, which have not previously been used as chiral ligands for transition metals in asymmetric catalysts,[14] and an aluminium phenoxide.

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Notes and references

‡ The experimental procedure for the formation of **3aa** (run 8 in Table 1) is as follows: to a solution of $Ni(acac)_2$ (14 mg, 0.05 mmol) and (*R*)-**11d** (23 mg, 0.1 mmol) in THF (5 mL) was added Me_3Al in a 1.0 M hexane solution (0.4 mL) at 0 °C under N_2. After stirring for 5 min, phenol (109 mg, 1.1 mmol) in THF (1 mL) was added to this solution, and the mixture was stirred for 5 min. To the dark red solution were added **2a** (180 mg, 2.2 mmol) and **1a** (82 mg, 1.0 mmol) at 0 °C, and the mixture was then stirred at room temperature for 2 h. Aqueous HCl (0.2 M, 30 mL) was added, and stirring was continued for 10 min. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ for 30 min, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–AcOEt = 14:1, *Rf* = 0.31) to give **3aa** (189 mg, 77%). Enantiomeric excess (ee) was determined to be 34% by chiral HPLC (column: Daicel CHIRALPAK AS, 0.46 × 25 cm; solvent: hexane–*i*PrOH = 19:1; flow rate: 0.2 mL min^{-1}; detector: RI; retention time: (+)-**3aa**, 19.9 min; (−)-**3aa**, 22.0 min).

§ When **3aa** was treated with $LiAlH_4$ in Et_2O at 0 °C, two alcohols were obtained in total 95% yield. One was determined to be **11** by NOE experiment of the corresponding 3,5-dinitrobenzoate. The other, although it was gradually decomposed, was confirmed to be **12**. On the other hand, the reduction of **3aa** using L-selectride® at −78 °C gave **12** in 81% yield along with a trace amount of **11**.

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