Effects of monodentate oxazoline ligands in Ni/Al-catalyzed regioselective cyclotrimerization of enones and alkynes†

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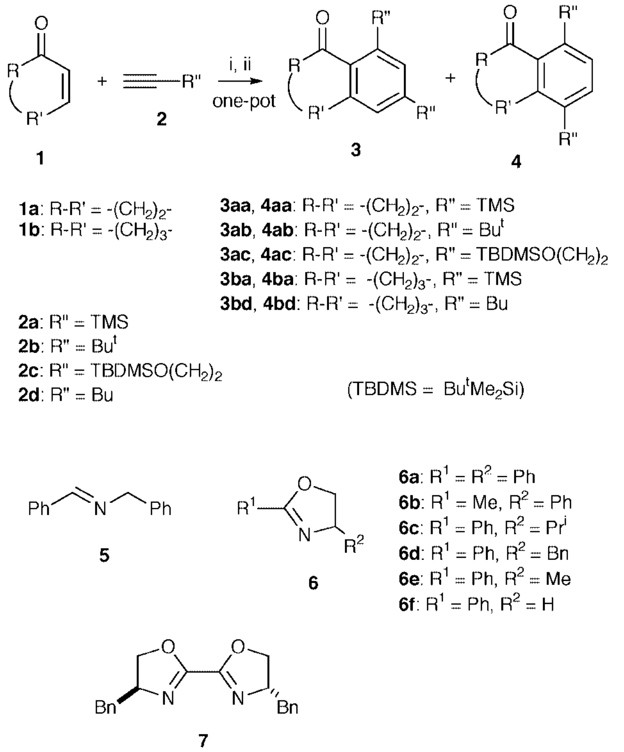
A nickel and aluminium system including monodentate oxazoline ligands catalyzed the regioselective cyclotrimerization of enones and alkynes.

Since the pioneering work by Reppe,[1] the cyclotrimerization of unsaturated hydrocarbons using various transition-metal catalysts has represented a new method for preparing six-membered cyclic compounds.[2] In particular, intramolecular reactions have been used as an efficient synthetic approach.[3] In contrast, two- or three-component intermolecular cyclotrimerization has not yet been shown to be useful, since it is more difficult to control the chemo-, regio-, and stereo-selectivity. We recently reported a new cyclotrimerization of enones **1** and alkynes **2** by the synergistic effects of nickel and aluminium catalysts (L = PPh_3 in Scheme 1).[4] In this reaction, however, regioselection was dependent on the nature of **2** used (*vide infra*). We report here, a more efficient catalytic system for regioselective cyclotrimerization of **1** and **2**.

We investigated the effects of some ligands (L) on regioselection in the cyclotrimerization of 2-cyclopenten-1-one **1a** with (trimethylsilyl)acetylene **2a** by the $Ni(acac)_2/L/Me_3Al/PhOH$ catalytic system (Table 1).‡ The cyclotrimerization adducts (regioisomeric mixture) obtained were treated with DBU in air to convert them to the corresponding aromatic compounds **3** and/or **4**, owing to the ease of regiochemical analysis by ^1H NMR spectroscopy. The reaction in the presence of PPh_3 or $P(C_6H_4Me\text{-}o)_3$ gave **4aa** as the sole product (runs 1 and 2), while the addition of other organophosphorus ligands or $AsPh_3$ failed (runs 3–6). In sharp contrast, the reaction using pyridine or **5** led to the selective synthesis of **3aa** (runs 7 and 8). Monodentate oxazoline ligands **6** strongly affected the regioselective cycloaddition (runs 9–14).[5,6] Most strikingly, when the reaction was carried out in the presence of **6d–f**, **3aa** was obtained in 95–96% selectivity (runs 12–14). Thus, ligands **6** in place of triarylphosphines caused *switching* of the regioselectivity in the cyclotrimerization. When a bidentate bis-oxazoline **7** (10 mol%) was used in the reaction,[7] the yield of **3aa** was low, even after 24 h (run 15).



Scheme 1 *Reagents and conditions*: i, $Ni(acac)_2$ (10 mol%), L (20 mol%), Me_3Al (80 mol%), PnOH (200 mol%), THF, room temp.; ii, DBU, air, overnight.

The results of the catalytic cyclotrimerization of a variety of enones **1** and alkynes **2** are summarized in Table 2. In our initial efforts to achieve the regioselective cyclotrimerization of **1** and **2** using a $Ni(acac)_2/PPh_3/Me_3Al/PhOH$ catalytic system, **2b** was reacted with **1a** to selectively give **4ab** (entry 1).[4] However, when the reaction was carried out in the presence of a Ni/Al catalytic system using **6e**, **3ab** was obtained predominantly (entry 2). A similar tendency was found in the reactions of **2a** with **1b** (entry 5 *vs.* 6). The product ratio of **8** and **9** derived from the reaction of **1c** with **2a** also depended on the nature of the employed ligands (L) (Scheme 2).[8] On the other hand, the reactions of alkyl-substituted alkynes such as **2c** and **2d** with **1** using **6e** gave a higher regioselection of **3** than those using PPh_3 (entries 3 *vs.* 4 and 7 *vs.* 8).

In summary, we have clarified the effects of monodentate oxazolines **6**, which have scarcely been used as ligands in catalytic reactions, in the Ni/Al-catalyzed cyclotrimerization of

Table 1 Cyclotrimerization of **1a** and **2a** in the presence of the $Ni(acac)_2/L/Me_3Al/PhOH$ catalytic system[a]

Run	L	Time/h	Yield[b] (%) (**3aa** + **4aa**)	Ratio[c] (**3aa**:**4aa**)
1[d]	PPh_3	2	33	0:100
2	$P(C_6H_4Me\text{-}o)_3$	2	49	0:100
3	PBu_3	24	Trace	—
4	$P(OPh)_3$	24	Trace	—
5	dppe[e]	24	No reaction	—
6	$AsPh_3$	24	Trace	—
7	Pyridine	24	6	72:28
8	**5**	24	12	80:20
9	**6a**	2	61	86:14
10	**6b**	2	60	72::8
11	**6c**	2	61	85:15
12	**6d**	2	59	95:5
13	**6e**	2	69	96:4
14	**6f**	2	59	96:3
15	**7**	24	23	97:3

[a] Reaction conditions as in Scheme 1. [b] Yield after purification by silica gel chromatography. [c] Determined by ^1H NMR. [d] See ref. 4. [e] 1,2-Bis(diphenylphosphino)ethane.

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† Electronic supplementary information (ESI) available: experimental and characterization data. See http://www.rsc.org/suppdata/cc/b0/b001151g/

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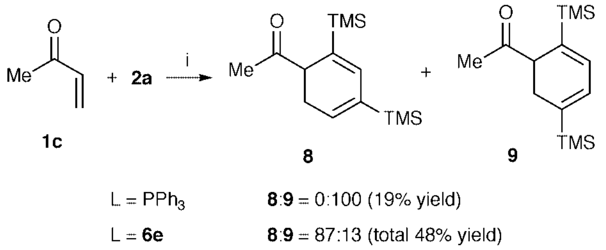
Table 2 Cyclotrimerization of **1** and **2** in the presence of the Ni(acac)$_2$/L/Me$_3$Al/PhOH catalytic system (L = PPh$_3$ *vs.* **6e**)[a]

Entry	1	2	L	Product(s) major, (minor)	Yield[b] (%) (**3** + **4**)	Ratio[c] (**3**:**4**)
1[d,e]	**1a**	**2b**	PPh$_3$	**4ab** (**3ab**)	45	11:89
2[e]			**6e**	**3ab**	67	100:0
3[d]	**1a**	**2c**	PPh$_3$	**3ac** (**4ac**)	81	92:8
4			**6e**	**3ac**	87	100:0
5[f]	**1b**	**2a**	PPh$_3$	**4ba** (**3ba**)	29	17:83
6			**6e**	**3ba**	78	100:0
7[d,g]	**1b**	**2d**	PPh$_3$	**3bd** (**4bd**)	83	92:8
8[g]			**6e**	**3bd**	81	100:0

[a] Reaction conditions as in Scheme 1. Unless stated otherwise, the cycloadditions were performed with stirring for 2 h. [b] Yield after purification by silica gel chromatography. [c] Determined by ^{1}H NMR. [d] See ref. 4. [e] The aromatization was carried out with 0.2 M NaOH in MeOH. [f] Reaction time: 24 h. [g] Reagents: **1**:**2**:Ni(acac)$_2$:L:Me$_3$Al:PhOH = 1:2:0.05:0.1:0.4:4:1.



Scheme 2 *Reagents and conditions*: i, **1c** (1 equiv.), **2a** (2 equiv.) Ni(acac)$_2$ (10 mol%), L (20 mol%), Me$_3$Al (80 mol%), PnOH (200 mol%), THF, room temp., 24 h.

enones **1** and alkynes **2**. The reaction using **6** resulted in the selective formation of **3**, independent on the alkynes used.

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Notes and references

‡ *Typical experimental procedure* (entry 2 in Table 2): to a solution of Ni(acac)$_2$ (27 mg, 0.1 mmol) and **6e** (0.1 mmol) in THF (4 mL) was added Me$_3$Al in 1.0 M hexane solution (0.8 mL) at 0 °C under N$_2$. After stirring for 5 min, PhOH (190 mg, 2.0 mmol) was added, and the mixture was stirred for 5 min. To the resulting dark red solution were added **1a** (1.0 mmol) and **2b** (2.0 mmol) at 0 °C. After the addition was completed, the whole mixture was stirred at room temperature for 2 h. DBU (350 mg, 2.3 mmol) was added to this reaction mixture in air, and this was again stirred at room temperature overnight. Aqueous HCl (0.2 M, 30 mL) was added, and stirring was continued for 10 min. The aqueous layer was extracted with diethyl ether. The combined organic layer was washed with NaHCO$_3$ and then with brine, dried over MgSO$_4$ for 30 min, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–AcOEt, 14:1) to yield **3ab** (67%) as the sole product as a colorless oil; δ_H(400 MHz, CDCl$_3$, Me$_4$Si) 1.36 (s, 9 H, CH$_3$), 1.47 (s, 9 H, CH$_3$), 2.66 (t, *J* 6.1 Hz, 2 H, CH$_2$), 3.07 (t, *J* 6.1 Hz, 2 H, CH$_2$), 7.29 (s, 1 H, =CH), 7.40 (s, 1 H, =CH); δ_C(100 MHz, CDCl$_3$, Me$_4$Si) 25.85, 29.75, 31.12, 35.37, 35.95, 37.54 (CH$_3$, CH$_2$ and C), 121.20, 122.26, 132.30, 151.41, 157.81, 158.80 (Ar), 206.07 (CO); IR(neat) 1705 (ν_{CO}) cm^{-1}; GC–MS (EI, 70 eV) *m/z* (rel int, %) 244 (M$^+$, 55), 229 (100). Anal. Calc. for C$_{17}$H$_{24}$O: C, 83.55; H, 9.90. Found: C, 83.51; H, 9.99%.

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8 Attempted conversion of a mixture of **8** and **9** to the corresponding aromatic compounds by treatment with base (DBU or NaOH/MeOH) failed.