

Enantioselective Michael Addition of Diethyl Malonate on Substituted Chalcone Catalysed by Nickel-Sparteine Complex

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Abstract

A series of transition metal with Sparteine a novel chiral catalyst was facilely synthesized, all of which contain a chiral Sparteine unit as a bidentate ligand. These bidentate chiral auxiliaries were found to be an efficient chiral catalyst in nickel-mediated, enantioselective Michael addition of Diethyl malonate to substituted chalcone. The corresponding adducts were obtained in good yields (80-91%) under simple and clean reaction condition.

Keywords: NiCl₂; Sparteine; Chalcones; Diethyl malonate; Michael addition

Introduction

Enantiopure bidentate ligands of transition metal complexes with, oxygen, phosphorus and nitrogen donor sites have been subjected to considerable attention and their active potential as chiral catalyst in asymmetric synthesis was discovered [1-4].

A wide variety of bidentate ligands with transition metal complexes have been investigated along with various types of catalytic activity with donors as well as acceptor in Michael addition reaction due to their potent catalytic activity some ligands show excellent enantioselectivity in organic transformation [5-7]. In general, for enantioselectivity of chiral catalysts, modular ligand structures and orientation towards substrate have proved to be advantageous [8], since ligand fine-tuning by varying structural fragments or relative position of substituents to the active site of catalyst or substrate is expected to allow their optimal adjustment to the specific reaction mechanism [9,10].

Among carbon-carbon bond forming reactions, nickel-mediated reaction has found broad application in asymmetric synthesis [11,12]. The chiral bidentate ligands and nickel complex catalysed asymmetric Michael addition of ester compounds α , β -unsaturated enones is one of the most attractive strategies from a synthetic point of view (Scheme 1). Since the discovery by Nelson and S. chirographer Metal-ligand complex has added new value to nickel-mediated enantioselective Michael addition reaction [13,14]. In addition to the metal-ligand complex has been rapidly developed into a powerful tool for the construction of a C-C stereoselective bond [15,16]. The divalent metal complexes with Sparteine have been intense study in thermodynamic and kinetic for the formation complex [17,18].

To develop efficient chiral ligands is a central issue in the research

of asymmetric catalysis [19]. Nitrogen-containing chiral ligands have distinct advantages, including easy to synthesis, highly stable and more importantly, nitrogen atom that can stabilize the central metal at a high valence [20,21]. Reasoning that, nitrogen-containing ligands are frequently used in asymmetric synthesis [22,23]. There are several practical benefits nitrogen-containing chiral ligands such as simple reaction operation, mild reaction condition and environmentally being reagents and these reagents are used for the synthesis of various natural products and bioactive molecules. For the recent years, our laboratory shown that Sparteine can function as a chiral catalyst for Michael addition reaction [24], Inspired by our previous result, we have developed one more catalytic methodology for asymmetric Michael addition [25], and also synthesized amino acid and its analogous containing the amide moiety [26]. Here in, we report the nitrogen-containing Sparteine bidentate ligands with transition metal complexes as chiral catalyst for enantioselective Michael addition reaction of diethyl malonate on chalcone (Scheme 1).

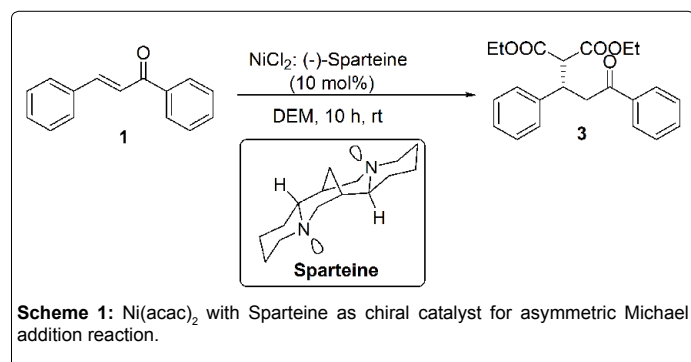
Experimental Section

General

All products were characterized by ¹H NMR, ¹³C NMR, were recorded on Varian Mercury 300 MHz spectrometer. IR spectra were recorded on a Shimadzu FTIR-8400 with samples loaded as thin films on KBr plate, neat or with DCM as indicated. Mass spectra were recorded at an ionization potential of 70 eV and Melting points recorded on digital instrument are uncorrected.

Typical experimental procedure

In a dry flask NiCl₂ (13 mg, 10 mol%) and (-)-Sparteine (0.024 mL, 10 mol%) in dry Toluene (5 mL) was stirred under nitrogen at room temperature for 6.0 h, slowly added chalcone (0.393 g, 1.89 mmol) pinch by pinch, reaction mixture can be stirred additional 30 min and finally



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Diethyl malonate (0.345 mL, 2.26 mmol) in 2 mL Dry Toluene was added slowly and then reaction mixture can be stirred until full consumption of starting material. Then all volatile materials concentrated to dryness in vacuo. Then reaction mixture quenched with dil. HCl and extracted with ethyl acetate. Separate the organic layer and dried over Na₂SO₄ and purified by column chromatography with Pet ether/EtOAc (90:10%) to afford desired product 3a in 88% yield with 86% ee.

(R)- Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate: White solid, m. p. 64-67°C; [α]_D²⁵ -20.7° (c=0.68 CHCl₃), lit²³. -23.2 (c=0.68 CHCl₃, 96 % ee) KBr (cm⁻¹) 2945, 2850, 1736, 1680, 1604, 1525, 1352, 1250. ; ¹H NMR (300 MHz, CDCl₃): δ =7.90-7.85 (m, 2H; Ar), 7.51-7.56 (m, 1H; Ar), 7.39-7.50 (m, 2H; Ar), 7.25-7.22 (m, 4H; Ar), 7.18-7.15 (m, 1H; Ar), 4.21-4.14 (m, 3 H; CH, OCH₂), 3.91 (q, J=7.1 Hz, 2H; OCH₂), 3.85 (d, J=9.6 Hz, 1H; CH), 3.41-3 (m 2H CH₂), 1.27 (t, J=7.1 Hz, 3H; CH₃), 1.03 (t, J=7.1 Hz, 3H; CH₃); ¹³C NMR (75 MHz, CDCl₃): 197.5, 168.3, 167.1, 140.4, 136.6, 132.8, 128.4, 128.3, 128.2, 128.1, 127.1, 61.9, 61.5, 57.7, 42.4, 40.6, 14.0, 13.8; MS (GC/MS) m/z: 369.32; ESI-HRMS (m/z) calcd. for C₂₂H₂₄O₅Na ((M+Na)⁺): 391.1521, Found: 391.235.

Results and Discussion

Despite its outstanding performance Sparteine catalysed reaction in asymmetric synthesis [27], Sparteine-Nickel catalysed enantioselective Michael addition reaction of diethyl malonate on chalcone a furnished γ -ester ketone 3. We initially screen Ni(acac)₂ with Sparteine as chiral catalyst for asymmetric Michael addition reaction. A mixture of diethyl malonate and chalcone in dry toluene was stirred at 25°C for 5 h in presence of 10 mol% Ni(acac)₂ with Sparteine as chiral catalyst to afford 3a with 80 % ee with 85 % yield. This result prompted us to explore an efficient metal complex with sparteine in Table 1. When reaction was conducted with NiCl₂ 3a is obtained in 90 % yield with 86 % ee (entry 2), while other transition metal complexes with Sparteine were observed less enantioselectivity (entry 3-6). It was noted that Sparteine: NiCl₂ as more effective catalytic system than other catalytic system for Michael addition reaction.

Yield of product after purification by chromatography

We screened various polar and non-polar solvents (Table 2) for Michael addition reaction the enantioselectivity was observed essentially good when reaction performed in toluene as compare to other solvents including DCM and Chloroform (entry 1, 2). Even highly polar solvents Ethanol, Methanol, THF, afford the Michael adduct 3a with lower enantioselectivity (Table 2). Thus, toluene is the most suitable solvent for Michael addition reaction of diethyl malonate and chalcone (Table 2, entry 4). Using 10 mol % of catalyst 1a, Michael adduct was isolated in 90 % yield with 86% enantioselectivity within 12 h at ambient temperature.

The influence of the two experimental parameters (solvent and catalyst) was studied and the experiment that probe to the scope of chalcone substrate (1a-1i) that can be easily prepared by aldol condensation [28] as shown in Scheme 2 and summarized in Table 3. Under optimized conditions, a variety of substituted chalcone were tested to investigate the generality of the reaction. The asymmetric Michael addition of diethyl malonate on chalcone was conducted with 10 mol % of catalyst in toluene at 25°C for 5 h. As illustrated in Table 3, good enantioselective (80-88% ee) were obtained with good to excellent yields after isolated pure products by column chromatography. The enantiomeric excess values of the keto esters and their derivatives were determined by GC or Specific rotation as compare to reported

| Entry | Catalyst | Time (hr) | Yield (%) ^b | ee% |
|-------|--------------------------------------|-----------|------------------------|-----|
| 1 | (-) Sparteine: Ni(acac) ₂ | 10 | 85 | 80 |
| 2 | (-) Sparteine: NiCl ₂ | 11 | 90 | 86 |
| 3 | (-) Sparteine: Cu(acac) ₂ | 10 | 75 | 50 |
| 4 | (-) Sparteine: Co(OAc) ₂ | 10 | 64 | 44 |
| 5 | (-) Sparteine: Co(acac) ₂ | 12 | 80 | 62 |
| 6 | (-) Sparteine: CuCl ₂ | 13 | 79 | 54 |

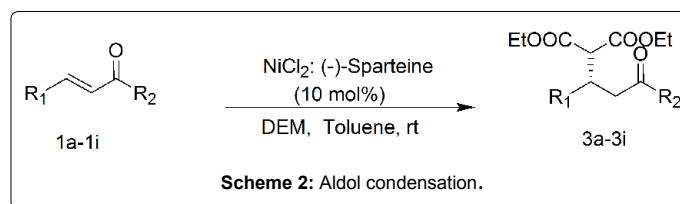
^aReaction Condition: i) Sparteine (10 mol%) and NiCl₂ (10 mol%), Chalcone (1.89 mmol), Diethyl malonate (2.26 mmol), Toluene, 25°C; ^byield of product after purification by chromatography

Table 1: Study of various Transition Metal complex with Sparteine for Michael Addition.

| Entry | Solvent | Time (h) | Yield (%) ^b | ee % |
|-------|-------------------|----------|------------------------|------|
| 1 | DCM | 11 | 90 | 86 |
| 2 | CHCl ₃ | 11 | 85 | 73 |
| 3 | THF | 10 | 85 | 58 |
| 4 | Toluene | 13 | 89 | 87 |
| 5 | MeOH | 10 | 83 | 30 |
| 6 | EtOH | 10 | 82 | 27 |

^aReaction Condition: i) Sparteine (10 mol%) and metal complex (10 mol%), Chalcone (1.89 mmol), Diethyl malonate (2.26 mmol), Toluene, 25°C;

Table 2: Michael Addition of Diethyl malonate to Chalcone Using Different Solvents.



| Entry | R ₁ | R ₂ | Product | Time (h) | Yield (%) ^b | ee % |
|-------|---|----------------|---------|----------|------------------------|------|
| 1 | Ph | Ph | 3a | 13 | 90 | 87 |
| 2 | 4-ClC ₆ H ₄ | Ph | 3b | 12 | 90 | 87 |
| 3 | 2-ClC ₆ H ₄ | Ph | 3c | 12 | 89 | 83 |
| 4 | 4-OMeC ₆ H ₄ | Ph | 3e | 13 | 85 | 85 |
| 5 | Ph | Me | 3f | 14 | 83 | 84 |
| 6 | 4-BrC ₆ H ₄ | Ph | 3g | 12 | 84 | 82 |
| 7 | 4-MeC ₆ H ₄ | Ph | 3h | 14 | 88 | 86 |
| 8 | 4-NO ₂ C ₆ H ₄ | Ph | 3i | 8 | 91 | 80 |

^aReaction Condition: i) Sparteine (10 mol%) and NiCl₂ (10 mol%), Chalcone (1.89 mmol), Diethyl malonate (2.26 mmol), Toluene, 25°C; ^b yield of product after purification by chromatography.

Table 3: Study of Michael addition of Diethyl malonate on various substituted chalcone.

data [19,22]. All products were characterized by spectroscopic data (¹H-NMR, ¹³C-NMR, IR and Mass).

Conclusion

We have developed Sparteine: NiCl₂ as a new catalytic system for Michael addition of diethyl malonate on substituted chalcone to provide Michael adducts with good enantioselectivity at ambient reaction condition. An advantage of this synthetic strategy includes simple and inexpensive catalyst, mild reaction, and easy work-up procedure. We continue to investigate the scope of Sparteine catalysed reaction.

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