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An improved Sparteine $TiCl_4$ Catalysed Enantioselective Michael Addition of Diethyl Malonate to Chalcone.

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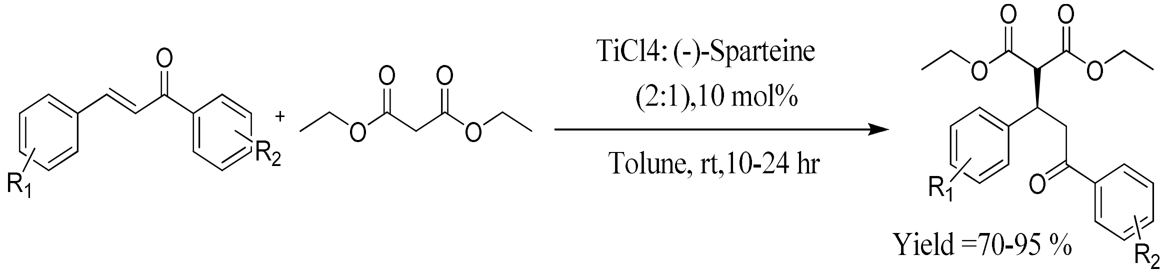
ABSTRACT

A simple synthetic strategy useful for the Michael addition of different malonate to chalcone by using sparteine: $NiCl_4$ complex with 80-92% yield with high enantiomeric purity i.e. 80-99% ee of the product has been developed. Sparteine is a naturally occurring chiral ligand with readily available $TiCl_4$ make an efficient catalyst system for the reaction. The reaction was performed with low catalyst loading. All the substrates are easily prepared in excellent yield and characterized by all spectroscopic methods.

KEYWORDS
Enantioselective, Chalcone, Sparteine, Malonate.

1. INTRODUCTION

Michael reaction is the conjugate addition of nucleophile or a carbanion to an α, β-unsaturated carbonyl compound. It is the most useful method for the formation of C-C, C-N, C-O bonds formation. Many asymmetric variants such as 1,3-dicarbonyl compounds exist for the asymmetric addition to nitroalkenes and substituted chalcone to develop a powerful tool in organic synthesis, as these are active and are versatile building blocks in agricultural and pharmaceutical compounds. Although there have been many reports of enantioselective Michael additions with chiral catalysts, including metal-based catalysts and multimetallic catalysts as well as organic catalysts, which include L-proline rubidium catalyst,[1] N-(3,5-di-tert-butyl-4-methoxy) benzylcincho-nidinium bromide,[2] calcium-BINOL,[3] amino alcohol aluminium complex,[4] under mild phase-transfer conditions of N-spiro C_2-symmetric chiral quaternary ammonium bromide possesses diaryl hydroxyl methyl functionalities,[5] bis(2-pyridinecarboxamido)-1, 10-spirobiindane (abbreviated as SIPAD) and bis(2-quinolinecarboxamido)-1,10-spirobiindane (abbreviated as SIQAD) with $Co(OAc)_2$,[6] nanocrystalline magnesium oxide,[7] Ramipril acid-derived N,N'-dioxide $Sc(OTf)_3$,[8] primary and secondary derived organodiamine catalyst.[9] Practical Michael additions of 1,3-dicarbonyl compounds to nitroalkenes remain largely unexplored to develop Michael addition. Herein, we report the development of an efficient chiral ligand that contains nitrogen which can stabilize metal ion and have distinct advantages including easy preparation, high stability, and recyclability. For these reasons, we employed sparteine $TiCl_4$ complex useful for the formation of a C-C bond via Michael addition of malonate to chalcone. Sparteine $TiCl_4$ before employed in Aldol type condensation and extensively used in the insertion of chirality in organic transformation.[10] Apart from organocatalyst few heterobimetallic complexes work well, as that contains a binol lanthanide complex and different alkali metal offer a versatile framework for asymmetric catalysts.[11] First time (-)-sparteine and $TiCl_4$ in combination used as the catalyst for Michael addition. This makes it extremely simple work compared to other approaches.



Scheme 1. Synthesis of (R)-diethyl 2-(4-methylene-3-oxo-1-phenylhept-5-en-1-yl) malonate.

2. MATERIALS AND METHODS

All solvents were purified and dried by standard procedures before use. IR spectra were recorded on a Shimadzu FTIR-8400 series instrument in cm^{-1}. Optical rotations were obtained on Jasco P-1020 digital Polarimeter; the chiral column used is the Phenomenex column. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury spectrometer on 300 and 75 MHz in $CDCl_3$ as a solvent. All HRMS and GCMS were recorded on Bruker Impact HD ESI source at Shimadzu Analytical Centre, University of Pune.

2.1. General procedure for synthesis of(R)-diethyl 2-(4-methylene-3-oxo-1-phenylhept-5-en-1-yl) malonate

In two neck round bottom flask was charged with a mixture of $TiCl_4$ (10 mol %) and (-)-Sparteiene (20 mol%) in dry Toluene (5mL) was added after 5 min. diethyl malonate (0.523g,3.26 mmol).The reaction mixture was stirred for 5 min. at -78°C. Chalcone (0.566g, 2.72mmol) was added slowly and reaction stirred until starting material was totally consumed. Evaporate the solvent to dryness, add ethyl acetate and transfer the mixture to separatory funnel and washed with dil. HCl. Separate the organic layer and dried over anhydrous sodium sulphate. Filter and dry on rotary evaporator to dryness and purified by silica gel column chromatography with hexane/EtOAc (85:15 %) to afford desired product in 92% with 99% ee.

(R)-Diethyl 2-(4-methylene-3-oxo-1-phenylhept-5-en-1-yl) malonate (1): Yield 92% Solid. $[\alpha]_D^{25}$ = -24.9° (c = 0.68 CHCl3), IR ($CHCl_3$, cm^{-1}) 2945, 2850, 1736, 1680, 1604, 1525, 1352, 1250. ^{1}H-NMR (200 MHz, $CDCl_3$, δ) 3.49 (s, 3H), 3.52-3.60 (m, 2H), 3.72 (s, 3H), 3.86-3.89 (d, 1H, J = 8.8 Hz), 4.19-4.25 (m, 1H), 7.17-7.26 (m, 5H), 7.27 (s, 4H), 7.39-7.44 (t, 2H, J = 7.4Hz), 7.50-7.52 (t, 1H, J = 7.4Hz), 7.89-7.91 (d, 2H, J = 7.4Hz). ^{13}C-NMR (50 MHz, $CDCl_3$,δ) 166.63, 168.11, 167.63, 148.24, 146.94, 136.23, 133.44, 129.21, 128.65, 127.95, 123.61, 56.45, 52.87, 52.64, 41.72, 40.25. HRMS (m/z): 391.2356 (M^++Na), Calculated: 391.6138(M^++Na).

(R)-Diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl) malonate (4): Yield 90% Solid. $[\alpha]_D^{25}$ = -23.1° (c = 0.6 $CHCl_3$,), IR ($CHCl_3$, cm^{-1}) 2982, 2906, 1732, 1687, 1597, 1491, 1448, 1367, 1303, 1155, 1031, 912. ^{1}H-NMR (300 MHz, $CDCl_3$, δ) 1.01-1.05 (t, 3H, J = 7.1 Hz), 1.21-1.26 (t, 3H, J = 7.1 Hz), 3.38-3.44 (dd, 1H, J = 16.6, 9.8 Hz), 3.50-3.53 (dd, 1H, J =16.6, 4.4 Hz), 3.77-3.80 (d, 1H, J = 9.8 Hz), 3.99-4.01 (q, 2H, J = 7.1 Hz), 4.24-4.12 (m, 3H), 7.21 (s, 4H,), 7.42-7.51 (t, 2H, J = 7.4 Hz,), 7.53-7.87 (t, 1H, J = 7.4 Hz), 7.87-7.90 (d, 2H, J = 7.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$,δ) 197.17, 168.04, 167.48, 138.95, 136.52, 132.78, 129.62, 128.53, 128.45, 127.97, 61.69, 61.41, 57.23, 42.32, 40.04, 13.93, 13.71. HRMS (m/z): 425.1939 (M^+ +Na), Calculated: 425.1132 (M^+ +Na).

(R)-Dimethyl 2-(3-oxo-1, 3-diphenylpropyl) malonate (1a): Yield 96 %, Solid, $[\alpha]_D^{25}$ = -12.3° (c = 1 $CHCl_3$), IR ($CHCl_3$, cm^{-1}) 2945, 2850, 1736, 1680, 1604, 1525, 1352, 1250. ^{1}H-NMR (300 MHz, $CDCl_3$, δ) 3.49 (s, 3H), 3.52-3.60 (m, 2H), 3.72 (s, 3H), 3.86-3.89 (d, 1H, J = 8.8 Hz), 4.19-4.25 (m, 1H), 7.17-7.26 (m, 5H), 7.27 (s, 4H), 7.39-7.44 (t, 2H, J = 7.4Hz), 7.50-7.52 (t, 1H, J = 7.4Hz), 7.89-7.91 (d, 2H, J = 7.4Hz).^{13}C-NMR (75 MHz, $CDCl_3$, δ): 166.63, 168.11, 167.63, 148.24, 146.94, 136.23, 133.44, 129.21, 128.65, 127.95, 123.61, 56.45, 52.87, 52.64, 41.72, 40.25.GC-MS : 340, Calculated: 340.

(R)-Dimethyl 2-(3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl) malonate (3a): Yield: 80%, Solid, $[\alpha]_D^{25}$ = -18.8° (c = 1 $CHCl_3$), IR ($CHCl_3$, cm^{-1}) : 3066, 2956, 2929, 1732, 1672, 1602, 1427, 1265, 1170, 1022, 815, 702, 561. 1H-NMR (300 MHz, $CDCl_3$, δ) : 3.41-3.46 (m, 2H), 3.49 (s, 3H), 3.72 (s, 3H), 3.84 (s, 3H), 3.87 (d, 1H J = 7.9 Hz), 4.13-4.21 (m, 1H), 6.87-6.90 (d, 2H J = 8.8Hz), 7.15-7.25 (m, 5H), 7.87-7.90 (d, 2H, J = 8.8Hz).^{13}C-NMR (75 MHz, $CDCl_3$, δ): 195.99, 168.72, 168.14, 163.39, 140.40, 130.34, 129.79, 128.40, 128.01, 127.12, 113.63, 57.29, 55.40, 52.61, 52.35, 41.93, 40.91. HRMS (m/z): 393.1329 (M^++Na), Calculated: 393.1314 (M^++Na).

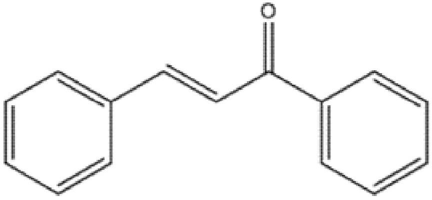
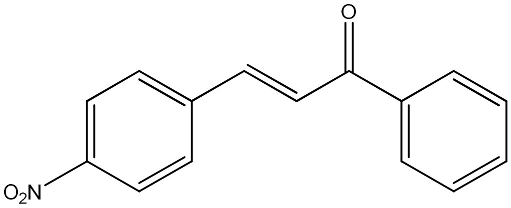
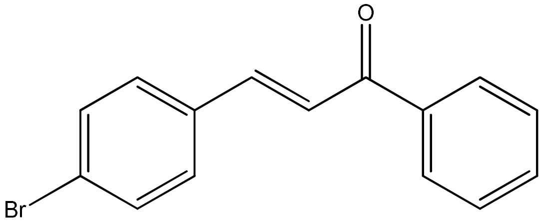
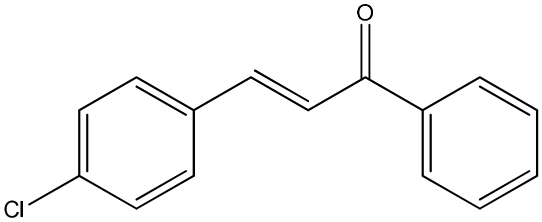
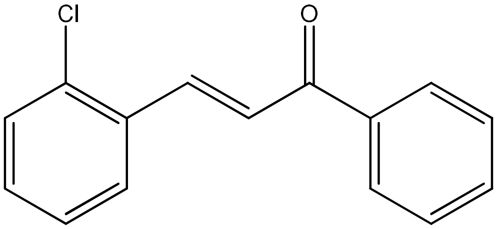
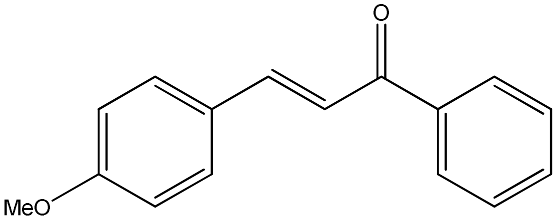
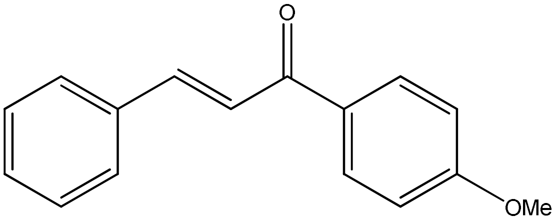
(R)-dimethyl 2-(3-(4-chlorophenyl)-3-oxo-1-phenylpropyl)malonate (2a): Yield :72%, Liquid, $[\alpha]_D^{25}$ = -9.3° (c = 1 $CHCl_3$), IR ($CHCl_3$, cm^{-1}): 3060, 2945, 2930, 1735, 1662, 1602, 1430.^{1}H-NMR (300 MHz, $CDCl_3$,δ) : 3.43-3.49 (App.m, 2H), 3.50 (s, 3H), 3.72 (s, 3H), 3.82-3.85 (d, 1H J = 9.4Hz), 4.13-4.16 (m, 1H), 7.23-7.26 (m, 5H), 7.40-7.41 (d, 2H J = 8.5Hz), 7.84-7.85 (d, 2H, J = 8.5Hz). ^{13}C-NMR (75 MHz, $CDCl_3$, δ) : 196.24, 168.57, 167.94, 140.06, 139.34, 134.90, 129.39, 128.72, 128.40, 127.88, 127.17, 57.04, 52.55, 52.29, 42.16, 40.66. HRMS (m/z): 397.0016 (M^++Na), Calculated: 397.0819 (M^++Na).

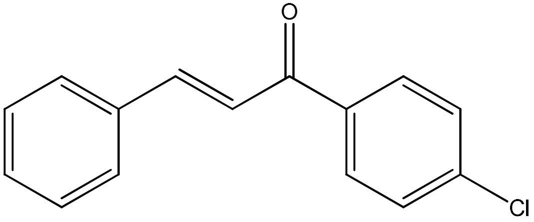
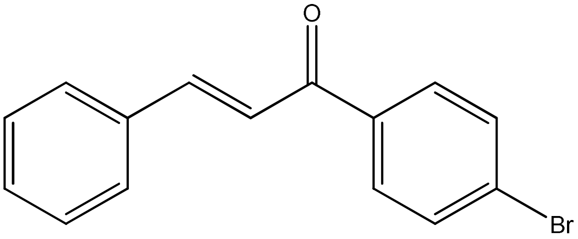
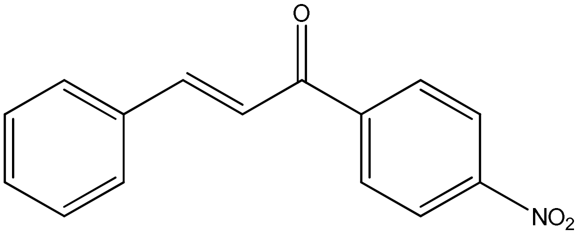
(R)-Dimethyl 2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl) malonate (4a): Yield: 80%, Colourless liquid, $[\alpha]_D^{25}$ = -6.2° (c = 1 $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 2955, 2852, 1735, 1683, 1604, 1521, 1348, 1259, 1157, 1020, 856, 750, 694.^{1}H-NMR (200 MHz, $CDCl_3$, δ): 3.49-3.62 (m, 2H), 3.55 (s, 3H), 3.75 (s, 3H), 3.82 (d, 1H, J = 8.8 Hz), 4.27-4.35 (m, 1H), 7.26-7.56 (m, 5H), 7.88-90 (d, 2H J = 8.2Hz), 8.12-18.15 (d, 2H, J = 8.2Hz).^{13}C-NMR (50 MHz, $CDCl_3$, δ): 166.63, 168.11, 167.63, 148.24, 146.94, 136.23, 133.44, 129.21, 128.65, 127.95, 123.61, 56.45, 52.87, 52.64, 41.72, 40.25. HRMS (m/z): 408.3175 (M^+ +Na), Calculated: 408.106 (M^++Na).

3. RESULTS AND DISCUSSION

The conjugate addition of malonate to chalcone derivative was performed with 10 mol % of catalyst generated in situ from sparteine and $TiCl_4$ in 2:1, where Toluene as solvent at -75° C afforded the desired product in 75 to 95 %.[12,13] The initial reaction of malonate with chalcone was examined in different solvents like THF, CH_3OH, DMF, and water. The reaction in water afforded very low yield (less than 10%) as it is found that the catalyst was decomposed. Whereas, the same reaction in toluene shown more than 90% yield. After verified the mole proportion of the catalyst to obtain maximum enantioselectivity of the product formation, it was found that neither 20 mole % nor the equivalent proportion of the catalyst useful to enhance the enantioselectivity of the product. Besides, this reaction was carried out in the presence of bases such as Et_3N, diisopropyl ethyl amine resulted in increases in the rate of the reaction with the introduction of less enantioselectivity of the addition product in a high yield. Under the optimized reaction conditions, various substituted chalcones acting as Michael acceptors were reacted with malonate and the results are summarized in Table I, II. It was interesting to note that all chalcone derivatives, regardless of the electronic and steric properties of the substituent, gave a similar level of yield (±10%) and moderate enantioselectivity around 80 to 99 % ee.

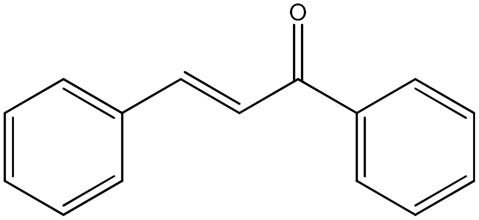
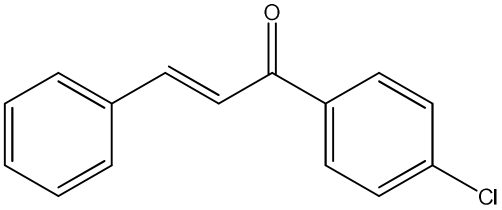
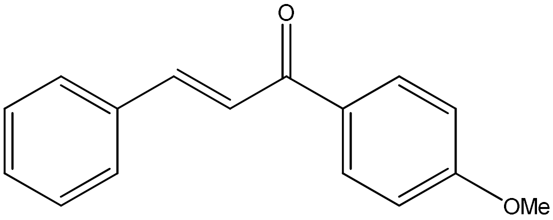
Table 1. The reaction of diethyl malonate and various chalcone.

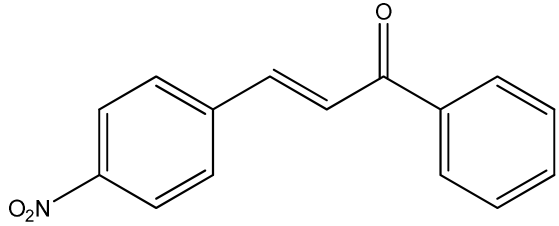
Sr. No.	Chalcones	Yield	Time	% ee
1		**92**	**12**	**99**
2		**95**	**10**	**98**
3		**88**	**14**	**96**
4		**90**	**14**	**96**
5		**80**	**18**	**98**
6		**75**	**24**	**80**
7		**75**	**24**	**85**

8		**78**	**20**	**85**
9		**78**	**22**	**86**
10		**70**	**24**	**80**

[a]All reactions performed at -75°C. [b]Yield represented after purification.

Table 2. Reaction of dimethyl malonate and various chalcone.

Sr. No.	Chalcones	Yield	Time	% ee
1a		**96**	**12**	**96**
2a		**86**	**18**	**80**
3a		**80**	**20**	**80**

4a		**96**	**10**	**96**

[a]All reactions were performed at -75°C..[b]Yield represented after purification.

The effect of the ester alkyl moiety of malonate on the yield and enantioselectivity was notable as diethyl moiety gives fewer yields with high enantioselective compared with dimethyl moiety which affords high yield with less enantioselectivity. In all cases, the substrate gives the desired products in high yields with moderate enantioselectivities. The electronic nature of the position of the substituent at the aromatic ring of both sides had little influence on the enantioselectivity. However, the electron-withdrawing groups on the conjugate side give high yield, while at oxy side reduces the yield. After a complete optimized study, the compound was characterized by the spectroscopic method. The compound (Table I entry - 4) is confirmed by the ^{1}H NMR data in which the CH of Benzylic position resonates at region δ. 4.24-4.12 as multiple. The two ethyl groups of ester resonate as doublet and triplet at δ. 3.38-3.44, 3.50-3.53 and 1.01-1.05, 1.21-1.26 respectively. Its mass spectrum is found 403.4473 (M^+ +Na) which confirm the product.

4. CONCLUSION

The reported organocatalytic methodology for the Michael addition of dimethyl malonate to chalcones, which furnished the products in more than 80% yield and high enantioselectivity up to 80-99%. Organocatalyst sparteine is readily and easily available material. The reaction required a very short time to complete the formation of the product.

5. ACKNOWLEDGMENTS

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