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Heterogeneous Jørgensen–Hayashi catalyst for asymmetric Michael addition of malonates to α,β-enals. Cooperative effect with $Ca(OTf)_2$

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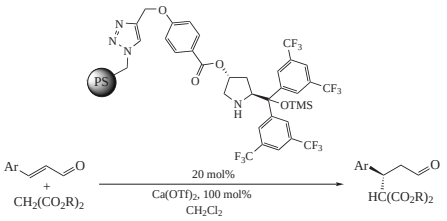
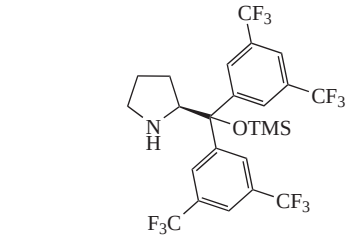
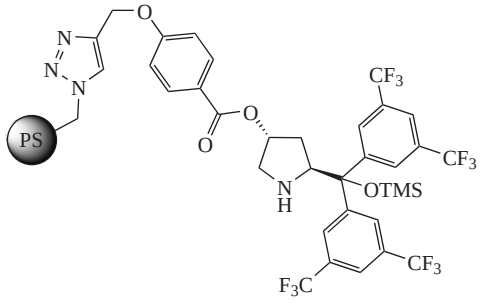
Heterogeneous chiral Jørgensen–Hayashi catalyst promotes enantioselective Michael addition of malonates at cinnamic aldehydes. In combination with $Ca(OTf)_2$, it provides high yields (up to 78%) and excellent enantiomeric excesses (up to 99%) of the adducts.



Jørgensen-Hayashi catalyst I of diarylprolinol silyl ether chemotype[1,2] (Figure 1) belongs to privileged organocatalysts which provide high yields and enantioselectivity *via* enamine or iminium ion activation in such fundamental transformations as aldol condensation, Mannich, Michael and Diels–Alder reactions.[3,4] Organocatalytic enantioselective addition of malonates to aromatic α,β-enals is a key step in the synthesis of vital medicaments Paroxetin and Femoxetin.[5] However, to achieve high yields and excellent enantiomeric purity of these products, catalysts are used in substoichiometric amounts (*ca.* 20 mol%). Application of immobilized analogues of these catalysts simplifies the product separation from catalysts by simple filtration and enables repeated use of the catalyst, which significantly improves efficiency of the process (TON). Immobilization of α,α-diarylprolinol trimethylsilyl ethers was described by a number of authors and was studied in aldol condensation and Michael addition reactions.[6–14] However, often enantiomeric excess was poor and recyclization was problematic. Previously we synthesized an easily recoverable heterogeneous bis[3,5-bis(trifluoromethyl)phenyl]prolinolsilyl ether immobilized onto polystyrene and demonstrated its satisfactory catalytic activity in the α-amination of aliphatic aldehydes *via* enamine substrate activation in 5 cycles.[15] In this work we extended its application for the reactions proceeding *via* iminium ion activation using an exemplary malonate addition to α,β-enals.



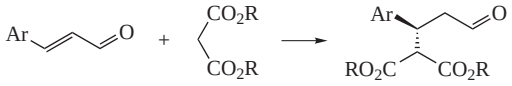
Jørgensen–Hayashi organocatalyst I



Heterogeneous Jørgensen–Hayashi organocatalyst II

Figure 1

The model reaction of dimethyl malonate (R = Me) with cinnamic aldehyde (Ar = Ph)[5,16–25] (Scheme 1) was carried out in the presence of 20 mol% α,α-bis[3,5-bis(trifluoromethyl) phenyl]prolinol trimethylsilyl ether immobilized onto polystyrene (catalyst II, Figure 1).



Scheme 1

This reaction is known to proceed in EtOH in the presence of the homogeneous catalyst I to give the product in 85% yield with 95% *ee* (Table 1, entry 1).[5] Under analogous conditions in the presence of the heterogeneous catalyst II, the same reaction did not occur at all (Table 1, entry 2). We have chosen CH_2Cl_2 among the solvents promoting the swelling of the polymeric support, but the reaction did not occur as well (Table 1, entry 3). It is known that the addition of malonates to aldehydes is accelerated in the presence of lithium salts[26] without loss of enantioselectivity, however, in our case the addition of lithium acetate was inefficient (Table 2, entry 4).

Table 1 Optimization of addition of dimethyl malonate $CH_2(CO_2Me)_2$ at cinnamic aldehyde PhCH=CHCHO (catalyst, 20 mol%, 36 h).

Entry	Catalyst	Additive (mol%)	Solvent	Isolated yield (%)	*ee*[a] (%)
1	Catalyst I	–	EtOH	85[5]	95
2	Catalyst II	–	EtOH	–[b]	–
3	Catalyst II	–	CH_2Cl_2	–[b]	–
4	Catalyst II	LiOAc (20)	CH_2Cl_2	–[b]	–
5	Catalyst II	$Ca(OTf)_2$ (20)	CH_2Cl_2	56	85
6	Catalyst II	$Ca(OTf)_2$ (100)	CH_2Cl_2	62	86

[a] By chiral HPLC. [b] Conversion 0% by ^1H NMR.

Table 2 Addition of malonates at cinnamic aldehydes [see Scheme 1; catalyst II (20 mol%), $Ca(OTf)_2$ (100 mol%), CH_2Cl_2, 72 h].

Entry	Ar	R	Isolated yield (%)	*ee*[a] (%)
1	Ph	Me	62	86
2	Ph	Et	44	86
3	Ph	Bn	78	92
4	4-$MeOC_6H_4$	Me	10	28
5	4-$MeOC_6H_4$	Bn	51	77
6	4-ClC_6H_4	Me	61	77
7	4-ClC_6H_4	Et	68	89
8	4-ClC_6H_4	Bn	74	85
9[b]	4-$O_2NC_6H_4$	Bn	76	99
10	2-$O_2NC_6H_4$	Bn	65	53
11	2-$O_2NC_6H_4$	Me	59	90

[a] By chiral HPLC. [c] With 20 mol% $Ca(OTf)_2$.

The problem was solved by the addition of calcium triflate, a hard Lewis acid activating the malonate (Table 1, entry 5).† Further increase in its amount did not notably improve the yield of the product (Table 1, entry 6). It is noteworthy that running the reaction in the presence of $Ca(OTf)_2$ but without organocatalyst gave no result, to prove that calcium salts act in cooperation with organocatalyst II. The attempt of the repeated use of the catalyst was not successful: in the second run the chemical yield decreased to 47% while enantioselectivity was as low as 11%.

The regularities of this reaction were established by varying substituent Ar in the enal and substituent R in the malonate (see Scheme 1). We found out that depending on the nature of Ar the influence of R on the reaction yield and enantioselectivity may be often significant (Table 2).

The introduction of electron donor methoxy group in the *para*-position dramatically decreased both the chemical yield and enantiomeric excess in the reaction with dimethyl malonate (entry 4), though with dibenzyl malonate the decrease was not so pronounced (entry 5). The introduction of electron withdrawing substituents in *para*-position led to high yields of the products and increased their enantiomeric purity (entries 6–10). Similar regularities were noted for the reaction mediated by homogeneous catalyst.[5,27] The highest enantiomeric excess (>99%) was achieved in the addition of dibenzyl malonate to *p*-nitrocinnamic aldehyde in the presence of 20 mol% catalyst II and 20 mol% $Ca(OTf)_2$ (entry 9).

In the case of the nitro group in *ortho*-position the yield and enantiomeric purity of the product were poorer (entry 10), however with dimethyl malonate the enantiomeric excess again was high (entry 11).

To conclude, cooperation of immobilized Jørgensen–Hayashi catalyst with $Ca(OTf)_2$ allows one to carry out addition of alkyl malonates to α,β-enals in good yields and with good to high (up to 99% *ee*) enantioselectivity. Heterogeneous catalyst can be easily removed by filtration.

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References

1 K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res*., 2012, **45**, 248.
2 A. Mielgo and C. Palomo, *Chem. Asian J*., 2008, **3**, 922.
3 H. Jiang, L. Albrecht, G. Dickmeiss, K. L. Jensen and K. A. Jørgensen, in *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2013, pp. 33–50.
4 H. Gotoh and Y. Hayashi, in *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*, eds. P. J. Dunn, K. K. Hii, M. J. Krische and M. T. Williams, Wiley, 2013, p. 287.
5 S. Brandau, A. Landa, J. Franzén, M. Marigo and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2006, **45**, 4305.
6 B. G. Wang, B. C. Ma, Q. Wang and W. Wang, *Adv. Synth. Catal*., 2010, **352**, 2923.
7 E. Alza and M. A. Pericàs, *Adv. Synth. Catal*., 2009, **351**, 3051.
8 P. Riente, C. Mendoza and M. A. Pericàs, *J. Mater. Chem*., 2011, **21**, 7350.
9 Y. Li, X.-Y. Liu and G. Zhao, *Tetrahedron: Asymmetry*, 2006, **17**, 2034.
10 M. Keller, A. Perrier, R. Linhardt, L. Travers, S. Wittmann, A.-M. Caminade, J.-P. Majoral, O. Reiser and A. Ouali, *Adv. Synth. Catal.*, 2013, **355**, 1748.
11 C. Roeben, M. Stasiak, B. Janza, A. Greiner, J. H. Wendorff and A. Studer, *Synthesis*, 2008, 2163.
12 M. C. Varela, S. M. Dixon, K. S. Lam and N. E. Schore, *Tetrahedron*, 2008, **64**, 10087.
13 T. E. Kristensen, K. Vestli, M. G. Jakobsen, F. K. Hansen and T. Hansen, *J. Org. Chem*., 2010, **75**, 1620.
14 F. Giacolone, M. Gruttadauria, P. Agrigento, V. Campisciano and R. Noto, *Catal. Commun*., 2011, **16**, 75.
15 A. A. Guryev, M. V. Anokhin, A. D. Averin and I. P. Beletskaya, *Mendeleev Commun*., 2015, **25**, 410.
16 I. Fleischer and A. Pfaltz, *Chem. Eur. J*., 2010, **16**, 95.
17 E. Alza, S. Sayalero, P. Kasaplar, D.Almaşi and M. A. Pericàs, *Chem. Eur. J*., 2011, **17**, 11585.
18 S. K. Ghosh, K. Dhungana, A. D. Headley and B. Ni, *Org. Biomol. Chem*., 2012, **10**, 8322.
19 O. V. Maltsev, A. S. Kucherenko and S. G. Zlotin, *Eur. J. Org. Chem.*, 2009, 5134.
20 O. V. Maltsev, A. S. Kucherenko and S. G. Zlotin, *Mendeleev Commun*., 2011, **21**, 146.
21 O. V. Maltsev, A. O. Chizhov and S. G. Zlotin, *Chem. Eur. J*., 2011, **17**, 6109.
22 A. Ma, S. Zhu and D. Ma, *Tetrahedron Lett*., 2008, **49**, 3075.
23 X. Companyó, M. Hejnová, M. Kamlar, J. Vesely, A. Moyano and R. Rios, *Tetrahedron Lett*., 2009, **50**, 5021.
24 M. Rueping, E. Sugiono and E. Merino, *Chem. Eur. J*., 2008, **14**, 6329.
25 P. T. Franke, B. Richter and K. A. Jørgensen, *Chem. Eur. J*., 2008, **14**, 6317.
26 Y. Wang, P. Li, X. Liang and J. Ye, *Adv. Synth. Catal.*, 2008, **350**, 1383.
27 C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente and S. Vera, *Angew. Chem. Int. Ed*., 2007, **46**, 8431.
28 M. Rueping, H. Sunden, L. Hubener and E. Sugiono, *Chem. Commun.*, 2012, **48**, 2201.

† *Addition of malonates to α,β-enals*. A mixture of appropriate aldehyde (0.6 mmol), malonate (0.3 mmol), additive (see Tables 1 and 2), catalyst II (obtained according to described procedure,[15] 80 mg, 0.06 mmol) in CH_2Cl_2 (1 ml) was stirred at room temperature for 72 h. After terminating the reaction, the mixture was filtered to separate the catalyst. The catalyst was washed with THF (5 ml), MeOH (5 ml) and THF (5 ml). The combined organic extracts were concentrated and the residue was chromatographed on silica gel using EtOAc in light petroleum. All analytical data of prepared Michael adducts (see Table 2) are consistent with those described in literature.[16,18,19,28]

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