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Research Article

N-Boc-Amino Acid Mediated Morita-Baylis Hillman Reaction of Methylphenyl Glyoxylate

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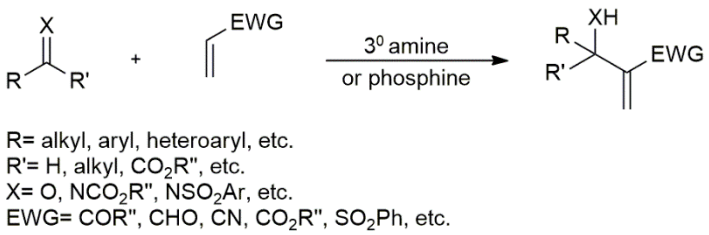
Abstract

The organocatalyzed Morita-Baylis Hillman (MBH) reaction of α-keto esters is a challenging carbon-carbon bond-forming reaction. We developed a catalytic system for the MBH reaction of methylphenyl glyoxylate with methyl vinyl ketone in a polar aprotic solvent. We used N-Boc-L-pipecolinic acid as a proton transfer mediator and 4-dimethylaminopyridine as the tertiary amine catalyst. We obtained the MBH adduct with a 66% yield in 48h. We proposed a detailed reaction mechanism involving a transition state that includes the hydrogen transfer by the acid functional group of N-Boc-L-pipecolinic acid.

Keywords: Morita-Baylis Hillman reaction, α-Keto ester, N-Boc-L-pipecolinic acid, 4-Dimethylaminopyridine.

1. Introduction

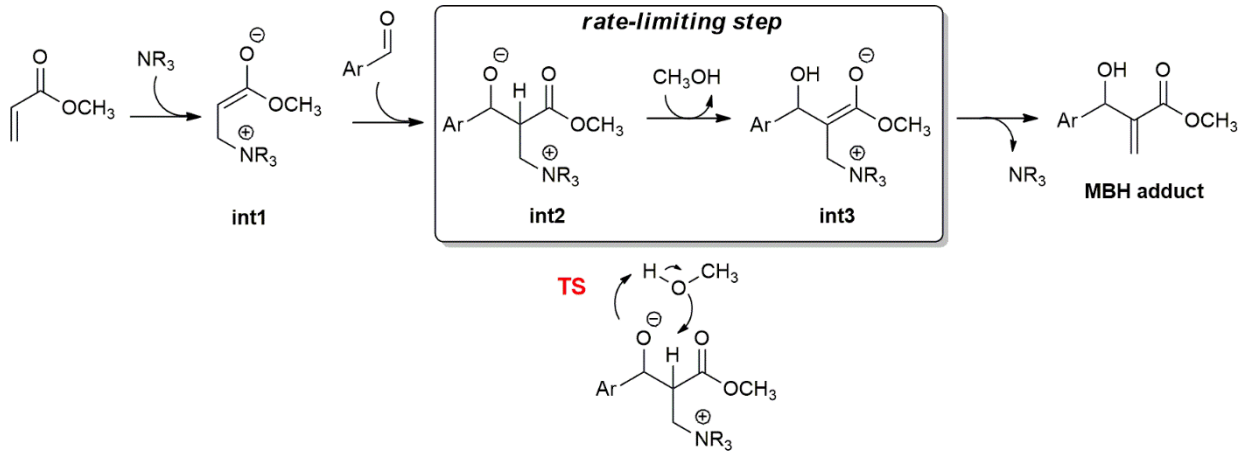
The carbon-carbon (C-C) bond-forming reactions are one of the most powerful tools in organic chemistry. Morita-Baylis Hillman (MBH) reaction is a practical C-C bond-forming reaction resulting in densely-functionalized products in the presence of Lewis bases such as tertiary amines and tri-substituted phosphines. Triphenylphosphine catalyzed traditional MBH reaction is between an aromatic aldehyde and methyl vinyl ketone [1] but can be extended to any activated alkene attached to a strong electron-withdrawing group and an electrophilic carbon such as an aldehyde or an imine (Scheme 1) [2-5].



Scheme 1. The classical MBH reaction catalyzed by amines and phosphines

MBH reaction has attracted more attention in recent years due to the commercially available starting materials, its atom-economical nature, multifunctional products and organocatalyzed mild reaction conditions [6,7]. MBH adducts such as acetates, bromides and carbonates are important synthons in the synthesis of biologically-active compounds and natural products [8]. Despite all these advantages, there are still limitations of MBH reactions of some substrates such as α-keto esters. Basavaiah et. al. reported the MBH reaction of α-keto esters with alkyl vinyl ketones and cyclic enones mediated by titanium tetrachloride [9, 10]. An organocatalytic version of the MBH reaction between cyclopent-2-enone and α-keto esters was reported by Shi and Zhang catalyzed by diphenylmethylphosphine and phenol additives [11]. However, the organocatalytic MBH reaction of α-keto esters remains unexplored.

In recent years, computational studies have also been performed to understand the MBH reaction mechanism and probable transition states to design more efficient organocatalysts [12-15]. We concentrated on the alcohol-mediated MBH mechanism proposed by Aggarwal as outlined in Scheme 2 [16]. According to the experimental and computational studies, the rate-limiting step of the reaction is the methanol-aided hydrogen transfer between intermediate 2 (int2) and 3 through the corresponding transition state (TS).



Scheme 2. Mechanism of the alcohol-mediated MBH reaction [16]

Amino acid/NR_3 co-catalyst systems are very common in asymmetric MBH reactions and promising results have been obtained with L-proline [17-19]. L-Pipecolinic acid has been used as a co-catalyst with *N*-methylimidazole in the asymmetric intramolecular MBH reaction by Aroyan et al. [20].

We evaluated N-Boc-L-amino acids as a mediator to transfer hydrogen between intermediate 2 and 3 (Scheme 2) in the tertiary amine catalyzed MBH reaction of methylphenyl glyoxylate with methyl vinyl ketone in *N*,*N*-dimethylformamide (DMF).

2. Materials and Methods

All chemicals and solvents were used as received from commercial suppliers and used without further purification. Silica gel F254 (Merck 5554) precoated plates were used for thin-layer chromatography (TLC). Infrared spectra were recorded on a Thermo-Nicolet 6700 FTIR. NMR experiments were performed on a Varian Mercury Plus 400 MHz spectrometer at ambient temperature using TMS as an internal standard. The elemental analyses were performed on a Costech ECS 4010 analyzer. Melting points were determined in open glass capillary tubes with an Electrothermal digital melting point apparatus.

2.1. General Procedure for the MBH Reaction

A mixture of methyl vinyl ketone (0.6 mmol, 0.05 ml), (0.3 mmol, 0.04 ml), 4-dimethylaminopyridine (DMAP) (0.1 mmol, 12 mg), N-Boc protected amino acid catalyst (0.1 mmol) in DMF (0.5 ml) was stirred at room temperature The reaction progress was monitored with TLC until methylphenyl glyoxylate was consumed. DMF was evaporated under vacuum and the crude product was purified with column chromatography.

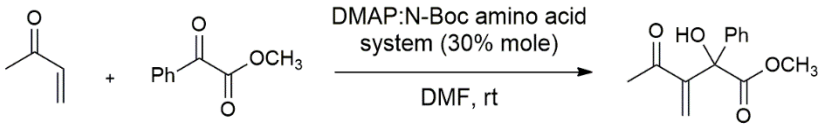
2.1.1. Methyl 3-hydroxy-4-methylene-2,5-dioxo-3-phenylhexanoate

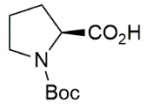
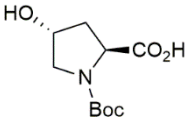
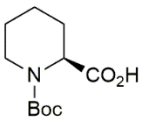
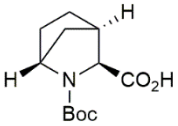
Colorless crystal, 66% yield, m.p. 76-77 °C. FT-IR, ν, cm–1: 3242 (O-H stretching), 2879 (C-H stretching), 1766 (C=O stretching), 1638(C=C stretching). 1H-NMR (400 MHz, CDCl3) δ ppm: 2.41 (s, 3H), 3.77 (s, 3H), 4.84 (bs, 1H), 5.54 (s, 1H), 6.22 (s, 1H), 7.33-7.39 (m, 3H), 7.56-7.58 (d, J = 8.0 Hz, 2H). 13C-NMR (101 MHz, CDCl3) δ ppm: 26.40, 53.18, 77.24, 78.73, 126.63, 128.26, 128.33, 129.68, 137.61, 150.86, 174.01, 200.45. Anal. calcd. for C13H14O4: C 66.66; H 6.02. Found: C 66.61; H 6.00.

3. Results and Discussion

We used a standard MBH reaction of methylphenyl glyoxylate with methyl vinyl ketone in DMF to determine the activities of N-Boc-protected amino acid catalysts (Table 1). Both amino acids and DMAP were inactive when they were used alone.

Table 1. Standard MBH reaction and structures of the catalysts

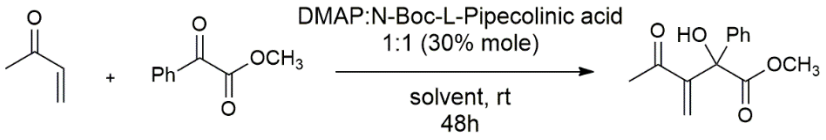


Catalyst	Time (h)	Yield (%)[a]
 Boc-L-proline (**1**)	48	33
 N-Boc-*trans*-4-hydroxypyrrolidine-2-carboxylic acid (**2**)	96	16
 N-Boc-L-pipecolinic acid (**3**)	48	66
 (1R,3S,4S)-N-Boc-2-azabicyclo[2.2.1] heptane-3-carboxylic Acid (**4**)	72	23

[a] Isolated yields

The catalytic activities of four different cyclic and N-Boc-protected L-amino acids were investigated. The best results were obtained with N-Boc-L-pipecolinic acid (**3**) with 66% yield in 48 hours at room temperature. We performed chiral HPLC analysis to check the enantioselectivity of the reactions, as the catalysts were chiral. However, all of the products were obtained in a racemic form. Then, we performed the reaction in different solvents to optimize the conditions (Table 2).

Table 2. Solvent optimization

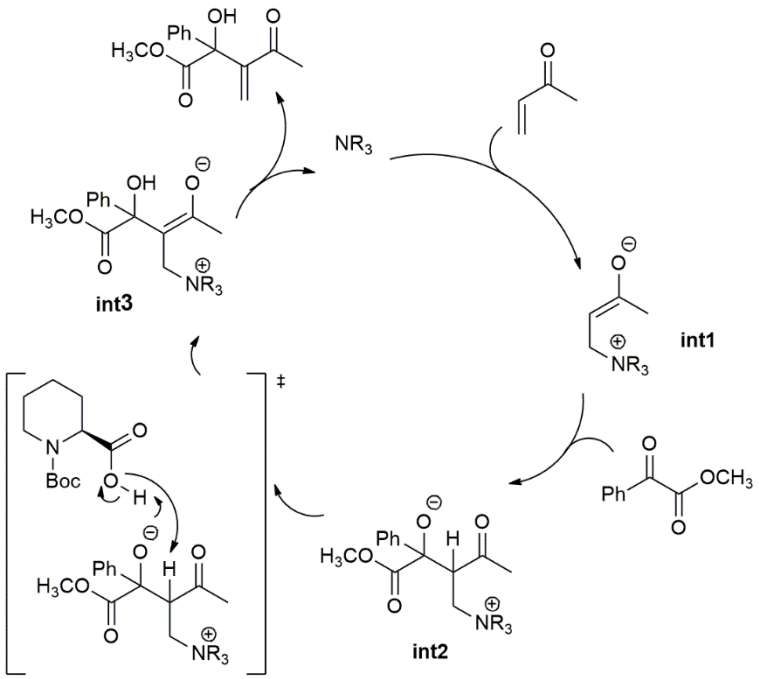


No	Solvent	Yield[a]
1	DMF	66
2	MeOH	trace
3	EtOH	trace
4	THF	-

[a] Isolated yields

The best results were obtained in DMF and only a trace amount of product formation was observed in alcohols such as methanol and ethanol while no product was obtained in tetrahydrofuran (THF).

According to these results, we also proposed a reaction mechanism mediated by **3** (Scheme 3).



Scheme 3. Proposed reaction mechanism for N-Boc-L-pipecolinic acid (**3**) mediated MBH reaction of methylphenyl glyoxylate

The failure of the catalytic system in terms of enantioselectivity was also explained by the role of **3** in the proposed reaction mechanism.

4. Conclusions

We developed a catalytic system for the MBH reaction of methylphenyl glyoxylate with methyl vinyl ketone. The recently-proposed reaction mechanisms revealed the important role of a proton transfer mediator in this reaction. We

designed our catalytic system according to the results of these mechanistic studies. We successfully performed the reaction with DMAP and N-Boc-L-pipecolinic acid. We also proposed a proper reaction mechanism. Our ongoing studies are related to the expansion of the substrate scope and the asymmetric version of this reaction.

5. Acknowledgments

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References

[1] Shi, M. and Liu, Y.-H. (2006). Traditional Morita–Baylis–Hillman reaction of aldehydes with methyl vinyl ketone co-catalyzed by triphenylphosphine and nitrophenol. Org.Biomol.Chem., 4: 1468-1470.

[2] Basavaiah, D., Rao, A. J., Satyanarayana, T. (2003). Recent Advances in the Baylis−Hillman Reaction and Applications. Chem.Rev., 103(3); 811- 892.

[3] Basavaiah, D. and Naganaboina, R. T. (2018). The Baylis–Hillman reaction: a new continent in organic chemistry-our philosophy, vision and over three decades of research. New J. Chem., 42; 14036-1406.

[4] Shukla, P., Asati, A., Patel, D., Singh, M., Rai, V. K., Rai, A. (2023). Novel Synergistic Catalysis by Ethylcarbodiimide Hydrochloride Salt and CuI Towards Morita-Baylis-Hillman Reaction. ChemistrySelect, 8; 571-574.

[5] Wang, C.-C. and Wu, X.-Y. (2011). Catalytic asymmetric synthesis of 3-hydroxyl-2-oxindoles via enantioselective Morita–Baylis–Hillman reaction of isatins. Tetrahedron, 67; 2974-2978.

[6] Crawshaw, R., Crossley, A. E., Johannissen, L., Burke, A. J., Hay, S., Levy, C., Baker, D., Lovelock, S. L., Green, A. P. (2022). Engineering an efficient and enantioselective enzyme for the Morita-Baylis-Hillman reaction. Nature Chemistry, 14; 313-320.

[7] Maity, S. and Szpilman, A. M. (2023). 2-Fluoroenones via an Umpolung Morita–Baylis–Hillman Reaction of Enones. Org. Lett., 25(7); 1218-1222.

[8] Reddy, T. N., and Rao, V. J. (2018). Importance of Baylis-Hillman adducts in modern drug discovery. Tetrahedron Letters, 59; 2859-2875.

[9] Basavaiah, D., Sreenivasulu, B., Reddy, R. M., Muthukumaran, K. (2001). The Baylis-Hillman Reaction: TiCl4 Mediated Coupling of Alkyl Vinyl Ketones with α-Keto Esters and Aldehydes. Synthetic Communications, 31(19); 2987-2995.

[10] Basavaiah, D., Sreenivasulu, B., Rao, A. J. (2003). Steric Factors Direct Baylis-Hillman and Aldol Reactions in Titanium Tetrachloride Mediated Coupling between α-Keto Esters and Cyclohex-2-enone Derivatives. J. Org. Chem. 68; 5983-5991.

[11] Shi, M. and Zhang, W. (2005). Organocatalysts of tertiary-phosphines and amines catalyzed reactions of α-keto esters with cyclopent-2-enone. Tetrahedron, 61; 11887-11894.

[12] Wei, Y. and Shi, M. (2013). Recent Advances in Organocatalytic Asymmetric Morita−Baylis− Hillman/aza-Morita−Baylis−Hillman Reactions. Chem. Rev., 113(8); 6659-6690.

[13] Price, K. E., Broadwater, S. J., Jung, H. M., McQuade, D. T. (2005). Baylis-Hillman mechanism: a new interpretation in aprotic solvents. Org. Lett., 7; 147-150.

[14] Liu, Z, Patel, C., Harvey, J. N., Sunoj, R. B. (2017). Mechanism and reactivity in the Morita-Baylis-Hillman reaction: the challenge of accurate computations. Phys. Chem. Chem. Phys., 19; 30647-30657.

[15] Seumer, J., Hansen, J. K. S., Nielsen, M. B., Jensen, J. H. (2023). Computational Evolution of New Catalysts for the Morita–Baylis– Hillman Reaction. Angew. Chem. Int. Ed., 62; e202218565.

[16] Robiette, R., Aggarwal, V. K., Harvey, J. N. (2007). Mechanism of the Morita-Baylis-Hillman Reaction: A Computational Investigation. J. Am. Chem. Soc., 129; 15513-15525.

[17] Tang, H., Zhao, G., Zhou, Z., Tang, Q. Z. C. (2006). Synthesis of some new tertiary amines and their application as co-catalysts in combination with L-proline in enantioselective Baylis-Hillman reaction between o-Nitrobenzaldehyde and methylvinylketone. Tetrahedron Lett., 47; 5717-5721.

[18] Chen, S.-H., Hong, B.-C., Su, C.-F., Sarshar, S. (2005). An unexpected inversion of enantioselectivity in the proline catalyzed intramolecular Baylis-Hillman reaction. Tetrahedron Lett., 46; 8899-8903.

[19] Shi, M., Jiang, J.-K., Li, C.-Q. (2002). Lewis base and L-proline co-catalyzed Baylis-Hillman reaction of arylaldehydes with methyl vinyl ketone. Tetrahedron Lett., 43(1); 127-130.

[20] Aroyan, C. E., Vasbinder, M. M., Miller, S. J. (2005). Dual Catalyst Control in the Enantioselective Intramolecular Morita-Baylis-Hillman Reaction. Org. Lett. 7(18); 3849-3851.