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Asymmetric Michael Addition Reaction of α-Aryl-Substituted Lactams Catalyzed by Chiral Quaternary Ammonium Salts Derived from Cinchona Alkaloids: A New Short Synthesis of (+)-Mesembrine

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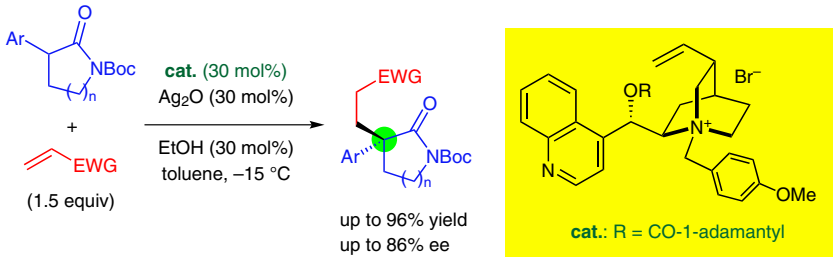

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Abstract The enantioselective Michael addition reaction of α-aryl-substituted lactams with electron-deficient olefins was efficiently catalyzed using chiral quaternary ammonium salts derived from cinchona alkaloids. This method was highly useful for the construction of an all-carbon-substituted quaternary carbon stereogenic center at the α-position of lactams in good to high yields and with good enantiomeric excess and could be applied to the short synthesis of (+)-mesembrine.

Key words asymmetric organocatalysis, lactams, Michael addition, cinchona alkaloids, mesembrine

All-carbon-substituted quaternary carbon stereogenic centers are common structural units found in numerous biologically active natural products, and hence considerable attention has been focused on the development of efficient methodologies to construct these molecules.[1] Among these, recent advances in organocatalytic asymmetric synthesis offer a highly useful and environment-friendly strategy.[2] Most typically, the organocatalytic asymmetric Michael addition reaction has been accepted as a reliable and convenient method, probably due to the versatility of designing Michael donors and acceptors as well as the pool of available chiral organocatalysts.[2,3]

In contrast to the several reports that are available on the use of normal aldehydes or ketones as Michael donors,[2,3] to the best of our knowledge, very little attention has been paid to the use of α-substituted lactams or lactones, except for benzene-fused homologues such as oxindoles.[2b,4,5] Presumably, this might be due to the weak acidity of α-protons in connection with severe steric congestion at the reaction center. Despite this fairly limited accessibility, we expected that the asymmetric Michael addition reaction of α-substituted lactams would provide an expeditious strategy for the construction of a potentially important framework of biologically interesting natural products in which an all-carbon-substituted quaternary carbon stereogenic center is a part of the stereoarray.[1]

However, our preliminary experiments showed that commonly used primary, secondary, and tertiary chiral amines were all unsatisfactory as organocatalysts for the present purpose.[6] This can be understood by considering that they are not reactive enough to invoke enamine activation[7] or to act as Lewis bases to abstract an α-methine proton of lactams.[8] Therefore, we turned our attention to the use of chiral phase-transfer catalysts derived from cinchona alkaloids as relatively strong organobases.[9] Herein, we report a novel strategy using quaternary ammonium salts **A** to **H** to achieve the required asymmetric Michael addition reaction of α-aryl-substituted lactams (Figure 1).[10]

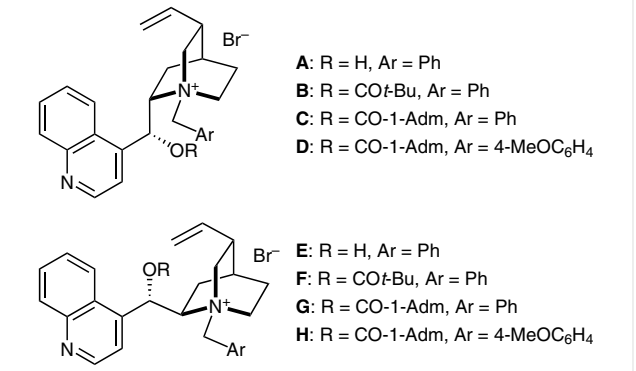


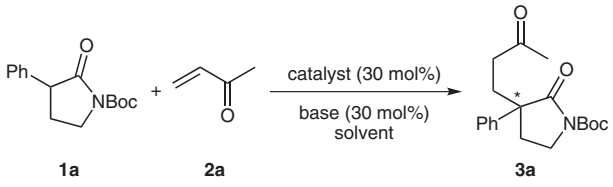
Figure 1 Cinchona alkaloid derivatives as catalyst

To establish the optimal conditions, we first examined the asymmetric Michael addition reaction of *N*-Boc-2-phenyl-γ-butyrolactam (**1a**) with methyl vinyl ketone (**2a**) in the presence of catalysts **A**–**H** under various conditions. The results are summarized in Table 1.[11]

We found that a series of cinchonidine-type salts **A**–**D** could smoothly promote the desired reaction, but the enantioselectivity was not so high (Table 1, entries 1–4). When a series of cinchonine-type salts **E**–**H** was used, the enantioselectivity improved considerably to form the Michael adduct **3a**, albeit with an opposite configuration (Table 1, entries 5–8). In particular, favorable results could be attained with the use of catalyst **H**, which contains the 9-hydroxy protecting group with a sterically bulky 1-adamantoyl group and a 4-methoxybenzyl group at the quinuclidine nitrogen center (Table 1, entry 8).[12] After we screened various inorganic base additives and reaction conditions, the best results in terms of yield and enantioselectivity were obtained with Ag_2O (30 mol%) in combination with EtOH (30 mol%) in toluene under lower temperatures (Table 1, entry 10 vs. entries 9, 11, and 12).[13] In addition, we found that Cs_2CO_3 and K_2CO_3 gave results comparable to those with inorganic bases (Table 1, entries 15 and 16). The use of CH_2Cl_2 or THF as a solvent or $CsOH{\cdot}H_2O$ as a base gave rather poor results, probably due to a background reaction (Table 1, entries 13, 14, and 17).

With our optimized reaction conditions in hand, we then explored the general scope of the reaction, and the results are summarized in Scheme 1.[11] All reactions were performed in toluene containing 30 mol% EtOH in the presence of 30 mol% of the respective catalyst **H** and Ag_2O. Among several Michael acceptors, methyl vinyl ketone (**2a**) and ethyl vinyl ketone (**2b**) reacted smoothly with lactam **1** to give the desired products in good to high yields (up to 96%) and with good enantioselectivity (up to 86% ee), while methyl acrylate (**2c**) and acrylonitrile (**2d**) showed lower reactivity in the present Michael addition system (**3c** and **3d**).[14] Lactam substrates containing an electron-donating

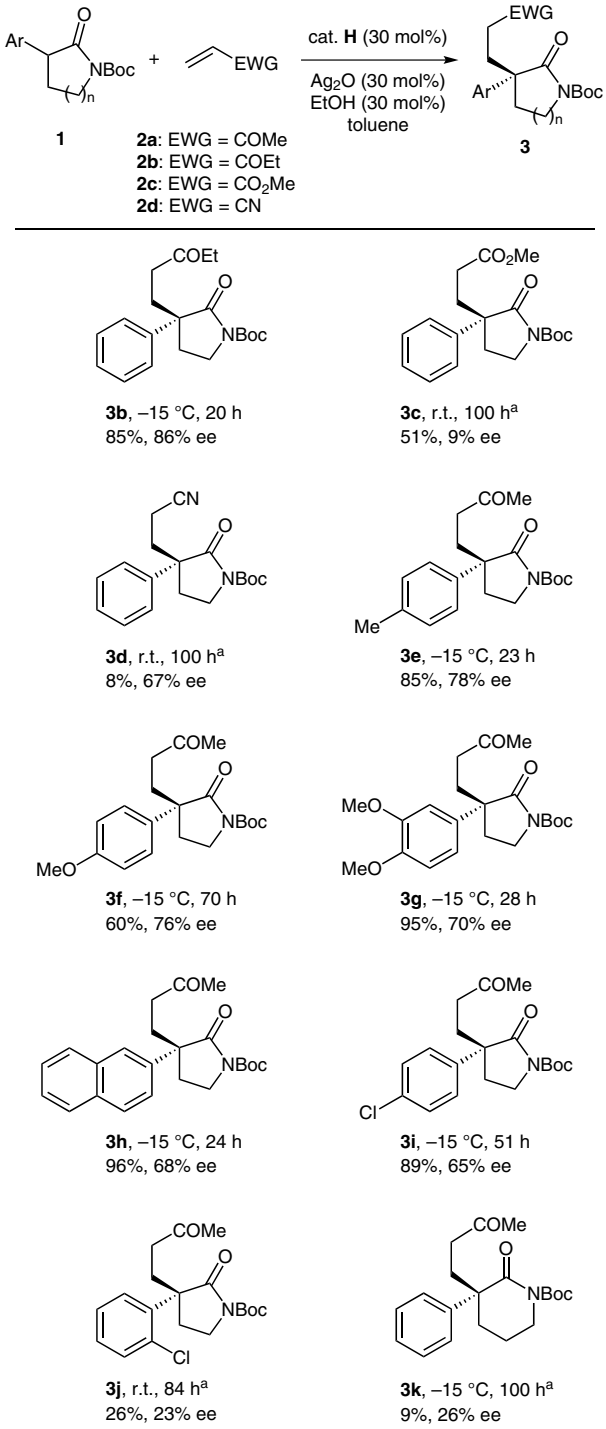
Table 1 Catalytic Asymmetric Michael Addition Reactions: Optimization[a]



1a **2a** **3a**

Entry	Catalyst	Base	Conditions	Yield (%)[b]	ee (%)[c]
1	**A**	Ag_2O	MeOH (30 mol%), toluene, r.t., 2.5 h	92	12
2	**B**	Ag_2O	MeOH (30 mol%), toluene, r.t., 16 h	94	29
3	**C**	Ag_2O	MeOH (30 mol%), toluene, r.t., 42 h	81	40
4	**D**	Ag_2O	MeOH (30 mol%), toluene, r.t., 8.5 h	62	32
5	**E**	Ag_2O	EtOH (30 mol%), toluene, r.t., 25 h	86	–11
6	**F**	Ag_2O	EtOH (30 mol%), toluene, r.t., 48 h	85	–40
7	**G**	Ag_2O	MeOH (30 mol%), toluene, r.t., 7 h	95	–60
8	**H**	Ag_2O	MeOH (30 mol%), toluene, r.t., 8 h	80	–68
9	**H**	Ag_2O	MeOH (30 mol%), toluene, –15 °C, 15 h	83	–83
10	**H**	Ag_2O	EtOH (30 mol%), toluene, –15 °C, 28 h	92	–85
11	**H**	Ag_2O	*i*-PrOH (30 mol%), toluene, –15 °C, 10 h	95	–77
12	**H**	Ag_2O	*n*-BuOH (30 mol%), toluene, –15 °C, 78 h	97	–84
13	**H**	Ag_2O	EtOH (30 mol%), CH_2Cl_2, –15 °C, 8 h	72	–60
14	**H**	Ag_2O	EtOH (30 mol%), THF, –15 °C, 8 h	33[d]	–51
15	**H**	Cs_2CO_3	EtOH (30 mol%), toluene, –15 °C, 30 h	97	–78
16	**H**	K_2CO_3	EtOH (30 mol%), toluene, –15 °C, 28 h	76	–80
17	**H**	$CsOH{\cdot}H_2O$	EtOH (30 mol%), toluene, –50 °C, 12 h	97	–33

[a] Reactions performed using 1.5 equiv of methyl vinyl ketone (**2a**) at a concentration of 0.17 M under the conditions listed. See the Supporting Information for detailed experimental procedures.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Unidentified polar substances were formed.

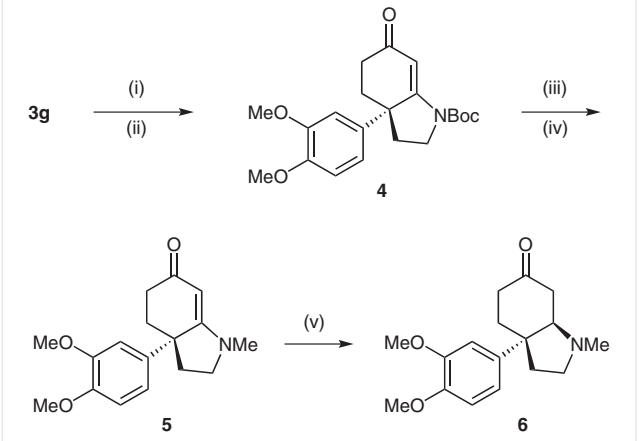


Scheme 1 Catalytic asymmetric Michael addition reactions: Generality. Reactions performed using 1.5 equiv of Michael acceptor **2** at a concentration of 0.17 M under the conditions listed. Isolated yields are shown. The absolute configuration of the products was surmised in analogy with **3g**. The ee was determined by chiral HPLC analysis. See the Supporting Information for detailed experimental procedures. [a] Unreacted starting material was recovered.

group on the aromatic ring were found to be suitable substrates compared with those having an electron-withdrawing group (compare **3e**–**h** with **3i** and **3j**). Unfortunately, 2-phenyl-substituted δ-valerolactam reacted only very slowly under these conditions, and the product **3k** was obtained in only 9% yield with 26% ee (–15 °C, 100 h). This can be ascribed to the severely decreased acidity of an α-methine proton of this substrate.[15] Finally, the absolute configurations of the newly formed Michael adducts were deduced by analogy to **3g** after its conversion into (+)-mesembrine (**6**, vide infra).

Upon evaluation of this synthetic methodology, we decided to pursue the synthesis of (+)-mesembrine (**6**). Due to its interesting biological activity and its unique structure of a hexahydroindole skeleton bearing a sterically congested aryl-substituted quaternary carbon center, this alkaloid has attracted considerable attention from synthetic chemists over the past several decades.[16] Our new short synthesis of **6** was developed as shown in Scheme 2.

First, a two-step strategy based on intramolecular aldol condensation of the Michael adduct **3g** by treatment with 2.0 equivalents of KO*t*-Bu in THF at room temperature followed by exposure to a catalytic amount of PTSA in refluxing toluene gave bicyclic cyclohexenone **4** in around 50% yield, which was increased to >99% enantiomeric excess by recrystallization from hexane–Et_2O. Boc-deprotection of **4** in $(CF_3)_2CHOH$ under microwave irradiation conditions[17] followed by N-methylation gave **5**[16d] in 86% yield.



Scheme 2 *Reagents and conditions*: (i) KO*t*-Bu, THF, r.t., 30 min; (ii) cat. PTSA·H_2O, MS 4 Å, toluene, Δ, 11 h; (iii) $(CF_3)_2CHOH$, MW, 150 °C, 40 min; (iv) MeI, NaH, THF, r.t.; (v) Li/liq NH_3, *t*-BuOH, THF, –78 °C, 30 min.

Finally, Birch reduction using Li/liq. NH_3 in THF–*t*-BuOH according to Zhang's method[16d] led to (+)-mesembrine (**6**) in 77% yield with 99% enantiomeric excess. This sample gave IR, ^1H NMR, and ^{13}C NMR data identical to the respective literature values.[16] On the other hand, the optical rotation was $[\alpha]_D^{19}$ +42.2 (*c* 0.15, MeOH), which is consistent with the literature value, $[\alpha]_D^{20}$ +43 (*c* 0.8, MeOH), reported

for (+)-mesembrine.[16j] Therefore, it can be concluded that the initial step for the Michael addition reaction on a lactam framework should preferably form the adduct **3g** with an *R* configuration.

Based on these experimental findings, we could propose a crucial structure in the transition state to explain the observed asymmetric induction (Figure 2). The contact ion pair between the negatively charged enolate of the nucleophile and the ammonium cation of the catalyst makes the donor molecule well-defined within the catalyst major groove. The presence of a sterically crowding adamantoyl substituent effectively blocks the approach of the incoming electrophile to the enolate from the bottom *Re*-face, thus making the *Si*-face attack more favorable.

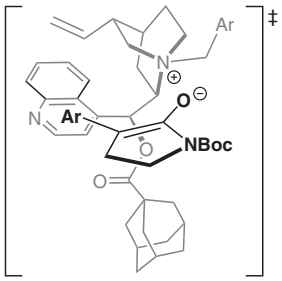


Figure 2 Plausible transition-state model

In summary, we have developed a highly enantioselective method for the asymmetric Michael addition reaction of α-aryl-substituted lactams with electron-deficient olefins catalyzed by chiral quaternary ammonium salts derived from readily available cinchona alkaloids. This method proved to be particularly useful for the construction of an all-carbon-substituted quaternary carbon stereogenic center at the α-position of lactams and highlighted its utility in a highly concise route to the asymmetric synthesis of (+)-mesembrine (**6**). Further studies on the application of this method to natural product synthesis are now in progress in our laboratory

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560090.

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(11) **General Procedure for the Asymmetric Michael Addition Reaction of Lactams**

The chiral ammonium catalyst was prepared by mixing a cinchona amine (0.06 mmol) and freshly distilled 4-methoxybenzyl bromide (0.06 mmol) in toluene (0.2 mL) at r.t. for 1 h. Then, Ag_2O (0.06 mmol) and EtOH (0.06 mmol) were added, and the mixture was stirred at r.t. for 20 min. After cooling to –15 °C, lactam (0.2 mmol) in toluene (0.8 mL) followed by the Michael acceptor (1.5 equiv) were added, and the reaction progress was monitored by TLC. After completion of the reaction, the mixture was directly purified by silica gel column chromatography (eluted with benzene–acetone, 12:1) to give the desired adduct. The ee of this compound was determined by chiral HPLC analysis.

(*R*)-*N*-Boc-2-(3-oxobutyl)-2-phenyl-γ-butyrolactam (3a)

Colorless needles; mp 97–99 °C (from hexane–Et_2O); R_f = 0.17 (hexane–acetone, 4:1). $[\alpha]_D^{19}$ +83.2 (*c* 1.0, EtOH, 79% ee). FTIR (KBr): ν = 1773, 1715, 1365, 1313, 1164 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53 (9 H, s), 2.03 (3 H, s), 2.10–2.16 (2 H, m), 2.19–2.29 (2 H, m), 2.41–2.45 (1 H, m), 2.53–2.62 (1 H, m), 3.48 (1 H, ddd, *J* = 10.0, 8.5, 8.0 Hz), 3.75 (1 H, ddd, *J* = 10.0, 8.0, 3.0 Hz), 7.26–7.41 (5 H, m). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 28.00 (3×), 29.91, 31.55, 32.17, 38.78, 42.95, 52.93, 83.02, 126.43 (2×), 127.37, 128.78 (2×), 139.04, 150.18, 175.56, 208.10. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.76; H, 7.60; N, 4.09. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46 × 25 cm, hexane–2-PrOH = 90:10, 0.3 cm^3/min): t_R (major) = 39.4 min; t_R (minor) = 43.0 min.

(12) We briefly examined the attachment on a quinuclidine nitrogen, but no improvements were observed using an anthracenylmethyl or 4-nitrobenzyl group.

(13) When the temperature was lowered to –30 °C, the reaction using Ag_2O as an inorganic base was completely impeded. Furthermore, the use of H_2O in place of EtOH caused only the racemic background reaction, and in the absence of EtOH no reaction was observed. The results imply that alcohol additives can effectively mix both the reagents and catalysts in the reaction medium.

(14) Unfortunately, the use of phenyl vinyl ketone as a Michael acceptor gave only a complex mixture of products.

(15) In accordance with this observation, no reaction was observed for the 2-alkyl-substituted γ-butyrolactam even after prolonged reaction (r.t., 100 h).

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