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Organocatalyzed Asymmetric Synthesis of Morphans

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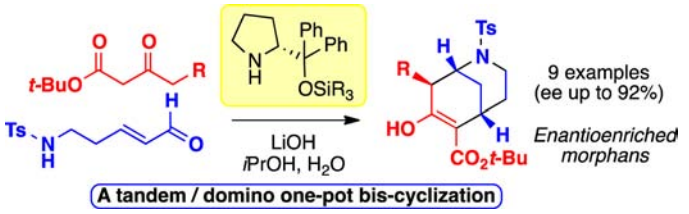
ABSTRACT



A general effective organocatalyzed synthesis of enantioenriched morphans with up to 92% ee was developed. The morphan scaffold was constructed in a one-pot tandem asymmetric organocatalyzed Michael addition followed by a domino Robinson annulation/aza-Michael intramolecular reaction sequence from easily available starting materials.

The morphan ring system (2-azabicyclo[3.3.1]nonane) features prominently in many complex and biologically active natural products as well as medicinal compounds of significant interest, including *Strychnos*,[1] madangamines,[2] some *Daphniphyllum* alkaloids[3] and the immunosuppressant FR901483[4] (Figure 1).

Despite the plethora of methods that have been developed for the formation of the morphan nucleus, to date[5] no general catalytic asymmetric strategy to polyfunctionalized enantiopure morphan ring systems has been developed.[6,7] Here, we outline an effective asymmetric organocatalyzed strategy to this nucleus, based on a tandem Michael addition/domino Robinson annulation and aza-Michael intramolecular reaction.

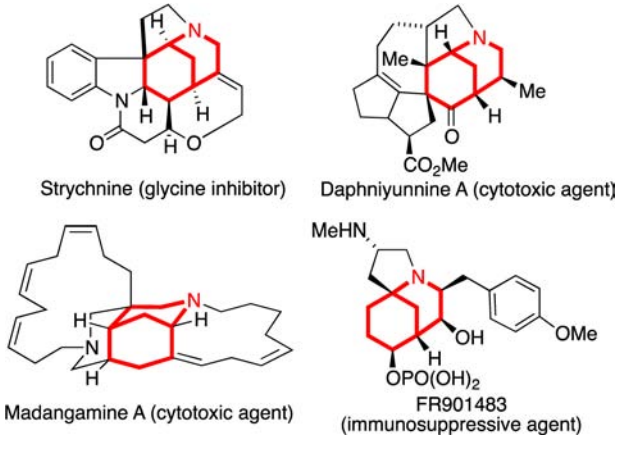


Figure 1. Natural products containing the morphan (2-azabicyclo-[3.3.1]nonane) nucleus.

Recently, we reported the synthesis of enantiopure decahydroquinolines via an organocatalyzed Robinson annulation/aza-Michael reaction, which constructed the ring system in one pot, generating three stereogenic centers

(1) (a) Cannon, J. S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 4288–4311. (b) Solé, D.; Bonjoch, J. *Chem. Rev.* **2000**, *100*, 3455–3482.

(2) (a) Amat, M.; Ballette, R.; Proto, S.; Pérez, M..; Bosch, J. *Chem. Commun.* **2013**, *49*, 3149–3151. (b) Quirante, J.; Paloma, L.; Diaba, F.; Vila, X.; Bonjoch, J. *J. Org. Chem.* **2008**, *73*, 768–771.

(3) Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499–5501.

(4) (a) Huo, H.-H.; Xia, X.-E.; Zhang, H.-K.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 455–465. (b) Bonjoch, J.; Diaba, F. *Stud. Nat. Prod. Chem.* **2005**, *32*, 3–60.

(5) For a review of approaches to morphan-containing natural products, see: Bonjoch, J.; Diaba, F.; Bradshaw, B. *Synthesis* **2011**, *7*, 993–1018. For a recently reported approach, see: Garrido, N. M.; Nieto, C. T.; Díez, D. *Synlett* **2013**, *24*, 169–172.

(6) For an organocatalyzed enantioselective method using a desymmetrization reaction, see: Diaba, F.; Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517–2519.

(7) For synthesis of enantiopure morphans using a chiral auxiliary, see: (a) G. Karig, G.; Fuchs, A.; Büsing, A.; Brandstetter, T.; Scherer, S.; Bats, J. W.; Eschenmoser, A.; Quinkert, G. *Helv. Chim. Acta* **2000**, *83*, 1049–1078. (b) Quirante, J.; Diaba, F.; Vila, X.; Bonjoch, J.; Lago, E.; Molins, E. *C. R. Acad. Sci.* **2001**, *4*, 513–521. (c) Amat, M.; Pérez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923.

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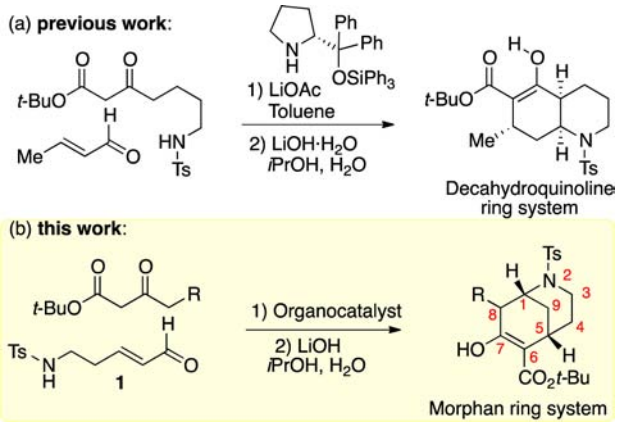
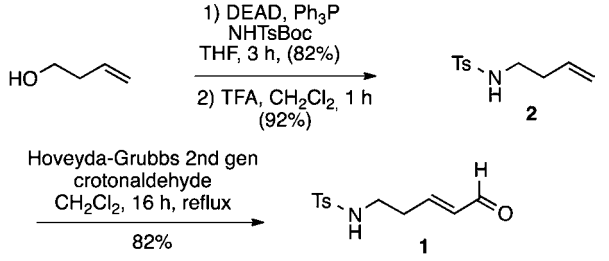
Scheme 1. Synthesis of Nitrogen-Containing Heterocycles by Forming Three Bonds in a One-Pot Reaction



in the process[8] (Scheme 1a). We postulated that this method could be adapted to access the morphan ring system by moving the tethered nucleophilic *N*-Tosyl group from the keto ester to the enal component (Scheme 1b). However, it was not clear at the outset that the direct application of the original method would be feasible, since the resulting enal **1** would now bear both nucleo- and electrophilic centers. Indeed, similar compounds separated by additional carbons have been used in organocatalyzed intramolecular aza-Michael reactions.[9] We hoped that in our case the formation of the azetidine ring by intramolecular cyclization would be sufficiently disfavored to allow the intermolecular Michael reaction.

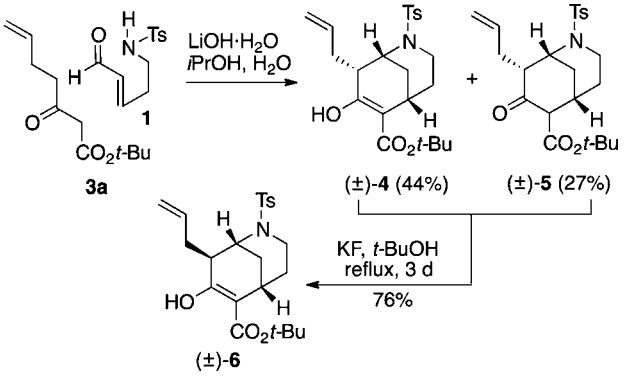
Scheme 2. Synthesis of Enal **1**



The required enal **1** was synthesized in a straightforward manner from 3-buten-1-ol via Mitsonobu coupling with *tert*-butyl tosylcarbamate[10] and removal of the Boc group with TFA, followed by a cross metathesis reaction of the resultant alkene **2** with the Hoveyda–Grubbs second generation catalyst and crotonaldehyde[11] (Scheme 2).

With enal **1** in hand, we began our studies by investigating the coupling reaction in the nonasymmetric form. Upon treatment of an equimolar mixture of **1** and the keto ester **3a** with $LiOH \cdot H_2O$ in *i*PrOH/H_2O, we were pleased to observe the formation of the desired morphan **4** (Scheme 3). A second, more polar compound **5** was also isolated, which was identified as the same cyclized product in its keto tautomeric form. Surprisingly, it was possible to separate these two compounds by column chromatography, and once isolated they did not undergo equilibration in solution,[12] allowing their NMR structures to be determined. In both cases, the allyl substituent was determined to be equatorial.

Scheme 3. Evaluation of Feasibility of Robinson/Aza-Michael Reaction in Racemic Form



Access to the axially positioned substituent product **6** was achieved by refluxing the mixture of **4** and **5** with KF in *t*-BuOH for 3 days.[13] To rationalize the observed stereochemistry of the allyl substituent, it was presumed that upon attack of the *N*-Tosyl group, the resulting enolate protonates from the less hindered top face to give **4** and **5**, with the allyl in the equatorial position (kinetic products). The resulting steric compression suffered by the allyl substituent with the tosyl group[14] was minimized in the kinetic isomer **4** by nitrogen inversion. The axial orientation of the *N*-tosyl group relieved the steric crowding with the equatorial side chain at C-8. This conformational change was deduced from a shielding at C-4 observed when comparing the ^{13}C NMR spectra of **4** and the thermodynamic isomer **6**. In the latter, the allyl group axially located at C-8 allowed the *N*-tosyl to adopt an equatorial disposition (Figure 2).

(8) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326–329.

(9) For the use of this type of compound for the formation of piperidines via organocatalysis, see: Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. For a general review on organocatalytic asymmetric aza-Michael reactions, see: Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058–11076.

(10) Teichert, J. F.; Zhang, S.; Zijl, A. W. v.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658–4660.

(11) For a related procedure, see: Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xaiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492.

(12) It should be noted, however, that upon prolonged standing the pure compounds would revert to mixtures of the enol/keto forms.

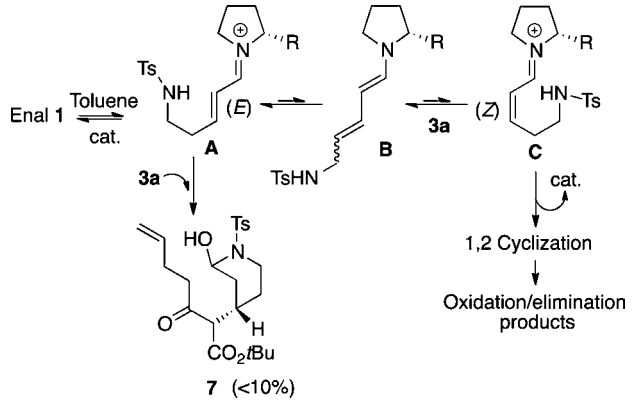
(13) For thermodynamic isomerization of α-substituted cycloalkanones using KF, see: Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010**, *132*, 5966–5967.

(14) For a related 1,3-syn interaction within the *N*-substituent and alkyl side chain in C-8 in morphan compounds, see: Bonjoch, J.; Casamitjana, N.; Quirante, J.; Torrens, A.; Paniello, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 377–381.

Figure 2. Stereochemical assignment of compounds **4** and **6**.

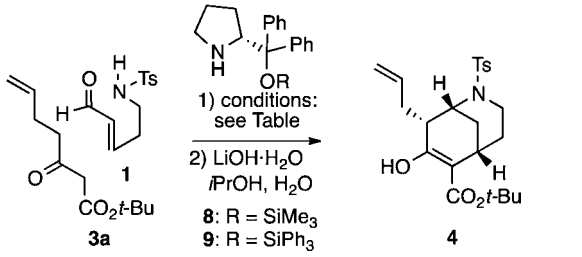
Having proof of concept, we then turned to investigate the reaction in asymmetric form. Unfortunately, upon treatment of keto ester **3a** with enal **1** in the presence of the Hayashi–Jorgensen catalyst **8**[15] in a range of organic solvents,[16] we observed only trace amounts of the Michael addition product **7**, which existed exclusively in its hemiaminal form (Scheme 4). While the keto ester **3a** was stable under the reaction conditions, enal **1** was slowly consumed into an unidentified product. We believe that the side reaction is a result of an isomerization of the double bond of **A** via the dienamine **B**[17] to form the cis isomer **C**, which

Scheme 4. Organocatalyzed Michael Reaction of **1** and **3a** and Loss of Enal **1** via a Parasitic Catalytic Cycle



then cyclizes to form a six-membered ring, followed by subsequent oxidation.[18] It should be noted that this side reaction did not occur in the absence of **3a**, indicating that the keto ester must somehow facilitate the isomerization by proton transfer processes. To prevent the undesired intramolecular reaction, protection of the free NH of **1** as an acetamide[19] was investigated. Unfortunately, only trace quantities of the coupled product were observed,[20] indicating that the Michael reaction is generally unfavorable. By carrying out the coupling reaction of **1** and **3** in the absence of any solvent, the reaction was noticeably accelerated and we were able to obtain moderate quantities of the coupled product **7**. Treatment of the crude mixture with LiOH in *i*PrOH/H_2O led to the cyclized product in 79% ee and moderate 38% overall yield for the two steps (Table 1, entry 1). Again, the product was isolated as a mixture of enol/keto forms (~3:1 ratio; only the enol form is shown for clarity). To improve the reaction, a series of additives (BzOH, TBAB,[21] $NaHCO_3$, LiOAc) were investigated, with significantly improved yields being obtained with the LiOAc (Table 1, entry 3). The use of water as an additive (10 equiv) led to both an increase in yield and ee (Table 1, entry 7). Carrying out the reaction at reduced temperature, however, proved to be detrimental (Table 1, entry 9). Switching to the more impeded catalyst **9**[8,22] gave

Table 1. Screening of Conditions[a] for Organocatalyzed Synthesis of Morphans



entry	additive (equiv)	R	temp	yield (%)[b]	ee (%)
1	–	TMS	rt	38	79
2	BzOH (0.1)	TMS	rt	34	51
3	LiOAc (0.1)	TMS	rt	61	79
4	$NaHCO_3$ (0.1)	TMS	rt	37	81
5	TBAB (0.1)	TMS	rt	43	75
6	H_2O (0.1)	TMS	rt	28	83
7	H_2O (10)	TMS	rt	69	88
8[c]	H_2O (10)	TMS	rt	41	80
9	H_2O (10)	TMS	0 °C	52	73
10	H_2O (10)	$SiPh_3$	rt	67	88
11	LiOAc (0.1)	$SiPh_3$	rt	66	86
12	LiOAc (0.1)	$SiPh_3$	0 °C	62	64
13	LiOAc(0.1)/H_2O(10)	$SiPh_3$	rt	52	90
14[d]	LiOAc(0.1)/H_2O(10)	$SiPh_3$	rt	55	92

[a] Conditions: 2 equiv of keto ester **3a**, 1 equiv of enal **1**, 10% catalyst, 3 h then add *i*PrOH (4 mL/mmol of enal), LiOH·H_2O (3 equiv), H_2O (10 equiv), 16 h. [b] Yield is given for enol and keto forms combined. [c] 1:1 Ratio of keto ester and enal used. [d] Reaction time 24 h for the initial step.

(15) (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215. (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.

(16) Solvents screened were toluene, CH_2Cl_2, and MeOH; all gave equally poor results so a detailed solvent screen was not undertaken.

(17) For isomerization of enals to dienamines via organocatalysis, see: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

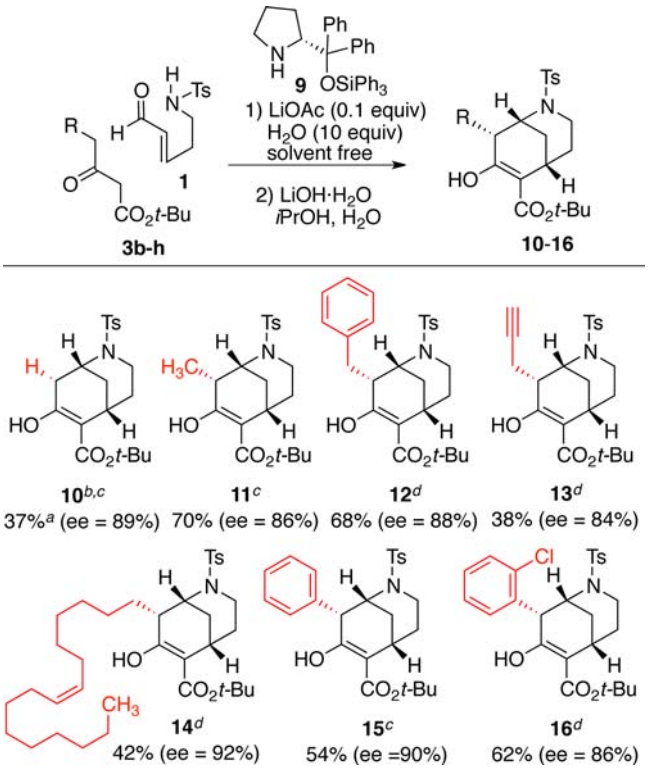
(18) For related intramolecular cyclization of N-Ts derivatives to form pyridines, see: Donohoe, T. J.; Bower, J. F.; Baker, D. B.; Basutto, J. A.; Chan, L. K. M.; Gallagher, P. *Chem. Commun.* **2011**, *47*, 10611–10613.

(19) Since N-Ts acetamides can be cleaved under mildly basic conditions, it was planned to liberate the NH-Ts group under the cyclization conditions, thus eliminating the need for a separate deprotection step.

(20) Presumably the formation of the hemiaminal (e.g., **7**) is important since it helps drive the reaction forward by removing the formed aldehyde from competition with the organocatalyst, as well as preventing a possible retro-Michael reaction.

(21) TBAB refers to tetrabutylammonium bromide. For its use, see: Duce, S.; Mateo, A.; Alonso, I.; Garcia Ruano, J. L.; Cid, M. B. *Chem. Commun.* **2012**, *48*, 5184–5186.

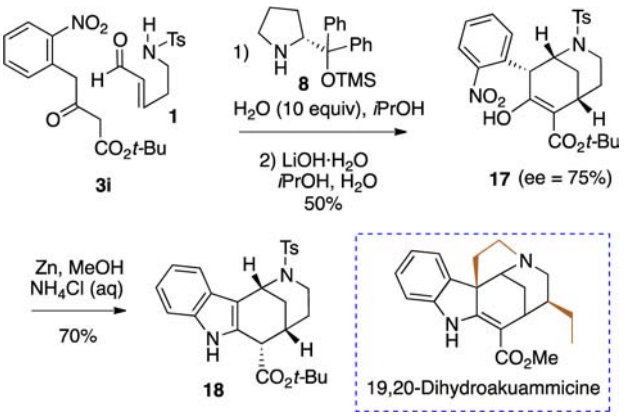
Scheme 5. Synthesis of C-8 Substituted Morphans[a]



[a] Conditions: 2 equiv of ketoester **3**, 1 equiv of enal, 10% catalyst, 24 h then add *i*PrOH (4 mL/mmol of enal), LiOH·H_2O (3 equiv), H_2O (10 equiv), 24 h. [b] Step ii required 48 h to reach completion. [c] Forms predominantly or exclusively as the enolic form. [d] Forms as a mixture of enol/keto forms; yields are given for both forms combined. For the tautomer ratio, see Supporting Information.

similar results to catalyst **8** when water was used as the additive (Table 1, entry 10), but it proved to be superior when LiOAc was used (in Table 1, compare entry 3 vs 11). Again, reducing the temperature resulted in significantly inferior results (entry 12). The use of both additives together, as opposed to individually, proved to be superior (Table 1, entry 14), with the enantioselectivity increasing to 92%.[23]

Scheme 6. Synthesis of Indolomorphan **18**



To explore the scope of the reaction, a number of varied keto ester substrates (**3b**–**h**)[24] were used in the coupling reaction. As can be seen in Scheme 5, the reaction works with a wide range of substrates, including both aliphatic and aromatic substituents, with some compounds being isolated predominantly in the enol form. Although in some cases the yields were moderate, we believe this reflects difficulties in mixing the reagents under solvent-free conditions.

To further expand the potential of the reaction, we proposed it should be possible to add a third tandem reaction using the C-8 substituent in an additional ring-forming step. The 2-nitrophenyl keto ester **3i** was coupled with enal **1** under modified conditions[25] to give morphan **17** possessing a latent indole moiety (Scheme 6). Treatment with Zn, NH_4Cl(aq)[26] gave indole **18**, which contains the core structure of curan-type alkaloids,[27] showing the potential of this methodology to rapidly access complex molecular scaffolds in a simple, straightforward manner.

In conclusion, the first effective catalytic route to poly-functionalized enantiopure morphans has been developed using a one-pot organocatalyzed Robinson/aza-Michael reaction. The convergency and potential flexibility of this method should open up new effective disconnection approaches for the total synthesis of morphan-containing natural products. Work in this direction is currently in progress.

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Supporting Information Available. Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353–357.

(23) The absolute configuration proposed for morphan **4** is based on the accepted mechanism of organocatalyzed Michael addition of β-keto esters upon enals: Jensen, K. L.; G. Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

(24) Keto esters **3** were prepared by coupling the correpsponding carboxylic acid with Meldrum's acid using DCC, followed by refluxing in *t*-BuOH. For an early use of this methdology, see: Li, B.; Franck, R. W: *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2629–2634.

(25) Due to the highly crystalline nature of **17** and the coupled product, mixing of the reagents proved difficult and the conditions of the initial organocatalytic step had to be modified. Heating was used to melt the substrates and the catalyst was switched to catalyst **8**, which, unlike catalyst **9**, exists as an oil.

(26) Bradshaw, B.; Etxebarria-Jardí, G.; Bonjoch, J. *Org. Biomol. Chem.* **2008**, *6*, 772–778.

(27) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230–7240.