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Catalytic, Asymmetric Michael Reactions of Cyclic Diketones with β,γ-Unsaturated α-Ketoesters

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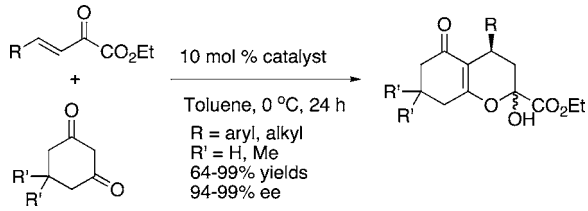
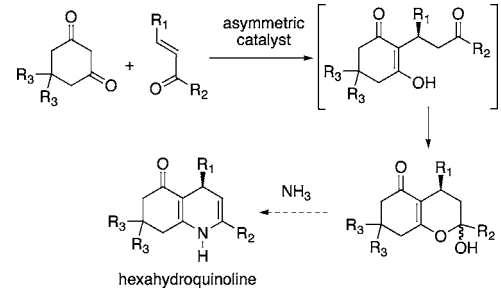
ABSTRACT



Newly synthesized cinchona alkaloid-derived pyrimidines function as effective asymmetric catalysts for the Michael reaction between cyclic diketones and β,γ-unsaturated α-ketoesters. The reactions of electrophiles with either aryl or alkyl γ-substituents give 64−99% yields and 94−99% ee.

The Michael reaction stands as one of the fundamental methods for creating carbon−carbon bonds. As this reaction also often results in the creation of stereocenters, much effort has focused on the discovery of catalytic, asymmetric versions of the Michael reaction.[1] Several excellent methods using metal complexes[2] or organic molecules as catalysts have emerged;[3] however, these methods all apply only to certain substrate classes. We were particularly interested in the addition of cyclic diones to enones, as the product of such a Michael reaction could potentially provide an advanced intermediate in the synthesis of the hexahydroquinoline class of calcium channel blockers (Scheme 1).[4] Although Itoh et al. have reported high enantioselectivities for the related addition of diones to unsaturated pyrazole amides,[2d] the highest enantioselectivity reported for the addition of diones to enones is 45%.[3d] Therefore, we set out to maximize the asymmetric induction of this type of reaction.

Scheme 1. Target Michael Reaction



Our results with the catalytic, asymmetric, interrupted Feist-Bénary (IFB) reaction strongly influenced our exploration of the Michael reaction.[5] The IFB reaction employs a dione nucleophile and an α-ketoester electrophile. In order to maximize the similarity between the IFB

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(2) (a) Jautze, S.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 9284–9288. (b) Agostinho, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2430–4231. (c) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651. (d) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979–981.

(3) (a) Chen, Y.-C. *Synlett* **2008**, 1919–1930. (b) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (c) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331. (d) Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067–5074.

(4) Rodrigo, G. C.; Standen, N. B. *Curr. Pharm. Des.* **2005**, *11*, 1915–1940.

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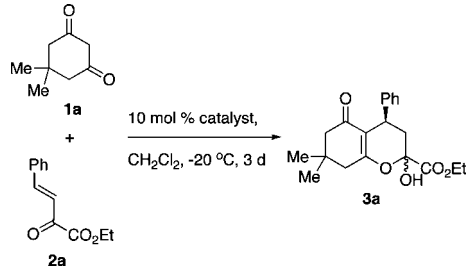
and Michael reactions, we chose β,γ-unsaturated α-ketoesters as the electrophiles for the Michael reaction. As we had found that pyrimidine-bis-cinchona alkaloid derivatives provide the highest enantioselectivity in the IFB reaction, we first tested these compounds as catalysts for the Michael reaction.

We used the reaction between dimedone (**1a**) and β,γ-unsaturated α-ketoester **2a** to screen for the optimal catalyst (Table 1). The product of this reaction cyclizes to form lactol **3a** as an equilibrating mixture of anomers. These anomers equilibrate slowly enough that they show up as separate compounds by ^{1}H and ^{13}C NMR but quickly enough that they do not resolve by chromatography. The trace of racemic **3a** on a Chiralpak AD HPLC column shows only two peaks for the two enantiomers. By screening catalysts (Figure 1) previously synthesized in our group,[5] we immediately found a promising catalyst, **4d**, which gives 84% ee. We also observed that increasing the bulk of the pyrimidine C_5-substituent led to more dramatic increases in enantioselectivity than increasing the size of the C_2-substituent (**5** to **4c** vs **5** to **4b**). We therefore postulated that converting the C_5-*t*Bu substituent into a triethylmethyl group would further improve the enantioselectivity.

Table 1. Catalyzed Michael Reaction of **1a** and **2a**



entry	catalyst	yield (%)	ee (%)[a]
1	quinuclidine	85	0
2	**4a**	58	59
3	**4b**	69	65
4	**4c**	55	74
5	**4d**	95	84
6	**5**	47	63

[a] Determined by HPLC analysis of the purified product.

Accordingly, we prepared four catalysts built on the C_2-*t*Bu-C_5-CEt_3-pyrmidine core. These new catalysts, **6a**, **6b**, **7a** and **7b**, were synthesized by the reaction of dichloropyrimidine **10** with quinidine (QDH), dihydroquinidine (DHQDH), quinine (QNH), and dihydroquinine (DHQNH), respectively (Scheme 2). We prepared **10** from known diester **8**[6] by pyrimidine formation and chlorination.[7] To our surprise, all substitution reactions of **10** with cinchona alkaloids afforded only the monosubstituted compounds.[8] The very bulky triethylmethyl group most likely blocks the 4-position of the pyrimidine from further attack by the alkaloid.

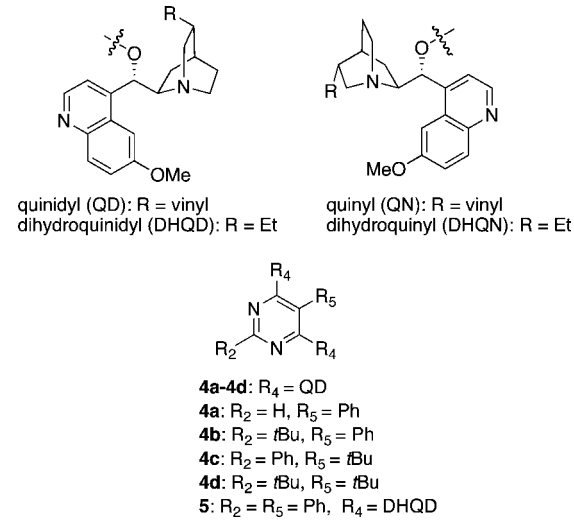
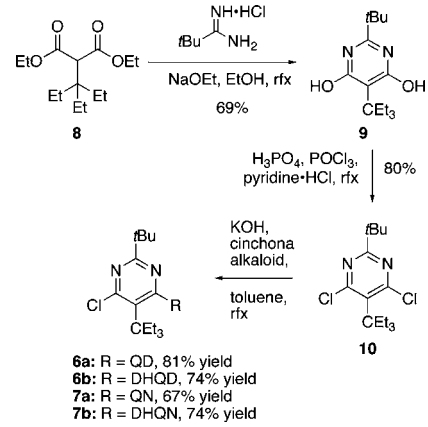


Figure 1. Cinchona alkaloid-derived pyrimidine organocatalysts.

Scheme 2. Synthesis of New Catalysts



Gratifyingly, catalyst **6a** afforded over 90% ee in the test reaction (Table 2, entry 1). The corresponding quinine-based catalysts gave lower enantioselectivity for the opposite enantiomer, but the dihydroquinine-based catalyst **7b** slightly outperformed quinine-based **7a** (entry 4 vs entry 3). We then studied the effects of temperature and solvent on the enantioselectivity with optimal catalysts **6a** and **7b**. Running the reaction at 0 °C did not lower the asymmetric induction but did improve the reaction rate and yields. The enantioselectivity began to suffer at room temperature, however, so we carried out the solvent screening at 0 °C. We found this reaction functions in several commonly used solvents besides

(5) Calter, M. A.; Phillips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566–14567.
(6) Holmberg, C. *Liebigs Ann. Chem.* **1981**, 748–60.
(7) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xe, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785–3786.
(8) We adapted the conditions for this step from ref 7. For another example of mono-substitution of a dichloropyrimidine with a cinchona alkaloid and use of the resulting compound as a catalyst for a different type of Michael reaction, see: Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4301–4305.

Table 2. Optimization of Reaction Conditions for the Michael Reaction of **1a** with **2a** using catalysts **6a**, **6b**, **7a**, and **7b**

entry	catalyst	solvent	temp (°C)	time (h)	% yield	% ee[a]
1	**6a**	CH_2Cl_2	−20	72	60	92
2	**6b**	CH_2Cl_2	−20	72	97	90
3	**7a**	CH_2Cl_2	−20	72	65	84[b]
4	**7b**	CH_2Cl_2	−20	72	97	88[b]
5	**6a**	CH_2Cl_2	0	24	78	92
6	**6a**	CH_2Cl_2	25	24	81	88
7	**6a**	PhMe	0	24	97	96
8	**6a**	PhMe	25	24	81	88
9	**6a**	PhH	0	24	92	94
10	**6a**	Et_2O	0	24	91	94
11	**6a**	THF	0	24	71	92
12	**6a**	MeOH	0	24	89	73
13	**6a**	CH_3CN	0	24	90	77
14	**6a**	DMF	0	24	59	46
15	**7b**	CH_2Cl_2	0	24	97	88[b]
16	**7b**	PhMe	0	24	89	92[b]

[a] Determined by HPLC analysis of the purified product. [b] (*S*)-Enantiomer is major product.

methylene chloride, such as benzene, toluene, ether, and tetrahydrofuran. However, toluene clearly provided the best enantioselectivities and therefore allowed dihydroquinine-based catalyst **7b** to provide synthetically useful levels of selectivity for the (*S*)-enantiomer.

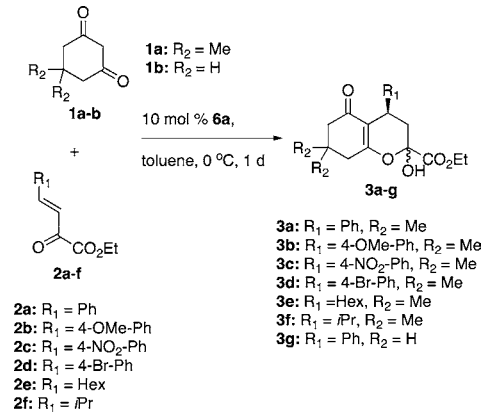
With the optimized reaction conditions in hand, we then tested the substrate scope of the reaction by varying the γ-substituent of the electrophile (Table 3). Changing the electronic nature of the aryl substituent in this position had no effect on the rate, yield, or enantioselectivity of the reaction (entries 1−3). We assigned the absolute stereochemistry of **3d** and, by analogy, the remaining Michael products as *R* by anomalous dispersion analysis of single crystal X-ray data. Alkyl-substituted enones also produced excellent results. We also found that catalyst recovered from the reaction mixture using silica gel flash chromatography gives the same results as the original one (entry 6, Table 3 vs entry 7, Table 2). Finally, we found that cyclohexane dione (**1b**) itself functions as a satisfactory nucleophile for the reaction.

The assays for the optical activity of compounds **3b**−**3d** and **3g** paralleled that for **3a**, but we needed to develop a new assay for compounds **3e** and **3f**, as these compounds did not possess a chromophore adequate for accurate HPLC analysis. We subjected these compounds to dehydrating conditions to afford dihydropyrans **11a** and **11b** (Scheme 3). The dihydropyrans gave excellent enantiomeric separations on the HPLC.

Finally, we have shown that the Michael adducts can be transformed into hexahydroquinolines with negligible loss of optical activity. Reaction of **3b** (96% ee) with ammonium acetate yields hexahydroquinoline **12** (94% ee) (Scheme 4).[9]

In summary, cinchona alkaloid-derived pyrimidine organocatalysts were synthesized and afforded excellent enantioselectivity in the asymmetric Michael reaction of β,γ-unsaturated α-ketoesters with cyclic diketones. The reaction runs under mild conditions in a variety of solvents under the influence of a readily available and recoverable catalyst, while tolerating functional group variation on the γ-carbon of the electrophile. We are currently exploring an expansion of the nucleophile and electrophile scope of this Michael reaction.

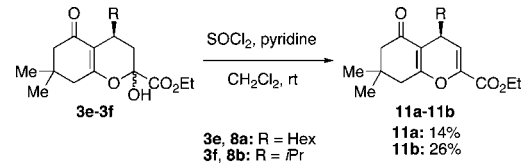
Table 3. Substrate Scope of the Michael Reaction



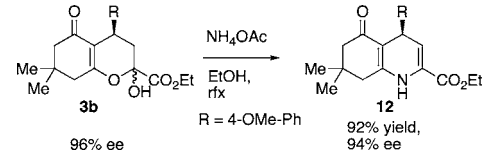
entry	nucleophile	electrophile	product	% yield	% ee[a]
1	**1a**	**2b**	**3b**	95	96
2	**1a**	**2c**	**3c**	96	99
3	**1a**	**2d**	**3d**	99	99
4	**1a**	**2e**	**3e**	74	95[b]
5	**1a**	**2f**	**3f**	64	94[b]
6[c]	**1a**	**2a**	**3a**	97	96
7	**1b**	**2a**	**3g**	89	97

[a] Determined by HPLC analysis of purified product. [b] Determined by HPLC analysis of the derived dihydropyran. [c] Reaction performed with recovered **6a**.

Scheme 3. Dehydration of **3e** and **3f**



Scheme 4. Conversion of **3b** into Hexahydroquinoline **12**



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Supporting Information Available: Complete experimental details and characterization data for all new compounds, along with the details of the X-ray structure of **3d** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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