JOC Article

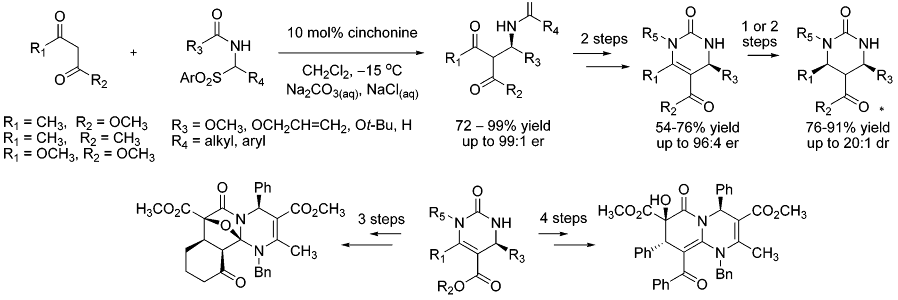
Asymmetric Mannich Reaction of Dicarbonyl Compounds with α-Amido Sulfones Catalyzed by Cinchona Alkaloids and Synthesis of Chiral Dihydropyrimidones

Sha Lou, Peng Dai, and Scott E. Schaus*

Department of Chemistry, Center for Chemical Methodology and Library Development, Life Science and Engineering Building, Boston University, 24 Cummington Street, Boston, Massachusetts 02215

seschaus@bu.edu

Received August 21, 2007



The highly enantioselective cinchona alkaloid-catalyzed Mannich reaction of dicarbonyl compounds with α-amido sulfones as acyl imine precursors is described. The reaction requires 10 mol % of the cinchona alkaloid catalyst, which serves as a general base to generate acyl imines *in situ*, and aqueous Na_2CO_3 to maintain the concentration of free alkaloid catalyst. The reaction products are obtained in good yields and high enantioselectivities, and in diastereoselectivities that range from 1:1 to >95:5. The cinchonine-catalyzed reactions provide practical access to highly functionalized building blocks which have been employed in the synthesis of chiral dihydropyrimidones, a class of compounds rich in diverse biological activity. Dihydropyrimidone modifications include a highly diastereoselective hydrogenation of the enamide moiety, using an H-Cube flow hydrogenator and a Rh(II)-mediated 1,3-dipolar cycloaddition to afford highly functionalized complex heterocycles.

Introduction

Amine-containing building blocks in optically enriched form are valuable synthons for organic synthesis.[1] A direct asymmetric Mannich reaction[2] provides practical methods to access such highly functionalized blocks.[3] A class of compounds readily accessed with these building blocks are 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones, compounds which possess wide-ranging pharmacological properties.[4] They have served as calcium channel modulators,[5] antihypertensive agents,[6] α-1a-antagonists,[7] mitotic kinesin Eg5 inhibitors,[8] neuropeptide Y(NPY) antagonists,[9] and melanin concentrating hormone receptor antagonists (Figure 1).[10] In most cases only one enantiomer was found to be biologically active.[11] Although the racemic form of dihyropyrimidinones is easily afforded *via* Biginelli reaction,[12] there are only a few procedures to synthesize this heterocyclic system in enantioenriched form, including chemical resolution,[13] enzymatic synthesis,[14] and Yb-[15] or chiral phosphoric acid-catalyzed[16] Biginelli reaction. The asymmetric addition of *β*-dicarbonyls to acyl imines[17] affords multifunctional chiral amines which can serve as starting materials for dihydropyrimidones and other pharmaceutically active hetero-

---

* Author to whom correspondence should be addressed. Phone: 01-617-353-2489. Fax: 01-617-353-6466.

[1] Reviews: (a) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) *Enantioselective Synthesis of a-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (c) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377−4379. (d) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (e) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794−5795. (f) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290−4299.

[2] For reviews: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094. (b) Denmark, S.; Nicaise, J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, p 954. (c) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, *4*, 563−572. (d) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102−112.

10.1021/jo701777g CCC: $37.00

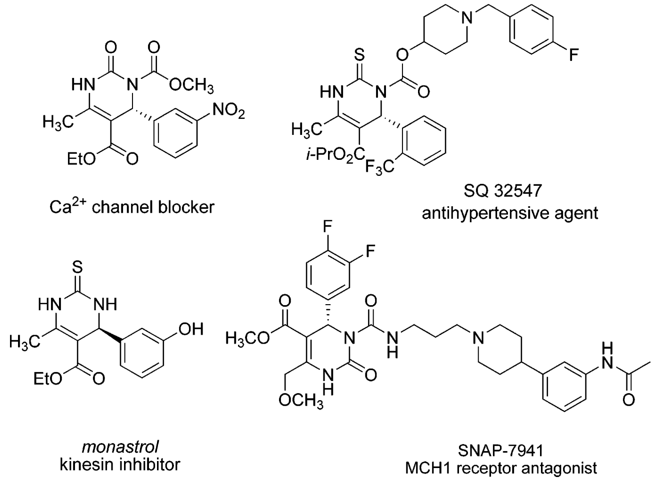


FIGURE 1. Representative bioactive dihydropyrimidones.

cycles.[18] Although aryl acyl imines and α,*β*-unsaturated imines are easily accessed, aliphatic acyl imines are difficult to isolate because reactive imine functionality tends to tautomerize to enamine under normal conditions.

α-Amido sulfones[19] are bench-stable precursors to *N*-acylimines that have proven useful in a wide range of enantioselective reactions including aza-Henry reactions,[20] imine alkylations,[21] and aldehyde–imine cross-coupling reactions.[22] Under basic conditions, α-amido sulfones are readily converted to the corresponding acyl imine.[23] We recently described the asymmetric Mannich reactions of *β*-keto esters to acyl imines catalyzed by the cinchona alkaloids.[24] In an effort to create a more general Mannich reaction methodology for the practical synthesis of chiral dihydropyrimidones that includes a broader range of *β*-dicarbonyl nucleophiles and aliphatic acyl imine electrophiles, we have developed a biphasic cinchona alkaloid-catalyzed Mannich reaction utilizing α-amido sulfones as acyl imine precursors (Scheme 1). A diverse chiral pilot dihydropyrimidones library containing over 200 compounds was generated with use of asymmetric Mannich reaction products as scaffolds.

Results and Discussion

Asymmetric Mannich Reactions of α-Amido Sulfones. We began our investigation with the addition of methyl acetoacetate **3** to the α-amido sulfones **4** using cinchonine **1** as the catalyst (Table 1). Aqueous Na_2CO_3 in a saturated solution of NaCl was used to consume the sulfinic acid produced during the course of the reaction and maintain the basic reaction conditions for imine formation. Saturation of the aqueous layer with NaCl prevented the aqueous phase from freezing at −15 °C, the temperature required for optimal enantioselectivities. Other bases

---

(3) For recent examples: (a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843. (c) Zhuang, W.; Sabby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476−4478. (d) Marigo, M.; Kjaersgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359−2367. (e) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338−339. (f) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583−2599. (g) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677−3680. (h) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777−8785. (i) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc*. **2005**, *127*, 16408−16409. (j) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365−4368. (k) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564−4567. (l) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc*. **2006**, *128*, 2778−2779. (m) Mitsumori, S.; Zhang, H.; Cheong, P.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc*. **2006**, *128*, 1040−1041. (n) Zhang, H. L.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc*. **2006**, *128*, 9630−9631. (o) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc*. **2006**, *128*, 14010−14011. (p) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc*. **2007**, *129*, 288−289. (q) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2007**, *129*, 500−501. (r) Guo, Q-X.; Liu, H.; Guo, C.; Luo, S-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc*. **2007**, *129*, 3790−3791.

(4) For reviews on dihydropyrimidones, see: (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879−888. (b) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043−1058.

(5) (a) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O' Reilly, B. C.; Schwart, J.; Malley, M. *J. Med. Chem.* **1992**, *35*, 3254−3263. (b) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med Chem.* **1995**, *38*, 119−129. (c) Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289−294.

(6) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806−811.

(7) (a) Nagarathnam, D.; Miao, S. W.; Lagu, B.; Chiu, G.; Fang, J.; Dhar, T. G. M.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F. Q.; Wong, W. C.; Sun, W. Y.; Tian, D.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Kling, P.; Schneck, K.; Benedesky, R.; Harrell, C. M.; Vyas, K. P.; Gluchowski, C. *J. Med. Chem.* **1999**, *42*, 4764−4777.

(8) (a) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971−974. (b) Haggarty, S. J.; Mayer, T. U.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. *Chem. Biol.* **2000**, *7*, 275−286. (c) Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger, R. M.; Ransom, R. W.; Kling, P.; Reiss, D.; Broten, T. P.; Schorn, T. W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703−2718.

(9) Bristol-Myers Squibb Co.: *Expert Opin. Ther. Pat.* **1999**, *9*, 321−325.

(10) Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; Deleon, J.; Lagu, B.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. H. J.; Forray, C. *Nat. Med.* **2002**, *8*, 825−830.

(11) (a) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1−116. (b) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630−645.

(12) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360−416. (b) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937−6963.

(13) (a) Kleidernigg, O. P.; Kappe, C. O. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2057−2067. (b) Lewandowske, K.; Murer, P.; Svec, F.; Frechet, J. M. J. *J. Comb. Chem.* **1999**, *1*, 105−112. (c) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473−5480. (d) Kontrec, D.; Vinkovic, V.; Sunjic, V.; Schuiki, B.; Fabian, W. M.; Kappe, C. O. *Chirality* **2003**, *15*, 550−557.

(14) Schnell, B.; Strauss, U. T.; Verdino, P.; Faber, K.; Kappe, C. O. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1449−1453.

(15) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386−16387.

(16) Chen, X.; Yu, X.; Liu, H.; Chun, L.; Gong, L. *J. Am. Chem. Soc.* **2006**, *128*, 14802−14803.

(17) (a) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359−2367. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356−5357. (c) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525−1529. (d) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896−2899. (e) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, *11*, 1191−1193. (f) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048−6049.

(18) (a) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348−352. (b) Kim, D.; Wang, L.; Beconi, M.; Eiermann, G. J.; Fisher, M. H.; He, H.; Hickey, G. J.; Kowalchick, J. E.; Leiting, B.; Lyons, K.; Marsilio, F.; McCann, M. E.; Patel, R. A.; Petrov, A.; Scapin, G.; Patel, S. B.; Roy, R. S.; Wu, J. K.; Wyvratt, M. J.; Zhang, B. B.; Zhu, L.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2005**, *48*, 141−151.

SCHEME 1. Synthesis of Dihydropyrimidones via Asymmetric Mannich Reaction Catalyzed by Cinchona Alkaloids

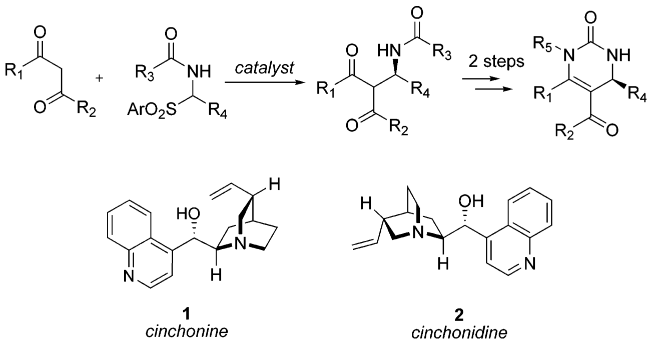
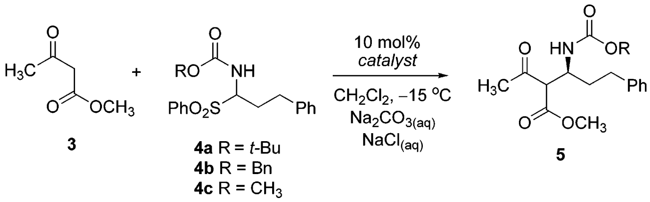


TABLE 1. Asymmetric Mannich Reactions of α-Amido Sulfones[a]

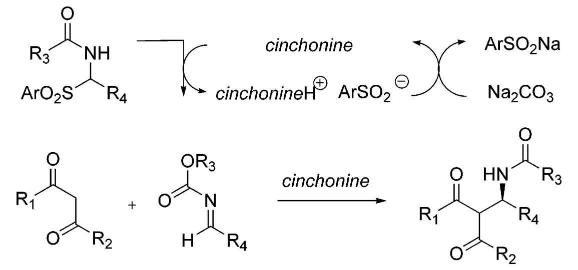


entry	catalyst	α-amido sulfone	% yield[b]	er[c]
1	**1**	**4a**	81	91.5:8.5
2	**1**	**4b**	88	90:10
3	**1**	**4c**	85	95:5
4[d]	**1**	**4c**	0	
5		**4c**	15	
6	**2**	**4c**	90	5:95[e]
7	quinine	**4c**	81	16:84[e]
8	quinidine	**4c**	62	86:14
9	hydroquinidine	**4c**	75	85.5:14.5

[a] Reactions were run with amido sulfone **4a**−**c** (0.5 mmol), ester **3** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.[d] The reaction was run without water, using 10 mol % Na_2CO_3. [e] Opposite sense of enantioselectivity.

were tested in the reaction, including KOH, DBU, and proton sponge, all of which resulted in lower enentioselectivities. The reaction of *N*-Boc sulfone **4a** and *N*-Cbz sulfone **4b** with **3** catalyzed afforded the corresponding *β*-amino esters in 81% and 88% yields, 1:1 diastereoselectivity, and 91.5:8.5 and 90:10 enantiomeric ratio (er), respectively (Table 1, entries 1 and 2). Higher enantioselectivity was obtained in the reaction of **3** with methyl carbamate sulfone **4c** (85% yield, 95:5 er) (entry 3). When cinchonidine **2** was used as catalyst, similar enantiomeric excess was attained with the opposite sense of enantioselectivity (entry 6). Other commercially available cinchona alkaloids such as quinine, quinidine, and hydroquinidine were not as effective as cinchonine in promoting enantioselective Mannich reactions.

SCHEME 2. Role of Cinchonine in the Mannich Reaction with α-Amido Sufones



Interestingly, the reaction did not proceed in the absence of water (Table 1, entry 4). Aqueous Na_2CO_3 alone was capable of promoting the reaction, albeit very slowly; only 15% conversion was observed in the absence of cinchonine after 48 h (entry 5). The reaction with phase transfer reagent benzyl cinchonium chloride as the catalyst did not give any desired product under biphasic conditions. These experiments strongly suggested that cinchonine acts primarily as a chiral base that promotes the generation of acyl imines from α-amido sulfones under biphasic reaction conditions. In addition, aqueous base sodium carbonate helps to maintain the basic reaction environment and regenerate active cinchonine to subsequently catalyze the addition of methyl acetate **3** to the acyl imines (Scheme 2).

Reaction Scope. The optimal reaction conditions for the reaction of **3** with **4c** proved general for a variety of *N*-methyl carbamate sulfones (Table 2). Nonsubstituted alkyl amido sulfone cleanly underwent the Mannich reaction to afford the desired Mannich product in greater than 85% isolated yields (Table 2 entries 1 and 2). Subsequent condensation with benzyl amine gave *Z*-enamines in high yields (>71%) and high er (95:5). α-Substituted (entries 3 and 4) and *β*-substituted (entry 5) alkyl amido sulfones reacted with **3** under the general conditions, although at a slower rate, to give the Mannich adduct in comparable yields and enantioselectivity. The substrates bearing benzyl-protected alcohol (entry 6) and double bond (entry 7) were also tolerated under optimized conditions. Aromatic *N*-methyl carbamate sulfones proved to be more reactive than aliphatic derivatives. The addition of **3** to phenyl amido sulfone (entry 8) took only 15 h to generate the Mannich product in quantitative yield and excellent er (98:2). Electron withdrawing (entries 9, 10, and 11) and electron donating (entries 12−14) substitution on the aromatic ring did not affect the reaction rate or enantioselectivity. Heteroaromatic amido sulfones (entries 15 and 16) were also tolerated under these conditions. The reaction rate and enantioselectivities were sensitive to the type of amido sulfone employed in the reaction. For slow reactions or reactions that resulted in lower enantioselectivities, we hypothesized that *p*-chlorophenyl sulfones used in the reaction would more readily eliminate to form the acyl imine. Allyl carbamate *p*-chlorophenyl sulfones were used in the Mannich reaction to achieve a higher reaction rate and higher enantioselectivity for aliphatic derivatives (entries 17−20), although

---

(19) (a) Review: Petrini, M. *Chem. Rev.* **2005**, *105*, 3949−3977. (b) Messinger, P. *Pharmazie* **1976**, *31*, 16−18.

(20) (a) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622−17623. (b) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975−7978.

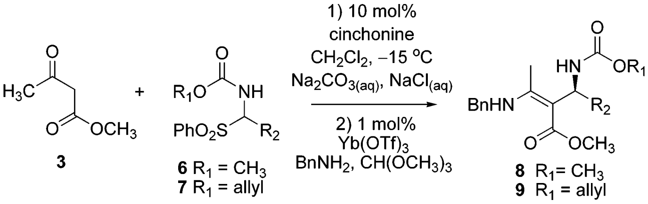
(21) (a) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941. (b) Zhang, H.-L.; Liu, H.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Synlett* **2005**, 615−618. (c) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694.

(22) (a) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654−1655. (b) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697.

(23) (a) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75−77. (b) Kanazawa, S. M.; Denis, J.-N.; Greene, S. E. *J. Org. Chem.* **1994**, *59*, 1238−1240. (c) Zawadzki, S.; Zwierzak, A. *Tetrahedron Lett.* **2004**, *45*, 8505−8506. (d) Morton, J.; Rahim, A.; Walker, E. R. H. *Tetrahedron Lett.* **1982**, *23*, 4123−4126.

(24) (a) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256−11257. (b) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003−2006.

TABLE 2. Asymmetric Mannich Reactions of β-Keto Ester 3[a]



entry	R_1	R_2	% yield[b]	yield (%)[c]	er[d]
1	CH_3	$PhCH_2CH_2$	85	**8a** (84)	95:5
2	CH_3	$PhCH_2$	87	**8b** (71)	95:5
3	CH_3	$(CH_3)_2CH$	84	**8c** (73)	96.5:3.5
4	CH_3	c-C_6H_{11}	85	**8d** (83)	92:8
5	CH_3	(CH3)$_2$CHCH$_2$	87	**8e** (75)	93.5:6.5
6	CH_3	$BnOCH_2$	92	**8f** (78)	97.5:2.5
7	CH_3	(s)-citronellyl	86	**8g** (81)	97:3
8	CH_3	Ph	99	**8h** (95)	98.5:1.5
9	CH_3	4-Br-C_6H_4	93	**8i** (83)	95:5
10	CH_3	3-F-C_6H_4	98	**8j** (82)	97.5:2.5
11	CH_3	3-CF3-C_6H_4	96	**8k** (84)	95.5:4.5
12	CH_3	4-CH3-C_6H_4	92	**8l** (96)	95:5
13	CH_3	3-CH3O-C_6H_4	93	**8m** (86)	95.5:4.5
14	CH_3	3,4-(OCH_2O)- C_6H_4	97	**8n** (82)	95.5:4.5
15	CH_3	2-C_4H_3O	90	**8o** (84)	96:4
16	CH_3	2-C_4H_3S	92	**8p** (88)	95.5:4.5
17[e]	allyl	$PhCH_2CH_2$	91	**9a** (81)	95:5
18[e]	allyl	$PhCH_2$	81	**9b** (78)	94.5:5.5
19[e]	allyl	$BnOCH_2$	90	**9c** (76)	95:5
20[e]	allyl	$(CH_3)_2CHCH_2$	88	**9d** (73)	94:6
21	allyl	Ph	95	**9e** (81)	95.5:4.5
22	allyl	4-Br-C_6H_4	90	**9f** (80)	95:5
23	allyl	3-F-C_6H_4	88	**9g** (83)	95:5
24	allyl	3-CF_3-C_6H_4	91	**9h** (82)	95.5:4.5
25	allyl	4-CH_3-C_6H_4	94	**9i** (84)	95:5
26	allyl	3-CH_3O-C_6H_4	86	**9j** (80)	94:6
27	allyl	3,4-(OCH_2O)-C_6H_4	82	**9k** (81)	93:7
28	allyl	2-C_4H_3O	88	**9*l*** (81)	95:5

[a] Reactions were run with α-amido sulfone (0.5 mmol), ester **3** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yield of isolated Mannich reaction product. [c] Yields of isolated enamine **8** and **9**. [d] Determined by chiral HPLC analysis. [e] *p*-Cl-Ph sulfones were used in the Mannich reactions.

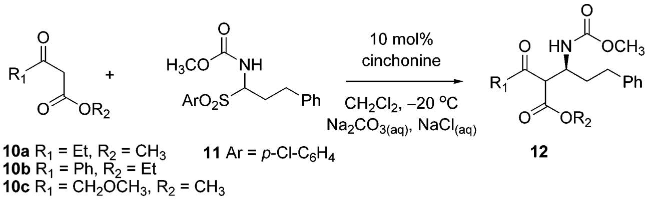
aromatic and heteroaromatic allyl carbamate phenyl sulfones worked just as well as methyl carbamate sulfones to afford Mannich adducts with high yield and high enantioselectivity (entries 21−28).

The reaction conditions proved to be general for the β-keto esters we surveyed in the reaction (Table 3). *p*-Chlorophenyl sulfones were used to achieve the best reaction rates and enantioselectivities. 3-Oxopentanoate (entry 1), benzoylacetate (entry 2), and 4-methoxy-3-oxobutanoate (entry 3) afforded the corresponding Mannich addition products in high er but with no diastereoselectivity.

The reaction conditions also proved to be highly effective in the Mannich reaction with 2,4-pentanedione **13** as the nucleophile (Table 4). Aliphatic and aromatic amido sulfones were examined in the reaction with **13** to afford the Mannich product with a similar level of selectivity. Cinchonidine was also successfully used to promote the Mannich reaction of **13** with a variety of α-amido sulfones to afford opposite enantiomers. In all cases the reaction proceeded cleanly with greater than 85% yields and excellent er (>95:5).

The malonates represent an important substrate for investigation in the asymmetric direct Mannich reaction because the products of the malonate Mannich reaction provide direct access to chiral β-amino acids.[25] However, dimethyl malonate **15** proved to be less reactive under standard conditions than β-keto ester **3** and diketone **13**. When aliphatic phenyl sulfone **4c** was used, the reaction afforded the Mannich adduct in less than 50% yield. *p*-Chlorophenyl sulfones were successfully utilized to increase the reaction rate (Table 5). Nonsubstituted aliphatic and aromatic α-amido sulfones (entry 1−6) reacted with dimethyl malonate smoothly to afford β-amino esters in good yield and high er (>95:5). However, the α-substituted substrate was less reactive, probably because of steric hindrance (entry 7). Low yields of the desired Mannich product were the result of an undesired reaction pathway to form the ene-amide (entry 8). α-Formamido sulfones were successfully used as a solution for the two problematic substrates. In both cases, the yields were higher than 70% and er values were higher than 95:5 (entries 9 and 10). When phenyl formamido sulfone was used in the Mannich reaction, quantitative yield and 99:1 er were observed (entry 11). Similar work was reported by Deng and co-workers using 9-thiourea cinchona alkaloid derivatives in the asymmetric

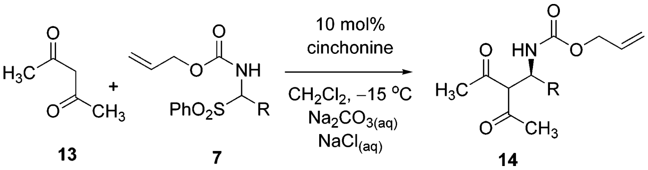
TABLE 3. Asymmetric Mannich Reactions of β-Keto Ester 10[a]



entry	dicarbonyls	yield (%)[b]	dr[c]	er[d]
1	**10a**	**12a** (86)	1:1	96:4
2	**10b**	**12b** (96)	1:1	92.5:7.5
3	**10c**	**12c** (85)	1:1	95:5

[a] Reactions were run with α-amido sulfones (0.5 mmol), dicarbonyls **10** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yields of isolated products. [c] Determined by H NMR. [d] Determined by chiral HPLC analysis.

TABLE 4. Asymmetric Mannich Reactions of Diketone 13[a]



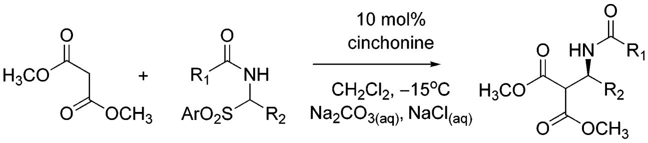
entry	R	yield (%)[b]	er[c]
1	$PhCH_2CH_2$	**14a** (88)	95:5
2	Ph	**14b** (91)	96.5:3.5
3	4-Br-C_6H_4	**14c** (90)	95.5:4.5
4	3-CF_3-C_6H_4	**14d** (87)	96:4
5	2-C_4H_3O	**14e** (88)	95.5:4.5
6	2-C_4H_3S	**14f** (86)	96.5:3.5

[a] Reactions were run with α-amido sulfones (4.0 mmol), diketone **13** (12.0 mmol), and catalyst (0.40 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

---

(25) (a) Myers, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960. (b) Sibi, M. P.; Asano, Y. *J. Am Chem. Soc.* **2001**, *123*, 9708−9709. (c) Zhou, Y.; Tang, W.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952−4953. (d) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowske, E. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918−9919. (e) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466−7469. (f) Liu, T-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878−1879.

TABLE 5. Asymmetric Mannich Reactions of Methyl Malonate 15[a]



15

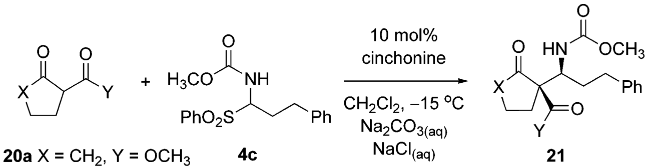
16 $R_1 = OCH_3$, Ar = *p*-Cl-C_6H_4
17 R_1 = H, Ar = *p*-Cl-C_6H_4

18 $R_1 = OCH_3$
19 R_1 = H

entry	R_1	R_2	yield (%)[b]	er[c]
1	OCH_3	$PhCH_2CH_2$	**18a** (86)	96:4
2	OCH_3	$CH_3(CH_2)_7CH_2$	**18b** (71)	95:5
3	OCH_3	$BnOCH_2$	**18c** (82)	97.5:2.5
4	OCH_3	Ph	**18d** (83)	95:5
5	OCH_3	4-Br-C_6H_4	**18e** (91)	95:5
6	OCH_3	3,4-(OCH_2O)-C_6H_4	**18f** (84)	95.5:4.5
7	OCH_3	$(CH_3)_2CH$	**18g**(58)	95:5
8	OCH_3	2,4,5-F-$C_6H_4CH_2$	**18h** (56)	85:15
9	H	$(CH_3)_2CH$	**19a** (72)	95.5:4.5
10	H	2,4,5-F-$C_6H_4CH_2$	**19b** (73)	97.5:2.5
11	H	Ph	**19c** (95)	99:1

[a] Reactions were run with α-amido sulfones (0.5 mmol), methyl malonate **15** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis.

TABLE 6. Asymmetric Mannich Reactions of Cyclic Dicarbonyls 20[a]



20a X = CH_2, Y = OCH_3
20b X = CH_2, Y = CH_3
20c X = O, Y = OCH_3

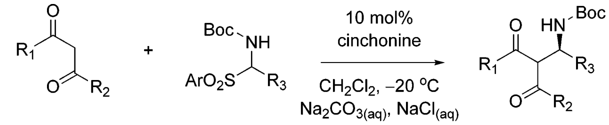
entry	dicarbonyls	yield (%)[b]	dr[c]	er[d]
1	**20a**	**21a** (91)	99:1	95:5
2	**20b**	**21b** (95)	99:1	98.5:1.5
3	**20c**	**21c** (84)	99:1	99.5:0.5

[a] Reactions were run with α-amido sulfones (0.5 mmol), dicarbonyls **20** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yields of isolated products. [c] Determined by H NMR. [d] Determined by chiral HPLC analysis.

addition of benzyl malonate to α-amido sulfones employing aqueous solutions of Cs_2CO_3 and CsOH for *in situ* generation of the imine.[26] Alternative approaches include using the cinchona alkaloid-derived phase transfer reagents to promote asymmetric Mannich reaction of α-amido sulfones.[27] In this case, *p*-anisyl malonate and aqueous K_2CO_3 were applied under the optimal reaction conditions to achieve high enantioselectivities.

We have also expanded the scope of this reaction to include cyclic α-substituted *β*-keto ester **20a**, *β*-diketones **20b**, and *β*-keto lactone **20c** (Table 6). Treatment of α-amido sulfone with these dicarbonyls catalyzed by 10 mol % cinchonine **1** under biphasic conditions afforded the corresponding products in high yield (84−95%), high diastereroselectivity (99:1 dr), and high enantioselectivity (>95:5 er) (Table 6, entries 1−3). The reaction provides a catalytic route toward the construction of cyclic *β*-amino esters with α-quaternary carbon centers as a supplement to our recent study.[11b,28]

TABLE 7. Asymmetric Mannich Reactions of N-Boc Sulfones 22[a]



3 $R_1 = CH_3$, $R_2 = OCH_3$
15 $R_1 = CH_3$, $R_2 = CH_3$
20 $R_1 = OCH_3$, $R_2 = OCH_3$

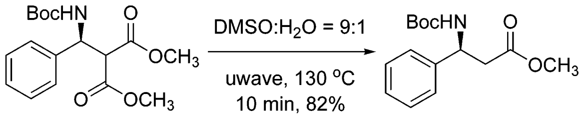
22a R_3 = Ph, Ar = *p*-Cl-C_6H_4
22b $R_3 = CH_2CH_2Ph$, Ar = *p*-Cl-C_6H_4

23

entry	dicarbonyls	α-amido sulfones	yield (%)[b]	er[c]
1	**3**	**22a**	**23a** (93)	97.5:2.5
2	**15**	**22a**	**23b** (97)	97.5:2.5
3[d]	**20**	**22a**	**23c** (81)	95:5
4	**3**	**22b**	**23d** (84)	95:5
5	**15**	**22b**	**23e** (90)	96:4

[a] Reactions were run with α-amido sulfones **22** (0.5 mmol), dicarbonyls (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at −15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] Reaction was run in acetonitrile (2.5 mL), CH_2Cl_2 (2.5 mL), and aqueous Na_2CO_3 in brine at −30 °C (2.5 mL).

Finally, we used *N*-Boc α-amido sulfones **22a** and **22b** in the Mannich reaction (Table 7). The reactions of methyl acetoacetate **3** and 2,4-pentanedione **15** to **22a** or **22b** afforded the desired product in high yield. Reactions involving dimethyl malonate **20** as the nucleophile required lower temperatures to achieve good enantioselectivities. Acetonitrile was added to run the reaction at −30 °C without freezing the aqueous layer. We were able to isolate the malonate adduct **23c** in 81% yield and 95:5 er. Subsequent decarboxylation under modified microwave conditions[29] furnished the *β*-amino ester in 82% yield while maintaining the enantiopurity (eq 1).



(1)

23a 95:5 er

24 95:5 er

Dihydropyrimidone Library Synthesis. Having established a practical method to both aliphatic and aromatic Mannich adducts with high er, we next carried out synthesis of a diversified 1,2-dihydropyrimidone library based on our previously reported methodology.[24]

The library contains three points of diversity. As illustrated in Scheme 3, two dicarbonyls and six α-amido sulfones were utilized to produce 12 scaffolds in both enantiomeric senses (>95:5 er). Eight different isocyanates either from commercial sources or derived from primary amines were utilized for the R_3 diversity element.[30] The synthesis of dihydropyrimidone is a two-step process: first, treatment of the Mannich product with catalytic $Pd(PPh_3)_4$ and dimethyl barbituric acid as the allyl scavenger in the presence of isocyanate afforded the corresponding unsymmetrical urea in 75−88% isolated yield; second, ring closure to the dihydropyrimidone was promoted by AcOH in EtOH under microwave conditions in 72−85% yield. Analysis by chiral HPLC revealed that there is no significant loss of enantiomeric excess in this procedure.

---

[26] Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603−606.

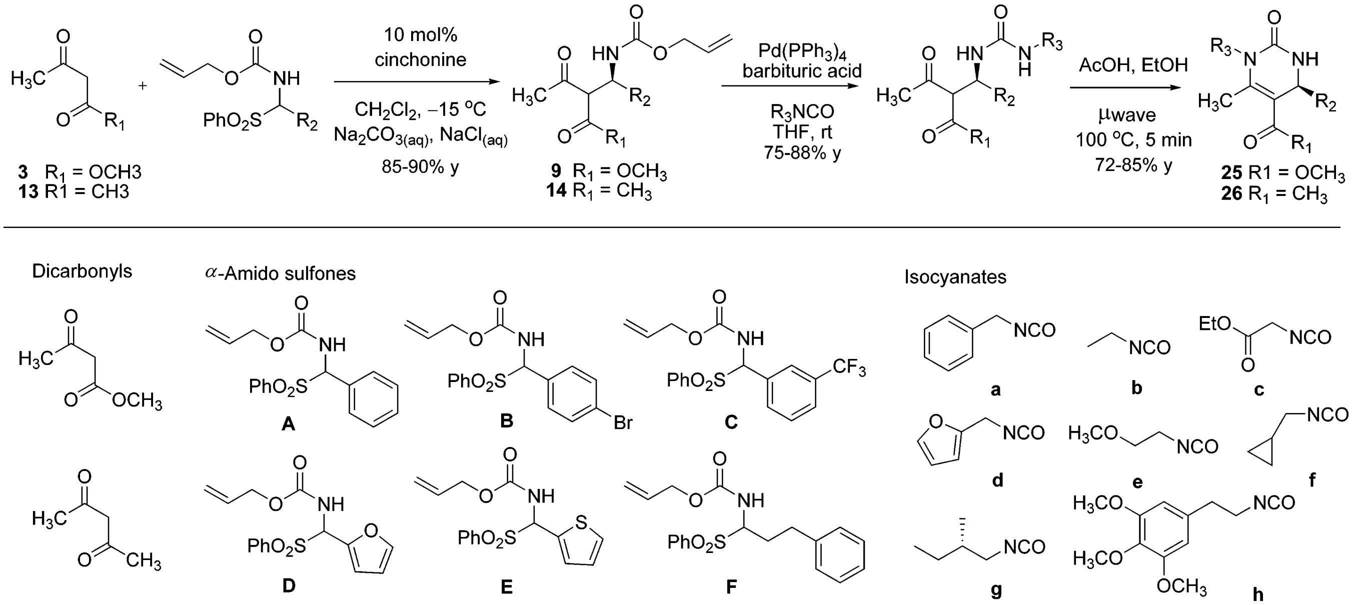
[27] Fini, F.; Bernardi, L.; Pettersen, D.; Ricci, A.; Sagarzabu, V. *Adv. Synth. Catal.* **2006**, *348*, 2043−2046.

[28] Cinchonine-catalyzed addition of *β*-keto esters to azodicarboxylates proceeds with a similar sense of stereochemical induction. Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115−2118.

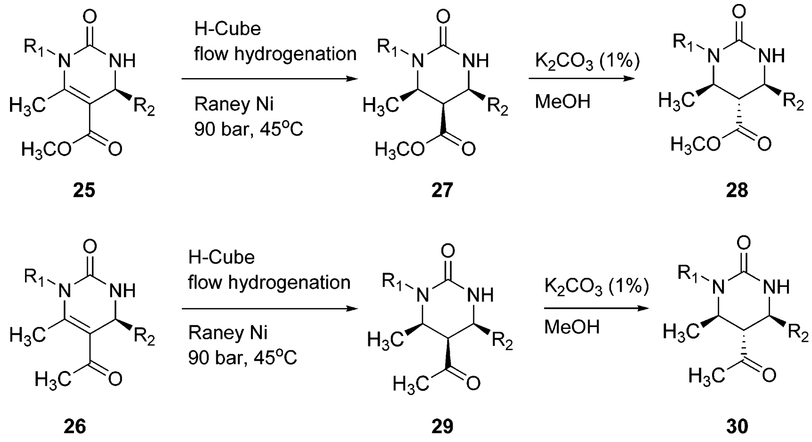
[29] Krapcho, A. P. *Synthesis*, **1982**, 805−822.

[30] Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang S.-L. *J. Org. Chem.* **1996**, *61*, 3929−3934.

SCHEME 3. Synthesis of Dihydropyrimidone Library



SCHEME 4. Hydrogenation of Dihydropyrimidone with H-Cube



A library containing 110 compounds has been synthesized. Scheme 4 illustrated some representative structures of this library. We performed an analysis of trace palladium content to ensure the palladium content was within a suitable range for biological assays. The result from our inductively coupled plasma mass spectrometry (ICP-MS) test revealed that, after flash chromatography, the palladium content was 12 ppm. The dihydropyrimidones were then treated with macroporous polystyrene-bound trimercaptotriazine (MP-TMT resin) to scavenge trace palladium. After the treatment, the palladium content was reduced to 0.9 ppm, which was comparable to negative controls. The library was next purified by reverse-phase HPLC. Samples were collected automatically based on the desired exact mass. Immediately following the purification process, each compound was evaluated for purity with analytical LC/MS/UV/ELSD (Evaporative Light Scattering Detector). The purified compounds were found to have purity higher than 98% (by both ELSD and UV).

Synthesis of Tetrahydropyrimidones by Flow Hydrogenation. The first approach toward modification of the dihydropyrimidone core was hydrogenation of the enamide to produce the corresponding tetrahydropyrimidone. Our strategy employed a flow hydrogenation reactor (H-Cube) due to faster catalyst screening capabilities, easier reaction optimization, and facilitated library synthesis.[31] Several catalysts, including Pd/C, Pt/Al_2O_3, Pt/C, and Raney-Ni, were initially screened. The initial results indicated that Raney-Ni provided the best conversion with fewer side reactions. Further optimization of the reaction conditions focused on reaction pressure, temperature, and solvent. After considerable experimentation, the best conditions were determined to be 90 bar of pressure at 45 °C, which provided complete conversion of most of the substrates investigated with the highest selectivities. It is interesting to note that subjecting **25** to comparable hydrogenation conditions (10% Pd/C or Raney Nickel) under benchtop conditions resulted in multiple hydrogenation products with little to no chemoselectivity or stereoselectivity.

Illustrated in Scheme 4, the tetrahydropyrimidones were

---

(31) (a) Jones, R.; Godorhazy, L.; Varga, N.; Szalay, D.; Urge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 110−116. (b) Franckevicius, V.; Knudsen, K. R.; Ladlow, M.; Longbottom, D. A.; Ley, S. V. *Synlett* **2006**, *6*, 889−892. (c) Desai, B.; Kappe, C. O. *J. Comb. Chem.* **2005**, *7*, 641−643.

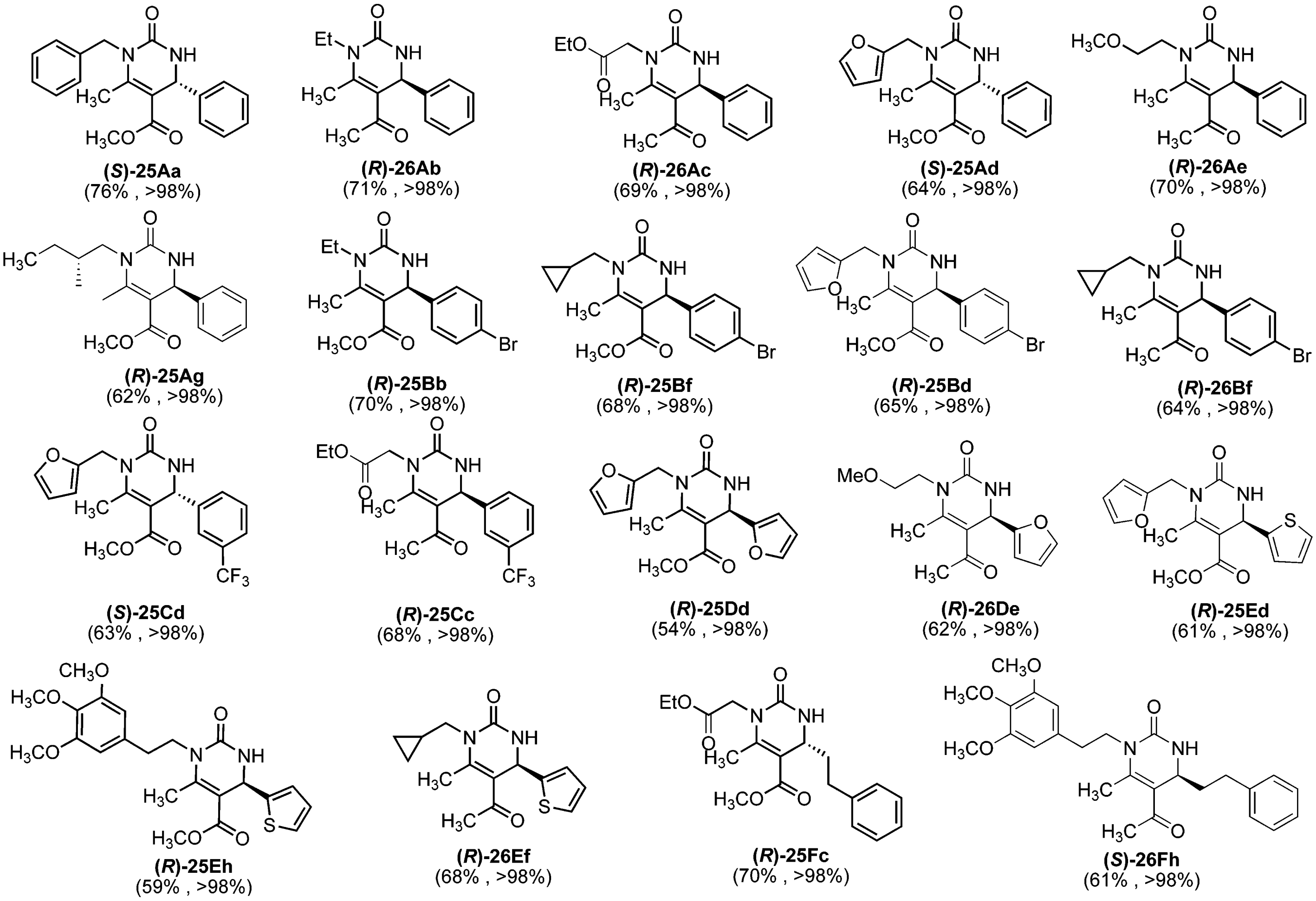


FIGURE 2. Representative structures of the dihydropyrimidone library (yield, purity by UV/ELSD).

produced as the result of *syn* addition of dihydrogen from the opposite face of the R_2 substituent. The diastereoselectivity was found to be greater than 20:1 (by LC-MS with ELSD detector). The stereochemistry was established by NOE experiments and coupling constants of C3 hydrogen with C2 and C4 hydrogens. We observed that the ketone-bearing tetrahydropyrimidone **29** underwent epimerization at the C3 position upon storage to form the more stable isomer **30**, while epimerization of the ester tetrahydropyrimidone **27** did not occur upon storage. Both compounds can be readily epimerized to the thermodynamically more stable isomer via treatment in MeOH with a catalytic amount of K_2CO_3.

Dihydropyrimidones containing heteroaromatic or cyclopropane moieties decomposed under the hydrogenation reaction conditions with no desired product isolated. These starting materials were excluded from further modification by hydrogenation. Figure 3 illustrates several representative structures afforded by the hydrogenation procedure.

Cycloaddition Reactions. In recent years, [3+2] cycloaddition has proven to be an effective strategy to rapidly build molecular complexity.[32] Padwa[33] and others[34] have pioneered this class of reactions using mesomeric betains, especially isomünchnones, in cycloaddition reactions. On the basis of this work and preliminary work by Kappe,[35] we investigated the possibility of using dihydropyrimidone-fused mesomeric betaine in the [3+2] cycloaddition to diversify the dihydropyrimidone core structure in order to synthesize highly complex bicyclic angular compounds.

We initially investigated the intermolecular 1,3-dipolar cycloaddition reactions using dihydropyrimidone **31a** (Scheme 5). Acylation of **32a** with methyl chlorocarbonyl acetate in benzene followed by diazo-transfer with *p*-acetamidobenzene sulfonylazide (*p*-ABSA) and DBU afforded diazo amide **32** in 83% yield. The isomünchnone dipole was formed *in situ* upon treatment with rhodium(II) acetate dimer and refluxed in benzene. In the presence of maleimide as a dipolarophile, the dipole intermediate underwent 1,3-dipolar cycloaddition to generate adduct **34a** in 91% yield. Only one diastereomer was isolated and the relative stereochemistry was determined by NOESY experiments. According to recent computational studies, the dihydropyrimidone ring has a boat-like conformation with the 4-aryl substituent in the pseudoaxial position.[36] This geometric arrangement probably resulted in the attack of the

---

[32] Review: (a) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263−309. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−270. (c) Jorgensen, K. A.; Gothelf, K. V. *Chem. Rev.* **1998**, *98*, 863−909. (d) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357−1374.

[33] (a) Padwa, A.; Price, A. T. *J. Org. Chem.* **1995**, *60*, 6258−6259. (b) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556−565. (c) Padwa, A.; Lynch, S. M.; Mejía-Oneto, J. M.; Zhang, H. *J. Org. Chem.* **2005**, *70*, 2206−2218. (d) Mejía-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275−3278. (e) England, D. B.; Padwa, A. *Org. Lett.* **2007**, *9*, 3249−3252.

[34] (a) Hodgson, D. M.; Lestrat, F.; Avery, T. D.; Donohue, A. C.; Brükl, T. *J. Org. Chem.* **2004**, *69*, 8796−8803. (b) Chen, B.; Ko, R. Y. Y.; Yuen, M. S. M.; Cheng, K.-F.; Chiu, P. *J. Org. Chem.* **2003**, *68*, 4195−4205. (c) Graening, T.; Bette, V.; Neudörfl, J.; Lex, J.; Schmalz, H. G. *Org. Lett.* **2005**, *7*, 4317−4320.

[35] Kappe, C. O.; Peters, K.; Peters, E.-M. *J. Org. Chem.* **1997**, *62*, 3109−3118.

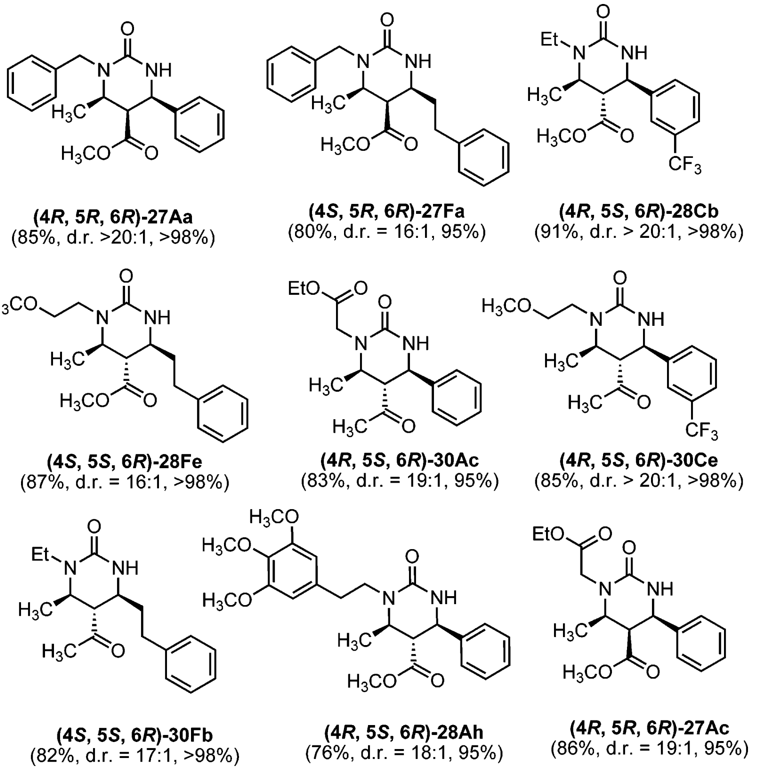
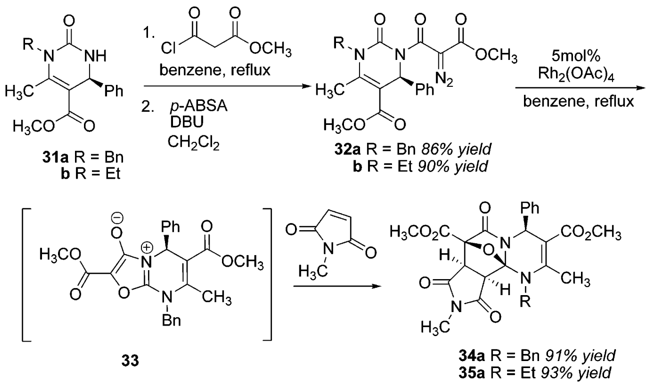


FIGURE 3. Representative structures of tetrahydropyrimidones (isolate yield, dr by LC/MS/ELSD, purity after preparative RP-HPLC purification by LC/MS/UV/ELSD).

SCHEME 5. Dipolar Cycloaddition Sequence



dipolarophile from the *anti*-face of the phenyl group. Similar results for related structures were obtained by Kappe and coworkers where the *exo*-cycloadduct was verified by X-ray crystal structure analysis. The stability of the cycloadduct was tested by stirring in pH 4, 7, and 10 aqueous buffers overnight at room temperature. No decomposition was observed under these conditions.

The substrate scope of [3+2] intermolecular cycloaddition was expanded by employing a variety of dipolarophiles in the reaction (Table 8). Dihydropyrimidones **32a** and **32b** derived from benzyl isocynate and ethyl isocynate were chosen as scaffolds for the cycloadditions. *N*-Methyl-*N*-phenyl maleimide and dimethyl maleate underwent cycloaddition cleanly under Rh(II)-catalyzed conditions to afford the corresponding oxygen-bridged bicycle product in high yield (entries 1−3). High regioselectivity was obtained when cyclohexenone, 5,6-dihydropyran-2-one, vinylnitrile, and chalcone were used as dipolarophiles (entries 4−7). The regioselectivity and facial selectivity were established by NMR experiments. Only one diastereomer was isolated from *exo*-addition of the dipolarophile. Dimethylacetylene dicarboxylate also readily underwent cycloaddition to afford the desired product in 2:1 diastereomeric ratio (entry 8).

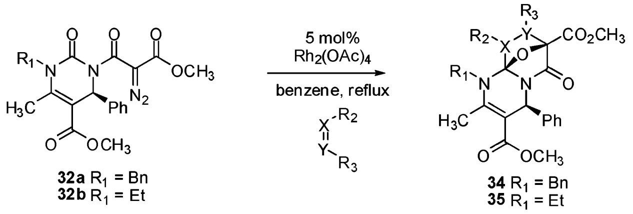
The use of methyl vinyl ketone as the dipolarophile resulted in the isolation of tertiary alcohol **36a** after silica gel column purification. Exposure of the crude cycloadduct to catalytic amounts of *p*-toluenesulfonic acid in CH_2Cl_2 resulted in the exclusive formation of tertiary alcohol **36a** in high yield (Table 9, entry 1). Dehydration for tertiary alcohols **36a** did not occur under acid-mediated condition possibly because it is difficult to build up the positive charge on the tertiary carbon attached with two electron withdrawing groups, ester and amide. The regioselectivity was confirmed *via* comparison of spectra data with similar compounds derived from dihydropyrimidone betaines.[35] This two-step sequence was successfully applied to other dipolarophiles. Methyl acrylate and acrylonitrile underwent cycloaddition smoothly and gave similar regioselectivities and high yields (entries 2 and 3). Benzalacetone and chalcone also yielded the corresponding tertiary alcohols in high diastereoselectivity (>20:1) (entries 4 and 5). The acid-catalyzed ring-opening conditions could also effect the ring opening of more stable bicyclic adducts derived from maleimide, cyclohexenone, and dihydropyranone (entries 6−9). In all cases, the tertiary alcohols were isolated in good yields (>73%).

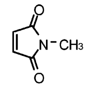
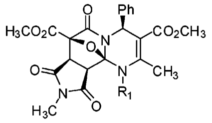
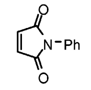
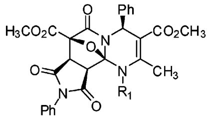
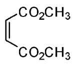
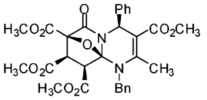
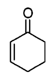
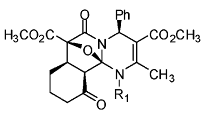
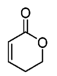
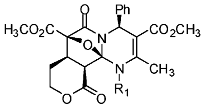
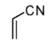
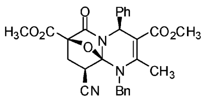
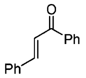
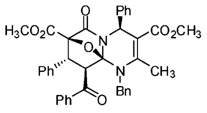
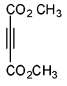
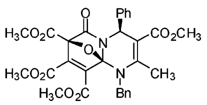
We next investigated the feasibility of intramolecular cycloaddition based on a dihydropyrimidone skeleton (Scheme 6). A β-methyl-substituted homoallylic alcohol **40** was synthe-

---

(36) (a) Kappe, C. O.; Fabian, W. M. F. *Tetrahedron* **1997**, *53*, 2803−2816. (b) Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, *56*, 1859−1862.

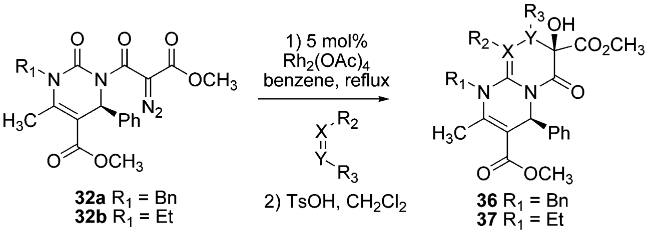
TABLE 8. Intermolecurlar Dipolar Cycloaddition Reactions[a]

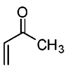
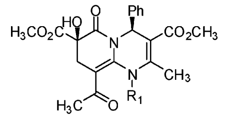
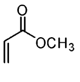
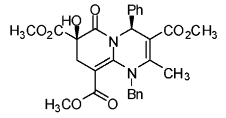
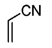
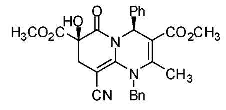
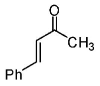
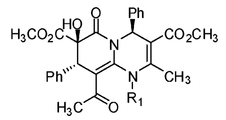
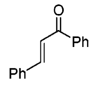
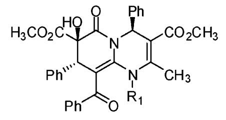
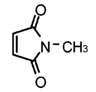
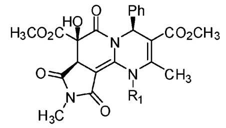
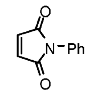
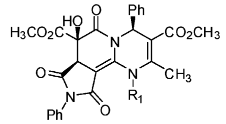
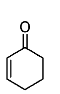
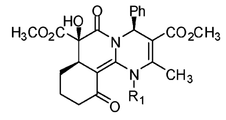
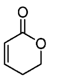
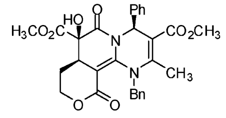


entry	dipolarophile	product	yield (%)[b]
1			**34a**(90) **35a**(93)
2			**34b**(88) **35b**(92)
3			**34c**(90)
4			**34d**(85) **35d**(83)
5			**34e**(86) **35e**(75)
6			**34f**(90)
7			**34g**(87)
8			**34h**(90) (dr = 2 :1)[c]

[a] Reactions were run with **32a** or **32b** (0.10 mmol) and $Rh_2(OAc)_4$ (2.5 mg) in benzene (2.0 mL) and reflux for 1 h, followed by flash chromatography on silica gel. [b] Yields of isolated products. [c] Determined by ^1H NMR.

TABLE 9. Cycloaddition and Oxo-Bridge Ring Opening[a]



entry	dipolarophile	product	yield (%)[b]
1			**36a**(90) **37a**(92)
2			**36b**(87)
3			**36c**(95)
4			**36d**(84) **37d**(65)
5			**36e**(95) **37e**(85)
6			**36f**(72) **37f**(74)
7			**36g**(72) **37g**(73)
8			**36h**(80) **37h**(76)
9			**36i**(73)

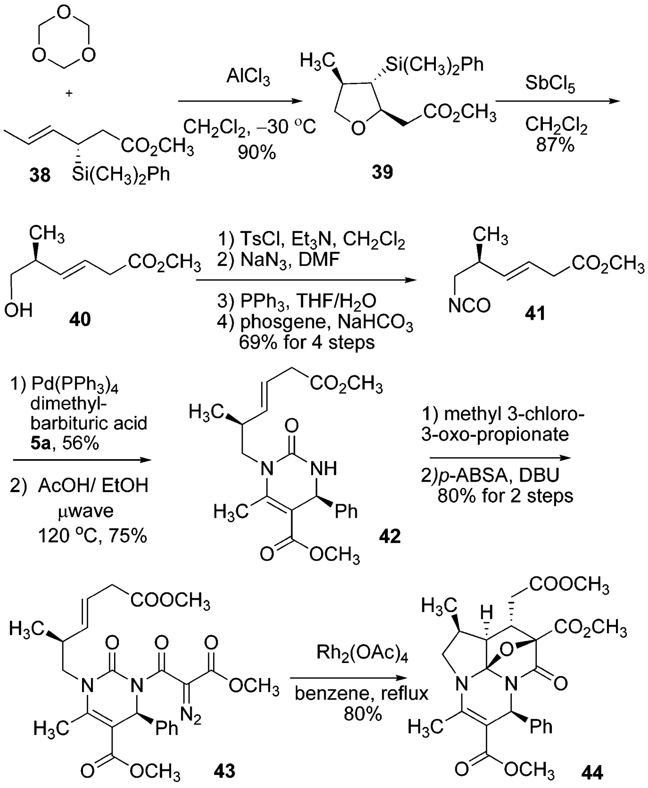
[a] Cycloaddition reaction crude mixture was filtered though a silica plug, concentrated *in vacuo*, and treated with TsOH (10 mol %) in CH_2Cl_2 (2.0 mL). The reaction solution was stirred overnight followed by flash chromatography on silica gel. [b] Yields of isolated products.

sized in two steps according to a reported procedure.[37] Selective condensation of 1,3,5-trioxane with chiral silane **38** provided tetrahydropyran **39** in 90% yield. Upon treatment with $SbCl_5$, tetrahydrofuran **39** underwent E_2-type elimination, providing homoallylic alcohol **40**. Subsequent formation of the tosylate followed by displacement with sodium azide afforded the corresponding homoallylic azide. The primary amine was obtained via a Staudinger reaction with use of a polymer supported triphenylphosphine in THF/H_2O. The isocyanate was obtained by treatment with phosgene under basic conditions. Dihydropyrimidone synthesis proceeded accordingly and construction of the dihydropyrimidone diazo amide **43** was obtained in reasonable yield after four steps. Finally, the cycloaddition

---

(37) Beresis, R.; Panek, J. S. *Bio. Med. Chem. Lett.* **1993**, *3*, 1609−1614.

SCHEME 6. Intramolecular Cycloaddition



reaction afforded the desired bicyclic adduct **44** in 80% yield and as a single diastereomer.

Conclusion

In summary, we have developed a general enantioselective Mannich reaction of β-dicarbonyls with α-amido sulfones as acyl imine precursors. The reactions were run under biphasic conditions requiring 10 mol % of the cinchona alkaloid catalyst and aqueous Na_2CO_3. We have obtained the reaction products in good yields and high enantioselectivities, and in diastereoselectivities that range from 1:1 to >99:1. A library of dihydropyrimidones was synthesized based on the cinchonine and cinchonidine-catalyzed Mannich reaction. Dipolar cycloaddition reactions were used to modify the dihydropyrimidone core and afforded highly functionalized complex, polycyclic structures. The use of the cinchona alkaloids as catalysts for the asymmetric Mannich reaction has proven effective at providing chiral building blocks for synthesis. As development of this asymmetric Mannich reaction continues, emphasis will be placed on the synthetic utility of the products obtained from the reaction. Ongoing investigations include the expansion of the current methodology and the use of chiral dihydropyrimidones in synthesis.

Experimental Section

General Procedure for Asymmetric Mannich Reaction of Dicarbonyls with α-Amido sulfones. A 25-mL one-necked round-bottomed flask equipped with a stir bar was charged with (+)-cinchonine (16.0 mg, 0.05 mmol), α-amido sulfone (0.50 mmol), and CH_2Cl_2 (5.0 mL). The solution was cooled to −15 °C. Dicarbonyl compound (1.50 mmol) and aqueous Na_2CO_3/NaCl (5.0 mL, 5 wt % Na Na_2CO_3 in deionized water saturated with NaCl) were sequentially added to the reaction mixture dropwise. The resulting biphasic solution was stirred at −15 °C for 48 h and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was quickly separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography over silica gel (elution with 15% to 40% EtOAc in hexanes) to afford the Mannich reaction products.

General Procedure for the Preparation of (*Z*)-Enamines (8a−p, 9a−*l*). An oven-dried 10-mL round-bottomed flask was charged with $Yb(OTf)_3$ (2.0 mg, 0.003 mmol), flamed dried under high vacuum, and purged with nitrogen. The flask was cooled to room temperature and charged with the β-ketone ester Mannich addition product (0.30 mmol). Trimethyl orthoformate (1 mL) and benzylamine (0.070 mL, 0.60 mmol) were sequentially added. The solution was stirred at room temperature under nitrogen for 4.0 h. The reaction mixture was subjected directly to flash chromatography over silica gel (elution with 15−20% ethyl acetate in hexanes) to give the enamines **8a−p** and **9a−*l***.

Characterization Data for Selected Compounds. (a) Methyl (*S*,*Z*)-4-(methoxycarbonyl)-5-(benzylamino)-1-phenylhex-4-en-3-ylcarbamate (8a): white solid; $[\alpha]^{23}_{D}$ −33.7 (*c* 1.0, $CHCl_3$); er 95:5; HPLC analysis, t_r major 14.5 min, t_r minor 18.0 min (ChiralcelOD-H column, hexanes:IPA = 98:2, 1.0 mL/min); ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, J = 6.0 Hz, 1H), 7.34 (m, 2H), 7.24 (m, 5H), 7.15 (m, 3H), 5.58 (d, J = 9.6 Hz, 1H), 4.46 (dd, J = 15.2, 9.6 Hz, 1H), 4.39 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H), 3.63 (s, 3H), 2.56 (t, J = 7.6 Hz, 2H), 2.14 (m, 1H), 1.95 (m, 1H), 1.93 (s, 3H). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 166.7, 157.8, 152.9, 142.1, 134.7, 125.1, 124.8, 124.7, 124.6, 123.7, 123.2, 122.0, 90.1, 48.1, 46.5, 45.7, 43.6, 33.4, 31.0, 18.9; IR (thin film, cm^{-1}) 3333, 3050, 2953, 1720, 1657, 1580, 1498, 1230, 1081; HRMS (CI/NH_3) *m/z* calcd for $(M + H)^+$ $C_{23}H_{29}N_2O_4$ 397.2049, found 397.2081.

(b) (*S*)-Allyl 4-acetyl-5-oxo-1-phenylhexan-3-ylcarbamate (14a): white crystals; $[\alpha]^{23}_{D}$ −56.2 (*c* 1.0, $CHCl_3$); er 95:5; HPLC analysis, t_r minor 9.4 min, t_r major 12.3 min (ChiralPakAD-H Column, hexane:IPA = 95:5, 1.0 mL/min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16−7.32 (5H), 5.90 (m, 1H), 5.61 (d, J = 10.2 Hz, 1H), 5.25 (m, 2H), 4.54 (m, 2H), 4.35 (m, 1H), 3.88 (d, J = 4.7 Hz, 1H), 2.74 (m, 1H), 2.61 (m, 1H), 2.24 (s, 3H), 2.10 (s, 3H), 1.96 (m, 1H), 1.74 (m, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 205.2, 203.8, 156.3, 141.1, 132.8, 128.8, 128.6, 126.4, 117.9, 69.6, 65.9, 50.8, 35.9, 33.0, 31.1, 30.1; IR (thin film, cm^{-1}) 3323, 1720, 1694, 1536, 1363, 1278, 1149, 1060, 700.

(c) Methyl (*R*)-2,2-di(methoxycarbonyl)-1-phenylethylcarbamate (18e): white solid; $[\alpha]^{23}_{D}$ −15.3 (*c* 1.0, $CHCl_3$); er 95:5; HPLC analysis, t_r major 9.2 min, t_r minor 12.7 min (ChiralcelOD-H column, hexanes:IPA = 95:5, 1.0 mL/min); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 6.39 (d, J = 8.4 Hz, 1H), 5.51 (dd, J = 8.4, 4.0 Hz, 1H), 3.92 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 168.6, 167.6, 156.6, 139.3, 128.9, 128.1, 126.4, 56.7, 54.2, 53.2, 52.8, 52.5; IR (thin film, cm^{-1}) 3387, 1720, 1500, 1220, 1130; HRMS (CI/NH_3) *m/z* calcd for $(M + H)^+$ $C_{14}H_{18}NO_6$ 396.1056, found 296.1065.

(d) *tert*-Butyl (*S*)-5-oxo-4-acyl-1-phenylhexan-3-ylcarbamate (23e): white solids; $[\alpha]^{23}_{D}$ −19.3 (*c* 1.0, $CHCl_3$); er 95:5; HPLC analysis, t_r major 8.5 min, t_r minor 6.1 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 5.40 (d, J = 10 Hz, 1H), 4.32 (br, 1H), 3.83 (d, J = 4.4 Hz, 1H), 2.81−2.55 (m, 2H), 2.22 (s, 3H), 2.09(s, 3H), 1.42 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 205.3, 204.0, 155.9, 141.3, 128.8, 128.5, 126.3, 79.8, 70.0, 50.3, 36.0, 32.9, 30.9, 30.2, 28.5; IR (thin film, cm^{-1}) 3446, 3390, 2951, 1720, 1650, 1591, 1499, 1453, 1253, 1193, 1090; HRMS (CI/NH_3) *m/z* calcd for $(M + H)^+$ $C_{19}H_{27}NO_4$ 334.1940, found 334.1973.

Acknowledgment. The authors acknowledge ThalesNano Nanotechnology, Inc. (Budapest, Hungary) for H-Cube instrumentation support. Assistance was provided by CEM Corporation (Matthew, NC) with microwave instrumentation and Symyx, Inc. (Santa Clara, CA) with chemical reaction planning software. The authors thank ChemAxon (Budapest, Hungary), Molinspiration Cheminformatics (Slovak Republic), and OpenEye Scientific Software (Santa Fe, NM) for academic software support. S.L. gratefully acknowledges a graduate research fellowship from Merck Research Laboratories−Boston. This research was supported by a gift from Amgen, Inc., an NSF CAREER grant (CHE-0349206), and the NIH (P50 GM067041 and P41 GM076263).

Supporting Information Available: Experimental procedures for synthesis of chiral dihydropyrimidones, flow hydrogenation, and [3+2] dipolar cycloadditions, characterization data for compounds **8a**−**p**, **9a**−***l***, **12a**−**c**, **14a**−**f**, **18a**−**g**, **19a**−**c**, **21a**−**c**, **23a**−**e**, dihydropyrimidone library members, tetrahydropyrimidones library members, **34a**−**h** and **36a**−**i**, chiral HPLC analysis for the Mannich reaction products, and HPLC/UV/ELSD/MS data for the representative library members. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701777G