Organocatalysis

DOI: 10.1002/ange.200801811

Asymmetric Catalysis: Resin-Bound Hydroxyprolylthreonine Derivatives in Enamine-Mediated Reactions**

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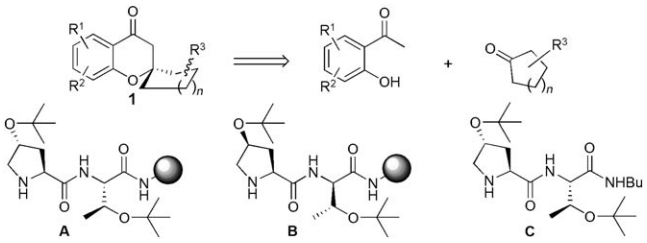
Control of relative and absolute stereochemistry with step-economy[1,2] presents a continuing challenge in organic synthesis.[3] Asymmetric crossed aldols have historically involved chiral auxiliaries or O-trapped organometallic intermediates; the latter operate by either a Zimmerman–Traxler or an open transition-state model.[4] However, auxiliaries lengthen syntheses, and organometallics typically require careful control of reaction conditions and have limited functional-group tolerance. Enamines, however, predominantly react at the C-terminus, and generally deliver products under ambient reaction conditions.[3] The C_2-symmetric *trans*-2,5-dimethylpyrrolidine reagent is used in asymmetric enamine reactions. However, it suffers from poor efficacy and is scarce. Although several asymmetric syntheses exist for the preparation of this reagent,[5] its limited commercial availability suggests that these lengthy protocols have not impacted supply.[6]

This problem has been somewhat alleviated by proline-derived organocatalysts, which have been under intense investigation in recent years and discussed in reports from the groups of Yamamoto[7] and Miller.[8] Reactions of supported (both hetero- and homogeneous)[9] and non-supported[10] organocatalysts have been reviewed. When applied to aldol condensations, heterogeneous supported organocatalysts often require high catalyst loading[11] and long reaction times,[12] while delivering varied enantioselectivities.[11–13] Non-supported organocatalysts often require extended reaction times,[14] have strict solvent requirements,[15] and produce variable yields.[16]

The group of Chandrasekhar was the first to use L-proline to prepare chromanones (**1**; Scheme 1)[17] in a method requiring the use of DMF, owing to the zwitterionic nature



Scheme 1. a) Retrosynthetic analysis of chromanones (**1**) and the structures of resin-bound catalyst **A**, its diastereomer **B**, and, the off-resin analogue of **A**, catalyst **C** (spheres represent Tentagel resin).

of proline.[18] Chromanones are medicinally pertinent heterocycles[19] and the chroman parent system has been found in natural products such as sappone B[20] and robustadial,[21] in addition to being a bioisostere for the hydantoin moiety.[22] Indeed, chromanones have many biomedical applications and, consequently, have received considerable synthetic attention.[23] The laboratories of Enders, McKervey, and Scheidt have reported asymmetric preparations of chromanones, however these routes have modest enantioselectivity,[24] and require advanced precursors.[25,26]

Clearly, there is a need to develop a practical asymmetric route to optically active chromanones and to advance asymmetric solid-phase catalysts for enamine-mediated reactions. Herein, we focus on TentaGel-bound (TG-bound) catalysts to facilitate recoverability and reusability as well as to expedite syntheses through microwave-assisted reactions.[27,28] We report the synthesis of resin-bound asymmetric pyrrolidine catalysts **A** and **B** (see Scheme 1), with applications toward the syntheses of optically active chromanones as well as other enamine-derived molecular targets.

The development of catalyst **A** is outlined in Table 1. Each catalyst (**A**, **D**–**G**) is bound to TentaGel resin, which was chosen for its relative inertness and hydrophilicity. The catalysts are prepared rapidly by solid-phase peptide synthesis.[29,30a] For catalyst evaluation, the starting materials, solvent, and relative quantity of catalyst (1 mol%) were held constant as the catalyst, temperature, and reaction time were varied. After the time indicated, all the samples were subjected to microwave irradiation for 11 min at 110°C.[31] Table 1, Entry 7 shows the reaction conditions and catalyst (catalyst **A**) yielding the highest enantiomeric excess (*ee*).[30b] An increase in *ee* is detected as substituents are altered from

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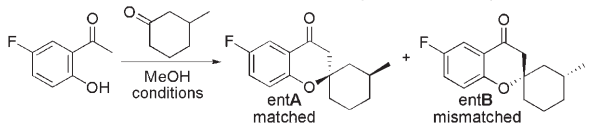
[**] This work was supported by the National Science Foundation (NSF; CHE-0614756) and the National Institute for General Medical Sciences (GM076151). NMR spectrometers used in this work were funded in part by the NSF (CHE-0443516 and CHE-9808183). RDC thanks the American Chemical Society's Division of Medicinal Chemistry for Predoctoral Fellowship support (sponsored by Sanofi-Aventis), the Howard Hughes Medical Institute for their Med into Grad Fellowship, and UC Davis for their R. Bryan Miller Graduate Fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200801811.

Table 1: Reaction conditions for the development of catalyst **A**

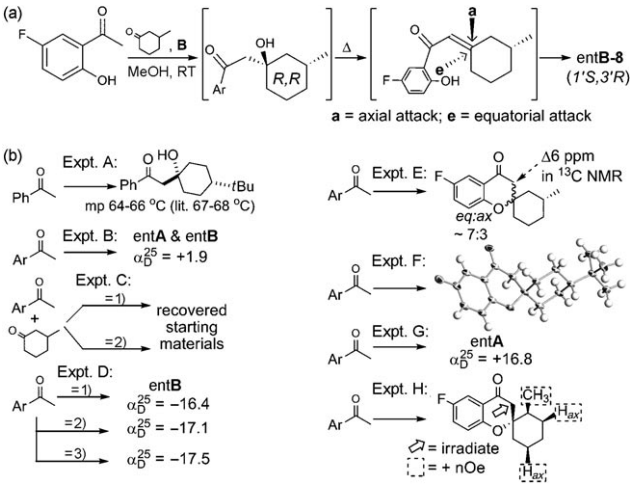


Entry	Catalyst[a]	T [°C]	t [h][b]	Yield [%]	ent**A**:ent**B**[c]
1	Pro-Phe-TG (**D**)	0	8	–	–
2	Pro-Phe-TG (**D**)	25	1	80	60:40
3	Pro-Ile-TG (**E**)	25	3	68	65:35
4	Pro-Ser(*t*Bu)-TG (**F**)	25	1	83	83:17
5	Hyp(*t*Bu)-Ser(*t*Bu)-TG (**G**)	25	1	86	70:30
6	Hyp(*t*Bu)-Thr(*t*Bu)-TG (**A**)	10	4	78	94:6
7	Hyp(*t*Bu)-Thr(*t*Bu)-TG (**A**)	25	1	86	98:2
8	Hyp(*t*Bu)-Thr(*t*Bu)-TG (**A**)	50	0.5	89	74:26

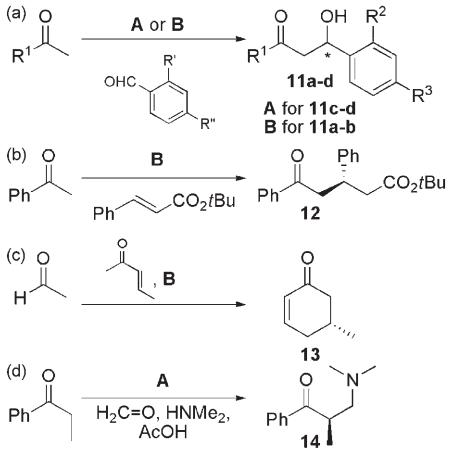
[a] All TG-bound catalysts give ent**A**/ent**B** with complete diastereoselectivity. [b] Each reaction was heated under microwave irradiation for 11 min at 110°C. [c]Ratio determined by chiral HPLC analysis[30b]

benzyl (amino acid Phe) to *sec*-butyl (Ile) to a linear *tert*-butyl-ether [Ser(*t*Bu)] to a branched *tert*-butyl-ether [Thr(*t*Bu)]. Another increase in *ee* is detected when 2-carboxamidopyrrolidine (Pro) is substituted with the bulkier *trans*-4-*tert*-butoxy-2-carboxamidopyrrolidine [Hyp(*t*Bu)]. The positioning of both sterically encumbering branched *tert*-butyl ethers on the α face allows the β face to react faster with the (*S*)-enantiomer of *rac*-3-methylcyclohexanone (2 equiv) at room temperature. The optimal range for kinetic resolution is within ±10°C of room temperature. If cooled further (Table 1, Entry 1), the enamine does not react with the ketone, and starting materials are recovered. If warmed to 50°C (Table 1, Entry 8), kinetic resolution is reduced.

A series of experiments, given in Scheme 2, were designed to determine the likely sequence of events in this tandem aldol/Michael reaction. The catalyst and acetophenone produce a resin-bound enamine, which undergoes diastereoselective equatorial attack[32a] onto the substituted cycloalkanone to yield a β-hydroxyketone (Expt. A; a known compound[33]). Room-temperature kinetic resolution was confirmed by the drastic reduction in *ee* when the reaction mixture is heated immediately with the catalyst (Expt. B). Heating without the catalyst (Expt. C) only resulted in recovery of starting materials. Use of the matched (*R*)-3-methylcyclohexanone yielded an identical result as did changing the catalyst (from **B** to **A**) prior to heating (Expt. D). Heating the reaction mixture without the catalyst resulted in reduced diastereoselectivity (equatorial:axial) for the phenoxy Michael addition (Expt. E).[21] Complete diastereoselectivity is obtained with catalyst **B** (as well as with catalyst **A**) suggesting that it functions as either a base or an α,β-unsaturated iminium species. Equatorial preference was confirmed by X-ray crystallography (Expt. F). Interestingly, an off-resin derivative of catalyst **A** (**C**; see Scheme 1) requires 10 mol% for comparable efficacy (Expt. G). Positive nOes confirm a *trans* relative configuration between the ether oxygen and 2-methyl moieties (Expt. H).[30c] The catalyst is recovered by filtration, and has been redeployed over forty times without loss of efficiency or turnover. This durability



Scheme 2. a) Following enantioselective enamine attack to give a single β-hydroxy ketone (e.g., *R,R* with **B**), subsequent heating yields an enone which undergoes diastereoselective equatorial Michael additon. b) Various experiments performed to investigate the mechanism to enantiopure chromanones where Ar = 5-F-2-HOC$_6$H$_3$: Expt. A: **B**, 4-*t*Bu-*c*-C$_6$H$_9$O RT, 2 h; Expt. B: **B**, 3-Me-*c*-C$_6$H$_9$O, Δ; Expt. C: 1) Δ; ΔΔ; Expt. D: 1) **B**, 3-Me-*c*-C$_6$H$_9$O, RT, 1 h; then Δ; 2) **B**, (*R*)-3-Me-*c*-C$_6$H$_9$O, RT, 1 h; then Δ; 3) **B**, 3-Me-*c*-C$_6$H$_9$O, RT, 1 h; filter **B**, add **A**; then Δ; Expt. E: 3-Me-*c*-C$_6$H$_9$O, RT, 1 h, filter **B**, then Δ; Expt. F: **B**, 4-*t*Bu-*c*-C$_6$H$_9$O, RT, 1 h, then Δ; Expt. G: Hyp(*t*Bu)Ser(*t*Bu)C(O)NHBu (**C**), 3-Me-*c*-C$_6$H$_9$O, RT, 1 h; Δ; Expt. H: 2-Me-*c*-C$_6$H$_9$O, RT, 1 h, then Δ.

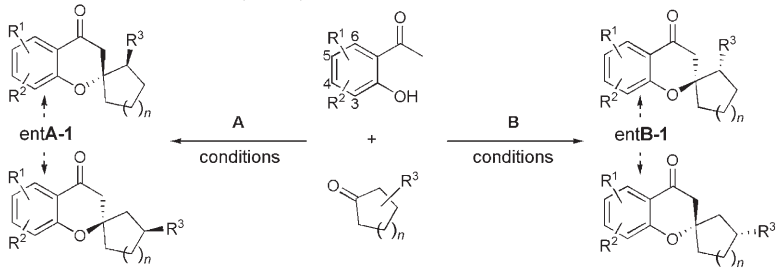


(e)

Cpd	$R^1/R^2/R^3/*$	% Yield	% *ee*
11a	Ph/Cl/H/(*S*)	68	94
11b	Ph/H/H/(*S*)	76	98
11c	Me/H/NO_2/(*R*)	79	95
11d	Me/H/Br/(*R*)	65	96
12	--	82	97
13	--	69	91
14	--	85	98

Scheme 3. Aldol, Michael, Robinson annulation, and Mannich reactions demonstrating the utility of catalysts **A** and **B**. Reaction conditions a) RT, 3-4 h; b) 0°C to RT, 6 h; c) 0°C to RT, 6 h, then microwave irradiation, 11 min, 110°C; d) RT, 5 h. e) Catalysts **A** and **B** can control α–δ stereocenters.

Table 2: Chromanones delivered by catalysts **A** and **B**.[a]



R^1, R^2		R^3	Catalyst	Product	Yield [%]	*ee* [%][b]	$[\alpha]_D^{25}$
4-OEt	$-CH_2CH(R^3)(CH_2)_2-$	CH_3	**A**	entA-**2**	78	97	+57.6
			B	entB-**2**	83	99	−56.8
4-OMe	$-CH_2CH(R^3)(CH_2)_3-$	CH_3	**A**	entA-**3**	71	95	−17.1
			B	entB-**3**	77	96	+16.8
4-F	$-CH_2CH(R^3)(CH_2)_3-$	CH_3	**A**	entA-**4**	83	94	+61.9
			B	entB-**4**	81	98	−62.5
$6\text{-}OCH_3$	$-CH_2CH(R^3)(CH_2)_2-$	CH_3	**A**	entA-**5**	86	93	−80.1
			B	entB-**5**	89	98	+80.4
5-Et	$-CH_2CH(R^3)(CH_2)_2-$	CH_3	**A**	entA-**6**	90	95	+33.9
			B	entB-**6**	83	97	−33.2
4-OEt	$-CH(R^3)(CH_2)_4-$	CH_3	**A**	entA-**7**	76	92	+49.9
			B	entB-**7**	80	95	−49.4
5-F	$-CH(R^3)(CH_2)_4-$	CH_3	**A**	entA-**8**	82	90	−57.3
			B	entB-**8**	87	93	+56.6
$5,6\text{-}(CH)_4$	$-CH(R^3)CH_2O(CH_2)_2-$	H	**A**	**9**	74	–	–
			B	**9**	70	–	–
5-Cl	$-CH(R^3)CH_2NAc(CH_2)_2-$	H	**A**	**10**	89	–	–
			B	**10**	94	–	–

[a] Catalyst (**A** or **B**), MeOH, RT, then microwave irradiation, 110°C, 11 min. The reaction gives complete diastereoselectivity and generally high enantioselectivity. [b] Percentage determined by chiral HPLC analysis.

can be attributed to neutral reaction conditions, limited heating time, and washing the resin with MeOH following filtration. Results of the syntheses of sampled chromanones are outlined in Table 2, with the 2- and 3-methyl groups being respectively *trans* and *cis* to the resultant ether (for full experimental data, see Supporting Information).[32b] This method is also effective at delivering the unreacted 3-methylcycloalkanone enantiomer with an average of 97% *ee* and 40% recovery providing facile access to enantioenriched 3-substituted cycloalkanones.[30d]

In preliminary assays, catalysts **A** and **B** were employed in a series of aldol, Michael, Robinson annulation, and Mannich reactions to deliver known compounds (Scheme 3).[34] In general, these catalysts were compatible with a variety of substrates, underwent addition at ambient temperatures in 3-6 h, and provided **11**–**14** in moderate to good yields with high *ee*.[35] Heating, either by conventional or microwave methods, is generally required for dehydration and cyclization, as demonstrated by the reactions outlined in Table 2 and in Scheme 3c. Catalysts **A** and **B** also exhibit stereochemical control of the α–δ centers, as summarized in Scheme 3e.

In summary, efficient pyrrolidine TG-bound catalysts have been developed that kinetically resolve a variety of substrates at ambient temperatures and with short reaction times. The catalysts are simple to prepare, easily recovered, and can be reused several times. These catalysts were utilized in a variety of enamine-mediated reactions with high facial selectivity and tolerate a variety of functional groups. Alternatively, the unreacted 3-substituted cycloalkanones are obtained with high optical purity, providing facile access to versatile synthetic precursors from readily available racemic starting materials.

Received: April 17, 2008
Published online: July 15, 2008

Keywords: asymmetric catalysis · heterocycles · heterogeneous catalysis · solid-phase synthesis · stereoselectivity

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