Organocatalysis

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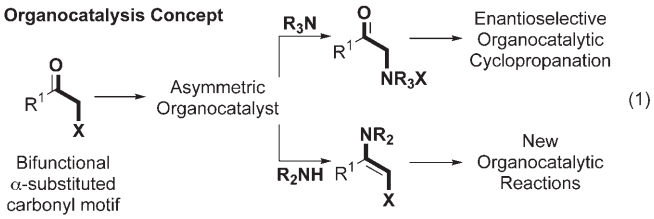
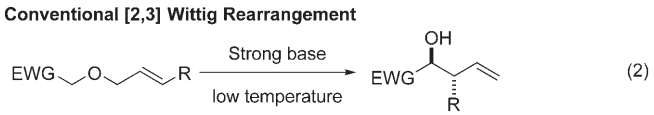
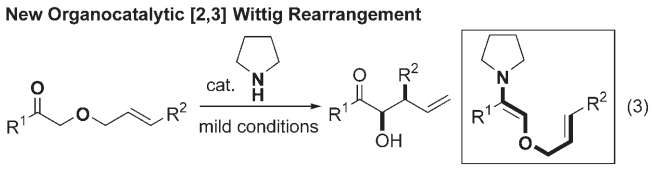
Organocatalytic Sigmatropic Reactions: Development of a [2,3] Wittig Rearrangement through Secondary Amine Catalysis**

*Andrew McNally, Brian Evans, and Matthew J. Gaunt**

Sigmatropic rearrangements represent a fundamental method for the installation of molecular complexity in organic molecules.[1] Both the [2,3] and [3,3] variations have found widespread use in the chemical synthesis of natural products and medicinal agents. Because of the importance of these reactions, the development of asymmetric methods for sigmatropic rearrangements has attracted significant interest from the synthetic community.[1,2] Over recent years, there has been a number of new advances in catalytic and enantioselective [3,3] Claisen type transformations;[3] however, there are few general catalytic methods for the corresponding [2,3] Wittig rearrangement.[4] Our efforts towards the development of novel organocatalytic reactions that exploit catalyst-induced new reactivity in bifunctional α-substituted carbonyl compounds [Eqs. (1)–(3)][5] led us to envision that







sigmatropic rearrangements could be developed through such a strategy. Herein, we describe a new organocatalytic [2,3] Wittig rearrangement by secondary amine catalysis through the intermediacy of an enamine [Eqs. (2) and (3)]. The new process operates under ambient and operationally simple conditions and also precludes the use of strong bases often required in conventional [2,3] Wittig rearrangements. Furthermore, this organocatalytic transformation provides an important platform for the development of a catalytic enantioselective [2,3] rearrangement.[6,7]

At the outset of this study, the catalytic rearrangement strategy was tested on ketone **1a** using 20 mol% pyrrolidine (**2a**) as the catalyst. We found that the rearrangement was effected in a range of solvents, although these reactions resulted in varying conversions as an equal mixture of *syn* and *anti* diastereomers (Table 1, entries 1–9). The reaction in methanol, however, showed complete conversion after 30 minutes and favored the formation of the *syn* isomer **3a** (d.r. = 3:1; Table 1, entry 10).[8a] This is notable as it displayed the opposite selectivity to reactions in all solvents tested, and the formation of the *syn* isomer is contrary to the conventional [2,3] Wittig rearrangement in which *E* alkenes generally form the *anti* isomer [Eq. (2)].[8b]

The influence of temperature was investigated next, and higher diastereoselectivities were achieved at lower temperatures (Table 1, entries 10–14). Complete conversion was observed at −5 °C, with a d.r. of 6.5:1 (**3a**/**4a**); however, the selectivity can be increased to 10:1 at −25 °C though the reaction was slower but still reached complete conversion after reaction for 90 h. The concentration of the reaction did

[*] A. McNally, Dr. M. J. Gaunt
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge, CB21EW (UK)
Fax: (+44) 122-333-6362
E-mail: mjg32@cam.ac.uk
Dr. B. Evans
GSK Medicines Research Centre
Gunnels Wood Road
Stevenage, Herts, SG1 2NY (UK)

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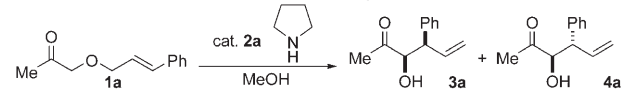
Table 1: Effect of solvent and temperature on the reaction.



Entry	Solvent	Catalyst loading	Conc. [M]	T [°C]	Conv. [%][a]	t [h]	d.r. (**3a**:**4a**)
1	PhMe	20	0.5	23	40	24	1:1.5
2	Et_2O	20	0.5	23	90	24	1:1
3	MeCN	20	0.5	23	60	24	1:1
4	THF	20	0.5	23	75	24	1:1.5
5	EtOAc	20	0.5	23	50	24	1:1.5
6	$CHCl_3$	20	0.5	23	90	24	1:1
7	DMSO	20	0.5	23	30	24	1:1
8	DMF	20	0.5	23	50	24	1:1
9	MeOH	20	0.5	23	100	0.5	3:1
10	MeOH	20	0.5	5	100	12	4:1
11	MeOH	20	0.5	−5	100	24	6.5:1
12	MeOH	20	0.5	−10	90	24	7:1
13	MeOH	20	0.5	−25	70[b]	24	10:1
14	MeOH	20	0.125	−5	100	24	6.5:1
15	MeOH	5	0.5	−5	100	96	8:1
16	MeOH	0	0.5	23	0	96	nr

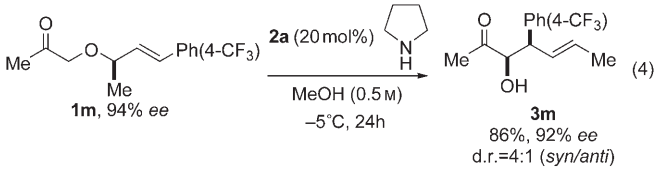
[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Conversion = 100% at 90 h. nr = no reaction. DMF = dimethylformamide, DMSO = dimethyl sulfoxide.

not significantly affect the rearrangement (Table 1, entry 14). However, the catalyst loading could be decreased, and with 5 mol% of **2a** the reaction reached completion in 96 h with a slightly improved d.r. of 8:1 at −5 °C (Table 1, entry 7).[9,10] No reaction is observed in the absence of **2a** (Table 1, entry 16). The ^{1}H NMR spectra of the crude reaction mixtures showed only the rearranged product, and in contrast to many other [2,3] sigmatropic reactions there was no sign of the competing [1,2] rearrangement product.[1b] These results demonstrate that the new organocatalytic [2,3] rearrangement was readily effected under mild and operationally simple conditions, and we believe this represents the first example of such a process.

A proposed mechanism for the reaction is shown in Scheme 1. Formation of an iminium ion is followed by tautomerization to the corresponding enamine, and the rearrangement possibly proceeds via the *syn* transition state (*syn* TS) to form **3a** after hydrolytic release of the catalyst.[11] The requirement of methanol as the solvent to attain good diastereoselectivity suggests that the protic solvent influences the rearrangement through a hydrogen-bonding interaction with the ether oxygen atom, thus stabilizing the developing negative charge and thereby accelerating the rearrangement. Interestingly, however, the reaction seems to have a narrow tolerance to the acidity of the solvent. In the presence of trifluoroethanol or using the HCl salt of **2a**, the reaction is severely retarded or nonexistent in the respective cases. The assistance of Brønsted acids as additives in catalytic reactions has been well documented,[12] and they have recently been successfully employed as cocatalysts in organocatalytic processes.[9] We are currently investigating whether such additives can further influence the rearrangement.

The scope of the organocatalytic [2,3] Wittig rearrangement was evaluated first by studying the effect of the substituent at the ketone carbonyl group in **1**. Table 2 shows the results of reactions that were optimized to reach completion within 24 hours at the given temperature. The diastereoselectivity of the rearrangement can be improved at lower temperatures, although with increased reaction times. The new reaction worked for a range of simple ketones and gave rearranged products in excellent yields of the isolated products and good diastereoselectivity (Table 2, entries 1–6). The alkene substituents were also varied (Table 2, entries 7–14), and electron-rich or -deficient aromatic groups could be used to good effect (Table 2, entries 7–9). Substrates containing trisubstituted alkenes, 1,3-dienes, and enynes readily reacted to form rearranged products in good yield (Table 2, entries 10–12). Products with a quaternary center were also formed in good diastereoselectivity from the corresponding trisubstituted alkene, thus expanding the scope and utility of the organocatalytic [2,3] rearrangement strategy (Table 2, entry 13). Finally, as a surrogate to the crotyl group, an allylsilane substrate (Table 2, entry 14) rearranged smoothly, and the resulting product could be readily converted into the desired propionate motif through desilylation.[13] In all cases, the *syn* isomer **3** was observed as the major product and the assignment was based on analogy to the proven stereochemistry of **3a**.[8a]

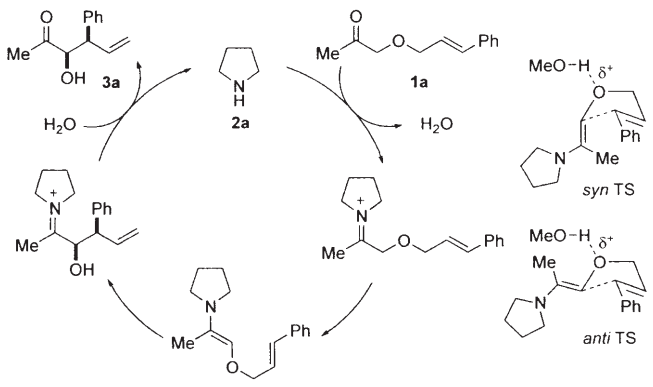
With an effective diastereoselective catalytic reaction in hand, we investigated a chirality transfer process in the organocatalytic [2,3] rearrangement. Methyl ketone **1m** (94% *ee*)[14] rearranged to **3m** and maintained the enantiomeric excess of the starting ketone [Eq. (4)]. This result



(4)

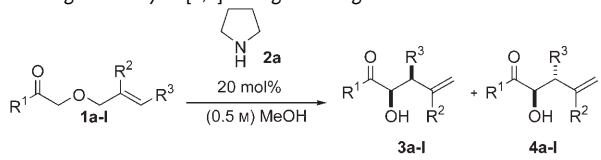
strongly suggests that the rearrangement proceeds through the conventional concerted mechanism as opposed to a stepwise ionic pathway. Moreover, an effective chirality transfer process represents an useful extension to this new catalytic methodology.

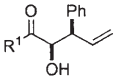
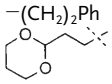
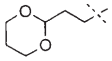
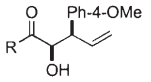
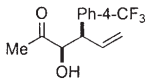
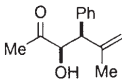
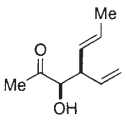
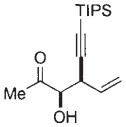
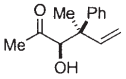
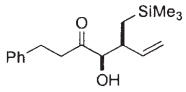
To investigate the potential of a catalytic asymmetric process, we tested the reaction with a chiral secondary amine



Scheme 1. Proposed mechanism of the rearrangement.

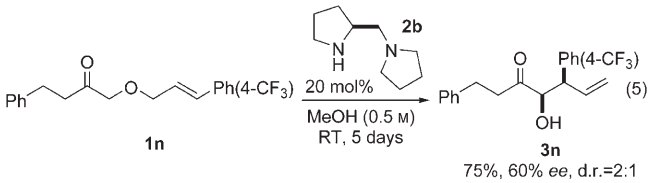
Table 2: Scope of the organocatalytic [2,3] Wittig rearrangement.[c]



Entry	R^1	R^3	Product		t [h]	T [°C]	Yield [%][b]	d.r. (**3**:**4**)
1	Me	Ph		**3a**	24	−5	84	6.5:1
2	Me	Ph		**3a**	24	−8	96	4:1
3	Et	Ph		**3b**	72	−15	92	6:1
4	$-(CH_2)_2Ph$	Ph		**3c**	24	−10	86	3:1
5		Ph		**3d**	24	−8	90	4:1
6		Ph		**3d**	72	−15	86	5:1
7	Et	4-OMePh		**3e**	24	−8	91	7:1
8	Me	4-OMePh		**3f**	24	−8	88	5:1
9	Me	4-CF_3Ph		**3g**	24	−12	90	4.5:1
10	Me	R^2 = Ph		**3h**	24	−8	73	2:1
11	Me			**3i**	24	5	82	3.5:1
12	Me			**3j**	24	23	84	1:1
13	Me	Me, Ph		**3k**	72	23	55	4:1
14	$-(CH_2)_2Ph$	$-CH_2SiMe_3$		**3l**	24	23	85	4:1

[a] R^2 = H for all entries, except entry 10, in which R^2 = Me. [b] Yield of the isolated product after chromatography.

catalyst. Diamine **2b** catalyzed the reaction and afforded the rearranged product **3** in 60% *ee* for the *syn* isomer **3g** [Eq. (5)].[15] To the best of our knowledge, this reaction is the first organocatalytic enantioselective [2,3] Wittig rearrangement and represents an exciting lead towards the development of a catalytic enantioselective process. Towards this end, we are currently designing catalysts that will control both the enantio- and diastereoselectivity of this reaction.



In summary, we have developed a new organocatalytic [2,3] Wittig rearrangement through secondary amine catalysis. This process displays a broad substrate scope and proceeds with good diastereoselectivity. The reaction conditions are remarkably mild, and the transformation is operationally simple to perform. We have also identified that allylic transposition of chirality can be achieved with an existing chiral centre and most importantly that a chiral pyrrolidine effects an organocatalytic enantioselective sigmatropic rearrangement. This process provides a platform for the further development of this reaction and related catalytic enantioselective rearrangement processes; these studies will be reported in due course.

Experimental Section

General Procedure: A precooled solution of pyrrolidine (20 mol%) in methanol (2 mL) was added to **1** (1 mmol), and the reaction mixture was stirred at the described temperature for the time stated. The reaction was quenched after completion with aqueous solution of hydrochloric acid (0.1M, 2 mL), and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with an aqueous saturated solution of sodium bicarbonate (10 mL), an aqueous saturated solution of brine (10 mL), dried over $MgSO_4$, and filtered. The resulting filtrate was concentrated in vacuo, and the crude product was purified by flash column chromatography on silica gel.

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[9] Interestingly, we see a slightly improved diastereoselectivity in the rearrangements with a lower catalyst loading, and we also observed slight changes in diastereoselectivity as the reactions approached completion. We propose that as the reaction approaches completion with higher catalyst loadings partial epimerization takes place at the α-position because of increased change of reformation of the iminium adduct of **3**. This behavior has been observed in enamine-based conjugate-addition processes; see: T. J. Peelan, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598.

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