A highly selective, organocatalytic route to chiral 1,2-oxazines from ketones

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A sequential, organocatalysed asymmetric reaction to access chiral 1,2-oxazines from achiral ketone starting materials is reported, which proceeds in moderate to good yields and excellent enantioselectivity.

One of the important goals in chemistry is to develop stereoselective transformations which generate useful structural components present in biologically active natural products.[1] Similarly, finding efficient ways of selectively preparing certain heterocyclic systems still provides a significant challenge in organic chemistry. Enantiopure 1,2-oxazines are potentially useful target heterocycles as they can be further derivatised into various useful groups by straightforward chemistry.[2]

Previously, two routes to this class of molecule have been predominant. They are the [4 + 2] cycloaddition between nitroso compounds and dienes, and the ring closing metathesis of suitable alkene precursors. However, the reaction of nitroso compounds with dienes can suffer from poor regiocontrol and the products are racemic without control induced by chiral substituents[3] or chiral auxiliaries.[4] These asymmetric methods also have a very limited substrate scope, generating only certain substitution patterns. Ring closing metathesis is more general and supplies useful regio- and stereocontrol. However, this must be imparted from particular chiral starting materials.[5]

We have recently demonstrated an efficient new route to chiral dihydro-1,2-oxazines from commercially available *achiral* aldehydes with excellent enantioselectivity using pyrrolidinyl-tetrazole **1a** as an organocatalyst in a tandem reaction sequence (Scheme 1).[6] The transformation involves an asymmetric organocatalytic α-oxyamination[7] with nitrosobenzene and the catalyst, using conditions similar to those developed by Zhong,[7a] to afford an intermediate which undergoes conjugate addition to a vinylphosphonium salt. The resulting ylide cyclises to the dihydro-1,2-oxazine *via* an intramolecular Wittig process[8] (Scheme 2).
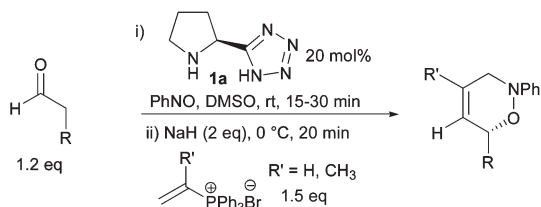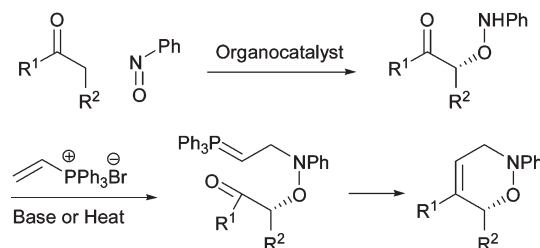
The use of pyrrolidinyl-tetrazole **1a** as a catalyst for this process was based on its improved properties when compared for example to L-proline. As with other chemistries developed independently by ourselves,[9] Yamamoto[10] and Arvidsson[11] where **1a** was an especially effective catalyst,[7f,g] it also proved to be the compound of choice in this work.

The initial conditions that we had developed previously for aldehydes,[6] however, were disappointingly ineffective when applied to ketonic substrates. As this was a severe limitation, we have devised a new protocol which is reported herein to solve this problem.

Firstly, the conditions employed for the α-oxyamination step were similar to those used by Yamamoto.[7g] These, crucially, use a much smaller excess of ketone (3 eq) such that the subsequent steps may be carried out in a single pot. Another benefit of these conditions was the use of reduced catalyst loading (5 mol%). It is also worth noting that slow addition of nitrosobenzene to a mixture of ketone and the pyrrolidinyl-tetrazole catalyst was necessary to minimise the formation of the homodimer of nitrosobenzene. However, the sequential Wittig process became problematic. The optimisation study was then centred on the cyclisation step from the α-oxyamination intermediates of cyclohexanone and butan-2-one (Table 1). After several bases, Wittig reagents and solvent systems had been investigated, the reaction from butan-2-one was found to be optimal by the use of KH as a base. A mixed solvent system (1 : 1 THF/DMSO) also noticeably increased the yield (Entry 15, Table 1). Moreover, these conditions facilitate the tandem nature of the reaction as the α-oxyamination step was carried out in DMSO. Remarkably, an excess of KH did not cause racemisation of the stereogenic centre generated during the α-oxyamination process (99% ee).

The absolute configuration of both the α-oxyaminated ketone intermediates and oxazine products was determined by correlation with the α_D values found from the analogous reactions using L-proline as catalyst.

Armed with this information, the scope of the ketone substrates (**7a–e**) was then investigated using catalyst **1a** (Table 2). We were

Scheme 1 Synthesis of dihydro-1,2-oxazines from aldehyde substrates.

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Scheme 2 Projected synthesis of chiral 1,2-oxazines.

Table 1 Optimisation reactions for the sequential Wittig step

Entry	2	Base	Solvent	Temp. (°C)	3	Product	Entry	2	Base	Solvent	Temp. (°C)	3	Product
1[12]	2a	—	MeCN	85	3a	5 (8%)[a]	9	2b	1.1 eq NaH	THF	0 → rt	3a	—
2	2a	1.1 eq NaH	THF	0 → rt	3a	5[b]	10	2b	1.1 eq NaH	DMF	0 → rt	3a	—
3	2a	1.1 eq ^{n}BuLi	THF	−78	3a	—	11	2b	1.8 eq NaH	THF	0 → rt	3a	4b (13)[a]
4	2a	1.1 eq NaH	DMF	rt	3a	—	12	2b	2.0 eq NaH	THF	0 → rt	3a	4b (28)[a]
5	2a	2.0 eq NaH	THF	0 → rt	3a	5[b]	13	2b	2.0 eq NaH	THF	0	3a	4b (29)[a]
6[13]	2a	1.3 eq NaH	DMSO	0 → rt	3a	—	14	2b	3.0 eq KH	THF	0	3a	4b (48)[a]
7[12]	2b	—	MeCN	85	3a	6a[b]	15	2b	3.0 eq KH	THF/DMSO	0	3a	4b (71)[a]
8[14]	2b	—	MeOH	20	3b	6b[b]							

[a] Isolated yields of material after chromatography. [b] Detected by crude ^{1}H NMR.

Table 2 Synthesis of 1,2-oxazines catalysed by L-pyrrolidinyl-tetrazole
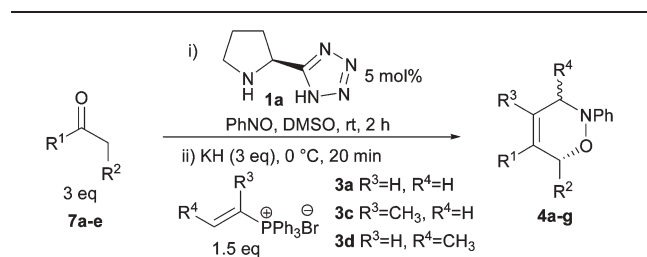
Entry	Ketone	3	1,2-Oxazine	Yield[a] (ee)[b] %
1	7a	3a	4a	60 (99)
2	7c	3a	4c	33 (99)
3	7d	3a	4d	51 (99)
4	7e	3a	4e	50 (99)
5	7b	3a	4b	46[c] (99)
6	7a	3c	4f	39 (99)
7	7a	3d	4g	65 (99)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC. [c] Reaction of 20 eq of 7b was conducted with 20 mol% of 1a.

pleased to find that the reaction conditions developed were indeed applicable to a range of ketones (3 eq) using just 5 mol% catalyst, to give moderate to good yields of product and excellent ee's throughout.† In only one case (Entry 5, Table 2), that of the linear butan-2-one substrate, was it necessary to use a higher excess of ketone (20 eq) and catalyst (20 mol%).

The use of more substituted vinylphosphonium bromide 3c in this reaction gave the tetrasubstituted 1,2-oxazine 4f (Entry 6, Table 2). It is also of note that the 1,2-oxazine 4g was generated with complete diastereoselectivity[15] and excellent enantioselectivity (Entry 7, Table 2).

The opposite enantiomer of the pyrrolidinyl-tetrazole catalyst, 1b was also applied to selected ketone examples to verify its use in these transformations. This was successful in providing the corresponding enantiomeric 1,2-oxazine products (Table 3).

Table 3 Synthesis of 1,2-oxazines catalysed by D-pyrrolidinyl-tetrazole

Entry	Ketone	1,2-Oxazine	Yield[a] (ee)[b] %
1	7a	8a	57 (99)
2	7e	8e	54 (99)
3	7b	8b	38 (99)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC.

Table 4 Synthesis of *cis*-allylic alcohols through N–O bond cleavage

Entry	1,2-Oxazine	Time (h)	Alcohol	Yield[a] (ee)[b] %
1	4a	48	9a	83 (99)
2	4c	18	9c	quant. (99)
3	4b	36	9b	88 (99)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC.

Cleavage of the N–O bond of selected examples liberated the synthetically useful free *cis*-allylic alcohols in high yield using zinc in methanolic HCl, with retention of enantiopurity (Table 4).‡

In summary, we have described a sequential one-pot synthesis of more substituted chiral 1,2-oxazines from commercially available *achiral* ketone starting materials. The products undergo facile N–O bond cleavage to provide *cis*-allylic alcohols, thus proving that these substrates could be elaborated to more useful building blocks. Further efforts to evaluate the use of these methods and their application to natural product synthesis and related processes are underway.

Notes and references

† Typical experimental procedure.
Synthesis of 1,2-oxazines. To a stirred solution of (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (7 mg, 0.05 mmol, 5 mol%) and the appropriate ketone (3.00 mmol) in DMSO (3 ml) was added a solution of nitrosobenzene (0.11 g, 1.00 mmol) in DMSO (2 ml) dropwise *via* syringe over 1 h. The reaction mixture was allowed to stir for a further 1 h, then vinyltriphenylphosphonium bromide (0.57 g, 1.50 mmol) was added. The resulting solution was added to a stirred suspension of KH (0.40 g, 30% in mineral oil, washed with hexanes, 3.00 mmol) in THF (5 ml) at 0 °C. After 2 h of vigorous stirring at 0 °C, the reaction mixture was quenched (NH₄Cl aq), extracted (3 × Et₂O) and washed (LiCl aq). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to provide the oxazine products.
‡ *Synthesis of cis-allylic alcohols via N–O bond cleavage.* To a stirred solution of the 1,2-oxazine (1 eq) in MeOH was added zinc powder (5 eq) and 3 N aqueous HCl (20 eq). The resulting suspension was stirred vigorously at room temperature until the reaction was determined to be complete by TLC. The reaction mixture was quenched (NaHCO₃), diluted (H₂O) and extracted (3 × EtOAc). The combined organic phase was dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to provide the desired compound.

1 (*a*) H. Terano, S. Takase, J. Hosoda and M. Kohsaka, *J. Antibiot.*, 1989, **42**, 145; (*b*) I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, T. Tada, S. Koda and Y. Morimoto, *J. Am. Chem. Soc.*, 1987, **109**, 4108; (*c*) M. Iwami, S. Kiyoto, H. Terano, M. Kohsaka, H. Aoki and H. Imanaka, *J. Antibiot.*, 1987, **40**, 589; (*d*) S. Kiyoto, T. Shibata, M. Yamashita, T. Komori, M. Okuhara, H. Terano, M. Kohsaka, H. Aoki and H. Imanaka, *J. Antibiot.*, 1987, **40**, 594; (*e*) K. Shimomura, O. Hirai, T. Mizota, S. Matsumoto, J. Mori, F. Shibayama and H. Kikuchi, *J. Antibiot.*, 1987, **40**, 600; (*f*) O. Hirai, K. Shimomura, T. Mizota, S. Matsumoto, J. Mori and H. Kikuchi, *J. Antibiot.*, 1987, **40**, 607; (*g*) Z. Hori, M. Yamauchi, T. Imanishi, J. Parello, M. Hanaoka and S. Munavall, *Tetrahedron Lett.*, 1972, 1877.
2 P. G. Tsoungas, *Heterocycles*, 2002, **57**, 915.
3 (*a*) P. F. Vogt and M. J. Miller, *Tetrahedron*, 1998, **54**, 1317; (*b*) J. Streith and A. Defoin, *Synlett*, 1996, 189; (*c*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137.
4 X. Ding, Y. Ukaji, S. Fujinami and K. Inomata, *Chem. Lett.*, 2003, **32**, 582.
5 (*a*) A. Le Flohic, C. Meyer, J. Cossy and J. R. Desmurs, *Tetrahedron Lett.*, 2003, **44**, 8577; (*b*) Y. K. Yang and J. Tae, *Synlett*, 2003, 2017; (*c*) Y. K. Yang and J. Tae, *Synlett*, 2003, 1043; (*d*) K. Koide, J. M. Finkelstein, Z. Ball and G. L. Verdine, *J. Am. Chem. Soc.*, 2001, **123**, 398.
6 S. Kumarn, D. M. Shaw, D. A. Longbottom and S. V. Ley, *Org. Lett.*, 2005, **7**, 4189.
7 For representative papers, see: (*a*) G. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247; (*b*) S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 10808; (*c*) A. Bogevig, H. Sunden and A. Cordova, *Angew. Chem., Int. Ed.*, 2004, **43**, 1109; (*d*) Y. Hayashi, J. Yamaguchi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2004, **43**, 1112; (*e*) Y. Hayashi, J. Yamaguchi, K. Hibino and M. Shoji, *Tetrahedron Lett.*, 2003, **44**, 8293; (*f*) Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 5962; (*g*) N. Momiyama, H. Torii, S. Saito and H. Yamamoto, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5374; (*h*) W. Wang, J. Wang, H. Li and L. Liao, *Tetrahedron Lett.*, 2004, **45**, 7235; (*i*) D. B. Ramachary and C. F. Barbas, III, *Org. Lett.*, 2005, **7**, 1577.
8 E. E. Schweizer, J. E. Hayes and E. M. Hanawalt, *J. Org. Chem.*, 1985, **50**, 2591.
9 (*a*) A. J. A. Cobb, D. M. Shaw and S. V. Ley, *Synlett*, 2004, 558; (*b*) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw and S. V. Ley, *Chem. Commun.*, 2004, 1808; (*c*) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold and S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 84; (*d*) C. E. T. Mitchell, S. E. Brenner and S. V. Ley, *Chem. Commun.*, 2005, 5346; (*e*) K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem. Commun.*, 2006, 66; (*f*) C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet and S. V. Ley, *Org. Biomol. Chem.*, 2006, **4**, 2039; (*g*) V. Franckevičius, K. R. Knudsen, M. Ladlow, D. A. Longbottom and S. V. Ley, *Synlett*, 2006, 889.
10 H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983.
11 (*a*) A. Hartikka and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2004, **15**, 1831; (*b*) A. Hartikka and P. I. Arvidsson, *Eur. J. Org. Chem.*, 2005, 4287.
12 R. J. Linderman and A. I. Meyers, *Tetrahedron Lett.*, 1983, **24**, 3043.
13 H. E. Zimmerman and L. M. Tolbert, *J. Am. Chem. Soc.*, 1975, **97**, 5497.
14 W. A. Kinney, M. Abou-Gharbia, D. T. Garrison, J. Schmid, D. M. Kowal, D. R. Bramlett, T. L. Miller, R. P. Tasse, M. M. Zaleska and J. A. Moyer, *J. Med. Chem.*, 1998, **41**, 236.
15 Assigned by 700 MHz NOESY spectrum.