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Enantio- and diastereoselective Darzens condensations

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Abstract—A cobalt(salen) complex has been shown to catalyse the asymmetric Darzens condensation between α-haloamides and aldehydes, allowing both the relative and absolute stereochemistry of the epoxy-amide products to be controlled. Under optimal conditions, *cis*-epoxides can be obtained diastereoselectively with up to 50% enantiomeric excess, whilst by changing the leaving group and base, *trans*-epoxides can be produced diastereoselectively with up to 43% enantiomeric excess.

In recent years we have been investigating the use of metal(salen) complexes as catalysts for various carbon–carbon bond forming reactions. Titanium^{IV} and vanadium^{V}(salen) complexes have been shown to catalyse the asymmetric addition of various cyanide sources to aldehydes and ketones, whilst copper^{II} and cobalt^{II}(salen) complexes catalysed the asymmetric alkylation of enolates of α-amino esters.[1] Epoxides are particularly versatile synthetic intermediates which can readily be converted into a wide range of polyfunctional compounds. The asymmetric epoxidation of electron-rich alkenes was pioneered by Sharpless,[2] and subsequently developed by Jacobsen[3] and Katsuki.[4] In contrast, the asymmetric epoxidation of α,β-unsaturated carbonyl compounds can be achieved by organic or metal-catalysed processes.[5]

An alternative method for the synthesis of α,β-epoxy-carbonyl compounds and related compounds is the Darzens condensation between a carbonyl compound and an α-halo-carbonyl compound (or related species).[6] This reaction has been known for over 100 years, but only recently has progress been made in developing asymmetric variants of this epoxide synthesis. Aggarwal et al. have developed a highly enantioselective variation of the Darzens condensation to give *trans*-glycidic amides by replacement of the halide leaving group by a chiral sulfonium salt.[7] In contrast, Arai et al. have used cinchona alkaloid derivatives as chiral phase transfer catalysts for asymmetric Darzens condensations, obtaining enantioselectivities of up to 86% for cyclic α-chloroketone substrates,[8,9] up to 79% for reactions involving α-chloroacetophenone,[9,10] and up to 83% for reactions involving chloromethyl phenyl sulfone.[11] Similarly, Bakó, Tőke and co-workers have reported the use of chiral aza-crown ethers for the same purpose, achieving up to 74% ee for the Darzens condensation between benzaldehyde and α-chloroacetophenone.[12] Most recently, Arai et al. reported the use of a synthetic bis-ammonium salt as an asymmetric phase transfer catalyst for the Darzens condensation of *N*,*N*-diphenyl α-haloamides, obtaining predominantly the *cis*-epoxides with up to 64% ee for the *cis*-epoxide, and up to 70% ee for the minor *trans*-epoxide.[13]

However, there was no precedent for the use of metal complexes as asymmetric catalysts for the Darzens condensation. Therefore, in view of the ability of metal^{II}(salen) complexes to catalyse the formation of enolates under phase transfer conditions,[1] we decided to investigate the use of similar complexes as catalysts for the Darzens condensation. The reaction between α-haloamides **1a**–**c** and benzaldehyde (Scheme 1) was adopted as a test reaction since the epoxy-amide products **2a**,**b** can easily be transformed into a wide variety of other functionalized chemical intermediates[7,13] and we have shown[14] that the diastereoselectivity of these

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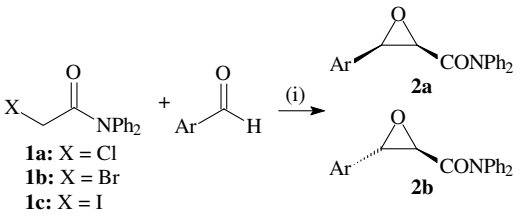
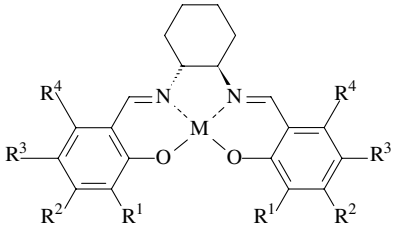


Scheme 1. Reagents and conditions (i) MOH (solid)/M′(salen) cat./CH_2Cl_2, 4–24 h, rt.

Darzens condensations can be controlled to produce either *cis*-**2a** or *trans*-epoxide **2b** by appropriate choice of base and solvent.

The Darzens condensation proceeds by a two step mechanism consisting of an aldol reaction followed by an intramolecular displacement of the halide leaving group.[6] The initial aldol reaction may or may not be reversible under particular reaction conditions and our results on the diastereoselectivity of reactions involving substrates **1a**–**c** suggest that chloroamide **1a** gives *trans*-epoxides **2b** via a thermodynamically controlled aldol reaction, whilst amides **1b**,**c** give *cis*-epoxides **2a** via a kinetically controlled aldol reaction.[14] An asymmetric catalyst for the Darzens condensation could induce asymmetry into either step of the mechanism. However, if the catalyst is involved in the aldol reaction then it will only be able to catalyse the kinetically controlled reactions involving α-bromo- or α-iodoamides **1b** and **1c**. In contrast, if the catalyst acts in the second step, through a dynamic kinetic resolution type process, then higher enantioselectivities would be expected for reactions involving α-chloroamide **1a** as the competing uncatalysed cyclisation is less effective in this case. Therefore, catalyst screening studies were carried out with substrates **1a**–**c**.



3: M = Cu, $R^1 = R^2 = R^3 = R^4 = H$
4: M = Co, $R^1 = R^2 = R^3 = R^4 = H$
5: M = $TiCl_2$, $R^1 = R^2 = R^3 = R^4 = H$
6: M = Cu, $R^1 = {}^tBu$, $R^2 = R^3 = R^4 = H$
7: M = Co, $R^1 = {}^tBu$, $R^2 = R^3 = R^4 = H$
8: M = Co, $R^1 = R^3 = {}^tBu$, $R^2 = R^4 = H$
9: M = VOCl, $R^1 = R^3 = {}^tBu$, $R^2 = R^4 = H$
10: M = $(Ti\text{-}O)_2$, $R^1 = R^3 = {}^tBu$, $R^2 = R^4 = H$
11: M = Cu, $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
12: M = Co, $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
13: M = Cu, $R^2 = OMe$, $R^1 = R^3 = R^4 = H$
14: M = Co, $R^2 = OMe$, $R^1 = R^3 = R^4 = H$
15: M = Ni, $R^2 = OMe$, $R^1 = R^3 = R^4 = H$
16: M = Cu, $R^3 = OMe$, $R^1 = R^2 = R^4 = H$
17: M = Co, $R^3 = OMe$, $R^1 = R^2 = R^4 = H$
18: M = Cu, $R^4 = OMe$, $R^1 = R^2 = R^3 = H$

An initial screening of copper^{II}, cobalt^{II} and titanium^{IV} dichloride complexes **3**–**5** as catalysts for the Darzens condensation between benzaldehyde and amides **1a**,**b** gave unpromising results as shown in Table 1. In all cases, less than 10% enantiomeric excess was observed for both the *cis*- and *trans*-products (Table 1, entries 1–6). However, the ratio of *cis*- to *trans*-epoxides formed in the catalysed reactions were different to those obtained from uncatalysed reactions under otherwise identical reaction conditions.[14] In addition, the chemical yields obtained from the catalysed reactions were higher than those obtained from uncatalysed reactions. Both of these factors suggested that the metal(salen) complex was having a favourable effect on the Darzens condensation, but that the complexes with unsubstituted salen ligands were not optimal for asymmetric induction.

As a result of our previous work on asymmetric catalysis using salen ligands,[1] we had a large number of salen ligands derived from diaminocyclohexane and substituted salicylaldehydes available, along with the corresponding metal complexes. These were screened for the Darzens condensation and selected results are included in Table 1. The introduction of *tert*-butyl groups *ortho*- to the phenols of the ligand, or both *ortho*- and *para*- to the phenols was not beneficial for catalysts derived from copper **6**, cobalt **7**, **8**, vanadium **9**, or titanium **10** (Table 1, entries 7–15). *ortho*-Substituents had a similarly negative effect on the enantioselectivity of copper^{II} and cobalt^{II}(salen) catalysts for asymmetric enolate alkylation, but had a positive effect on the enantioselectivity of titanium^{IV} and vanadium^{V} catalysts for asymmetric cyanohydrin synthesis.[1]

The presence of electron-donating methoxy groups on the aromatic rings was however found to be beneficial. When the methoxy groups were present *ortho*- to the phenols (catalysts **11** and **12**), they reversed the usual *trans*-selectivity observed with α-chloroamide **1a** and instead gave a similar *cis*-selectivity to that obtained using α-bromoamide **1b** (Table 1, entries 16–20). This was an indication that these catalysts might be interacting with the chloro-group of the substrate so as to make it a better leaving group. Moving the methoxy substituents *meta*- to the phenols (catalysts **13**–**15**) restored the *trans*-selectivity observed with substrate **1a** (Table 1, entries 21, 22, 24–26, 32) and the combination of copper^{II}(salen) complex **13** and sodium hydroxide gave a particularly large *trans*-selectivity (Table 1, entry 21).

However, the key feature of these reactions was the enantioselectivity obtained using cobalt^{II}(salen) complex **14** and potassium hydroxide. With α-chloroamide substrate **1a**, the major *trans*-epoxide **2b** was obtained with 29% enantiomeric excess (Table 1, entry 25). The enantioselectivity (for epoxide **2b**) was further increased to 39% by changing the base to rubidium hydroxide (Table 1, entry 26). Even more promisingly, use of α-bromoamide substrate **1b** gave the minor *trans*-epoxide **2b** with 44% enantiomeric excess and the major *cis*-epoxide **2a** with 42% enantiomeric excess (Table 1, entry 27). In this case, use of rubidium hydroxide as base diminished the enantioselectivity (Table 1, entry 28). α-Iodoamide **1c**

Table 1. Darzens condensation between α-haloamides **1a–c** and benzaldehyde catalysed by metal(salen) complexes **3–18**

Entry	Catalyst[a]	Substrate	Base	*cis*/*trans* ratio[b]	ee (*cis*)[c]	ee (*trans*)[c]	Yield (%)
1	**3**	**1a**	NaOH	1:7	4	1	68
2	**3**	**1a**	KOH	1:1	0	0	98
3	**3**	**1b**	NaOH	1.8:1	0	6	96
4	**4**	**1a**	KOH	1:1.8	4	7	79
5	**5**	**1a**	NaOH	1:12	0	9	99
6	**5**	**1b**	KOH	2:1	3.5	1	99
7	**6**	**1a**	NaOH	1:3.9	0	1.5	80
8	**6**	**1a**	KOH	1:1.5	0	4	67
9	**7**	**1a**	KOH	1:1.5	0	5	91
10	**7**	**1b**	NaOH	1:5.7	0	8	98
11	**7**	**1b**	KOH	2.2:1	3	5	67
12	**8**	**1a**	NaOH	1:5.6	0	4	85
13	**8**	**1a**	KOH	1:1.2	3	1.5	81
14	**9**	**1a**	KOH	1:1.3	0	2	79
15	**10**	**1a**	KOH	1:1.4	0	2	84
16	**11**	**1a**	NaOH	1.9:1	12	9	96
17	**11**	**1a**	KOH	2.7:1	2	2	69
18	**11**	**1b**	KOH	2:1	0	2	66
19	**12**	**1a**	KOH	2.1:1	9	2.5	93
20	**12**	**1b**	KOH	2.1:1	15	8	57
21	**13**	**1a**	NaOH	1:12	0	2.5	68
22	**13**	**1a**	KOH	1:1.5	5	2	79
23	**13**	**1b**	KOH	2.1:1	0	0	69
24	**14**	**1a**	NaOH	1:4.2	0	2	82
25	**14**	**1a**	KOH	1:2.7	3	29	84
26	**14**	**1a**	RbOH	1:1.8	9	39	84
27	**14**	**1b**	KOH	2.4:1	42	44	93
28	**14**	**1b**	RbOH	1.8:1	7	27	80
29	**14**	**1c**	NaOH	1.1:1	6	5	79
30	**14**	**1c**	KOH	2.6:1	45	36	92
31	**14**	**1c**	RbOH	2.7:1	14	20	58
32	**15**	**1a**	KOH	1:1.5	1	8	72
33	**15**	**1b**	KOH	1.8:1	9	9	71
34	**16**	**1a**	NaOH	1:7	0	2	84
35	**16**	**1a**	KOH	1:1.1	0	4	75
36	**16**	**1b**	KOH	2:1	0	3	61
37	**17**	**1a**	KOH	1.3:1	2.5	9	78
38	**17**	**1b**	KOH	2.1:1	11	10	98
39	**18**	**1a**	KOH	1:1.2	0	3	77

[a] In all cases, 2 mol % of the catalyst derived from (*R*,*R*)-diaminocyclohexane was used.
[b] Determined by ^{1}H NMR analysis of the unpurified mixture of epoxides **2a** and **2b**.
[c] Determined by chiral HPLC on a Daicel Chiralpack AD column. In each case the major enantiomer of the *cis*-epoxide was assigned (2*S*,3*S*)-configuration whilst the major enantiomer of the *trans*-epoxide was assigned (2*S*,3*R*)-configuration by comparison with literature data.[13]

was also tested as a substrate with catalyst **14** (Table 1, entries 29–31), and gave similar enantioselectivities, diastereoselectivities and chemical yields to those obtained using α-bromoamide **1b**.

The corresponding nickel^{II}(salen) complex **15** did not exhibit significant enantioselectivity (Table 1, entries 32 and 33), and moving the methoxy groups to other positions on the aromatic rings (complexes **16–18**) also diminished the asymmetric induction observed with copper^{II} and cobalt^{II} complexes (Table 1, entries 34–39).

From the data in Table 1, it is apparent that whilst copper^{II} based catalysts **11** and **13** gave good diastereoselectivities (Table 1, entries 17 and 21), only cobalt^{II}(salen) complex **14** used in conjunction with potassium or rubidium hydroxide gave significant enantioselectivities in the Darzens condensations (Table 1, entries 26, 27, 30). The higher enantioselectivity observed with α-bromoamide **1b** and α-iodoamide **1c** compared to α-chloroamide **1a** is consistent with the chiral salen complex being involved in catalysing the aldol step of the mechanism. Therefore, complex **14** and potassium hydroxide were adopted as the optimal catalyst and base for further work aimed at optimizing the reaction conditions. Increasing the amount of complex **14** used to 5 mol % or 10 mol % had no significant effect on the enantioselectivity but reduced the chemical yield by 20%.

Lowering the reaction temperature to 0 °C for reactions involving α-bromoamide **1b** did not significantly change the chemical yield or enantioselectivity, but at −40 °C no reaction occurred. In contrast, for α-chloroamide **1a**, lowering the reaction temperature to 0 °C lowered the **2a**:**2b** ratio to 1:1.5, but increased the enantioselectivity to 47% for epoxide **2a** and 41% for epoxide **2b**, albeit with a reduced chemical yield of 44%. Further reducing the reaction temperature to −40 °C inverted

Table 2. Darzens condensation between α-haloamides **1a**,**b** and aromatic aldehydes catalysed by complex **14**[a]

Entry	Substrate	Aldehyde	Base	*cis*/*trans* ratio[b]	ee (*cis*)[c]	ee (*trans*)[c]	Yield (%)
1	**1a**	2-ClC_6H_4CHO	RbOH	1:4.3	8	19	94
2	**1b**	2-ClC_6H_4CHO	KOH	1.5:1	18	26	84
3	**1a**	3-ClC_6H_4CHO	RbOH	1:2.0	5	25	97
4	**1b**	3-ClC_6H_4CHO	KOH	1.3:1	21	34	90
5	**1a**	4-ClC_6H_4CHO	RbOH	1:1.6	10	22	79
6	**1b**	4-ClC_6H_4CHO	KOH	1.6:1	29	46	86
7	**1a**	2-MeC_6H_4CHO	RbOH	*trans* only		26	83
8	**1b**	2-MeC_6H_4CHO	KOH	1.8:1	50	50	75
9	**1a**	3-MeC_6H_4CHO	RbOH	1:4.0	4	33	79
10	**1b**	3-MeC_6H_4CHO	KOH	1.7:1	30	45	76
11	**1a**	4-MeC_6H_4CHO	RbOH	1:4.2	3	21	76
12	**1a**	4-$MeOC_6H_4CHO$	RbOH	1:1.9	9	43	71
13	**1b**	4-$MeOC_6H_4CHO$	KOH	2.5:1	42	47	95

[a] In all cases, 2 mol % of catalyst **14** derived from (*R*,*R*)-diaminocyclohexane was used in dichloromethane at room temperature.
[b] Determined by ^1H NMR analysis of the unpurified mixture of epoxides **2a** and **2b**.
[c] Determined by chiral HPLC on a Daicel chiralpack AD column.

the *cis*/*trans* ratio (to 3.5:1 in favour of *cis*-epoxide **2a**) and gave enantioselectivities of 45% for *cis*-epoxide **2a** and 36% for *trans*-epoxide **2b**, values which are comparable to those obtained using α-bromoamide **1b** at room temperature. This indicates that at −40 °C, the Darzens reaction on α-chloroamide **1a** occurs under kinetic control with an irreversible aldol condensation. However, the chemical yield was only 19% under these conditions.

Reactions with α-bromoamide **1b** were also carried out at room temperature in ether, methanol, acetonitrile, DMF, THF and toluene. No reaction occurred in methanol, and all the other solvents gave lower enantioselectivities than that obtained in dichloromethane. However, the polar aprotic solvents acetonitrile and DMF did give very high diastereoselectivities for *cis*-epoxide **2a**; 12.4:1 for acetonitrile and exclusively *cis* (with 31% enantiomeric excess) for DMF, consistent with results obtained in the absence of a chiral catalyst.[14]

Finally, the Darzens condensation of other aldehydes with amides **1a**,**b** was investigated under the optimally enantioselective reaction conditions (Table 1, entries 26 and 27, respectively). Results of this study are given in Table 2, and in each case the trend that chloroamide **1a** favours the formation of *trans*-epoxides **2b** whilst bromoamide **1b** gives predominantly *cis*-epoxides **2a** was followed. Electron deficient aldehydes bearing chloro-substituents were generally not good substrates (Table 2, entries 1–6) as only the combination of 4-chlorobenzaldehyde and bromoamide **1b** with potassium hydroxide as base gave an enantioselectivity of greater than 40%, and then only for the minor *trans*-epoxide formed in the reaction (Table 2: entry 6). In contrast, electron-rich aromatic aldehydes containing methyl or methoxy substituents gave higher enantioselectivities for both the *cis*- and *trans*-epoxides (Table 2, entries 7–13) with the combination of 2-methylbenzaldehyde and bromoamide **1b** giving particularly high enantioselectivities when potassium hydroxide was used as base (Table 2, entry 8).

It is not possible to comment definitively on the origin of the asymmetric induction at this stage. Comparison of the data in Tables 1 and 2 shows that *trans*-epoxides **2b** are generally formed with higher enantioselectivity than *cis*-epoxides **2a**. *trans*-Epoxides would arise from a thermodynamically controlled chelated aldol reaction,[14] which suggests that the catalyst is involved in the subsequent ring closure step. However, for any aldehyde substrate, a higher enantiomeric excess of the epoxide is obtained when bromoamide **1b** or iodoamide **1c** is used as the enolate source, compared to that obtained using chloroamide **1a**. This is the reverse of the trend that might be expected if the catalyst was involved in catalysing the epoxide formation, but might be explained by the higher Lewis basicity of bromine and iodine allowing them to coordinate more effectively to the Co^{II}(salen) complex. Experiments to further enhance the enantioselectivities and to probe the reaction mechanism are in progress and will be reported in due course.

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