Tandem conjugate addition–elimination reaction promoted by chiral pyrrolidinyl sulfonamide (CPS)†‡

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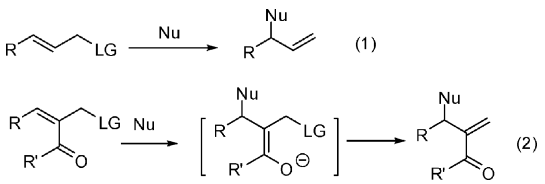
Chiral pyrrolidinyl sulfonamides have been found to promote the conjugate addition–elimination reaction between activated allylic bromides and 1,3-dicarbonyl compounds with high enantioselectivities and the highly functionalised products can be used to generate a variety of interesting enantiomerically pure compounds *via* simple transformations.

The S_N2' reaction (1) and the tandem conjugate addition–elimination reaction (2) which yields S_N2' type product are not often distinguished from one another. A possible approach towards asymmetric tandem conjugate addition–elimination (CA-E) is the installation of a chiral auxiliary as the leaving group (LG). Using chiral pyrrolidines as the auxiliary, Tamura showed that it is possible to achieve high diastereoselectivity with lithium diorganocuprates, leading to optically active 3-substituted 2-methylene-cycloalkanones.[1]



The α-methylene-β-hydroxycarbonyl compounds derived from Morita–Baylis–Hillman (MBH) reactions, also known as MBH adducts, can be modified to acetates or protected with BOC. When such MBH derivatives were used, catalytic amount of *Cinchona* alkaloids can be installed as the leaving group (LG) *in situ*.[2,3] Nucleophiles (Nu), such as amines and phenols, can then be inserted *via* a tandem CA-E reaction with moderate enantioselectivity. Allylic amination of MBH acetates with a similar strategy using catalytic chiral phosphines also resulted in moderate enantioselectivity.[4] A successful tandem CA-E reaction has been developed by Ramachandran for the addition of benzophenone imine of glycine *tert*-butyl ester to MBH acetates using quaternised *Cinchona* alkaloids under phase transfer conditions.[5] This is a useful method for the synthesis of glutamic acid derivatives.

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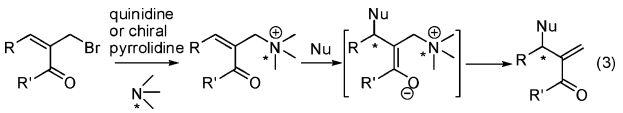
† We would like to dedicate this paper to Professor Andrew B. Holmes on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: General procedures and characterisations. CCDC reference numbers 692929–692932. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810905m



MBH adducts can also be transformed to allylic bromides in a single step using NBS.[6] These allylic bromides interact with amines *via* S_N2 or tandem CA-E reactions depending on the solvent and reaction conditions.[7] It was shown previously by Basavaish that with 2 equivalents of quinidine, alcohols and phenols can add in a tandem CA-E mode (3).[8] This is a synthetically useful reaction but examples with high enantioselectivities are rare. Thus, we designed a series of chiral pyrrolidinyl sulfonamides (CPS) (Fig. 1) to investigate the asymmetric transformations of activated allylic bromides *via* tandem CA-E reactions.

The CPS **1a–d** were easily synthesised from commercially available chiral amino alcohols. Formation of aziridines from the amino alcohols was followed by a regioselective ring opening reaction using pyrrolidine[9] (see ESI‡). In 3 steps, the CPS can be obtained in multigram quantities and high yields. We investigated the use of CPS **1a** in the tandem CA-E reaction of activated allylic bromide **2** (Table 1), which was previously not investigated as a substrate for this reaction. We have recently found that *S*,*S*′-dialkyl dithiomalonates are effective donors for chiral bicyclic guanidine catalysed Michael reactions[10] due to the high α-proton acidity. *S*,*S*′-Di-*tert*-butyl dithiomalonate **3a** was employed for the optimization of the reaction. While catalytic amounts of CPS can be employed, the reaction rate was too slow to be useful. We increased the amount of CPS to 2 equivalents for subsequent investigations. The reaction carried out in toluene (entry 1) proved to be low-yielding and reactions in polar solvents such as CH_2Cl_2 and CH_3CN were relatively faster and provided good levels of enantioselectivities (entries 2 and 3). Optimization based on making structural changes to CPS revealed that the *tert*-butyl group increases the enantioselectivity of the reaction (entry 4). When the pyrrolidine ring was replaced by a piperidine, there was a slight decrease of both yield and ee (entry 5). When the tosyl group was replaced by a bulkier 2,4,6-trimethylphenylsulfonyl group in CPS **1d**, we observed the best result (entry 6). The loading of CPS promoter could be reduced to 1.5 equivalents while the yield and enantioselectivity were maintained at a satisfactory level (entry 7).

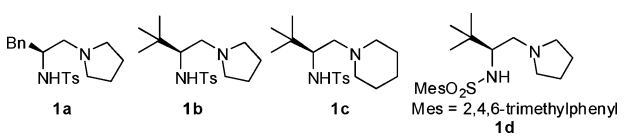
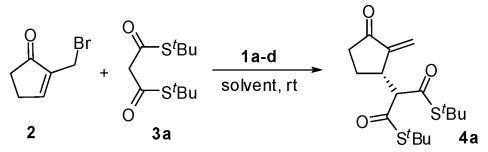


Fig. 1 Structures of chiral pyrrolidinyl sulfonamides (CPS) **1a–d**.

Table 1 Reaction between 2-(bromomethyl)cyclopent-2-enone and *S*,*S*′-di-*tert*-butyl dithiomalonate in the presence of CPS **1a–d**



2 **3a** **4a**

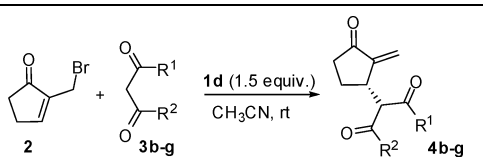
Entry	CPS (equiv.)	Solvent	Time/h	Yield (%)[a]	ee (%)[b]
1	**1a** (2.0)	Toluene	48	15	44
2	**1a** (2.0)	CH_2Cl_2	18	74	54
3	**1a** (2.0)	CH_3CN	16	88	59
4	**1b** (2.0)	CH_3CN	14	97	73
5	**1c** (2.0)	CH_3CN	20	74	70
6	**1d** (2.0)	CH_3CN	12	97	90
7	**1d** (1.5)	CH_3CN	12	97	90

[a] Isolated yield. [b] Chiral HPLC.

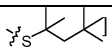
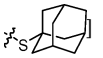
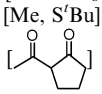
A series of 1,3-dicarbonyl compounds were explored as nucleophiles with the optimised conditions (Table 2). Sterically bulky donors such as *S*,*S*′-di-*tert*-octyl dithiomalonate **3b** and *S*,*S*′-di-adamantyl dithiomalonate **3c** afforded S_N2' type products with high enantioselectivities (entries 1–4). We are concerned about the high amounts of promoter required for this reaction. Fortunately, the CPS promoter **1d** can be recovered with 90% yield, using a simple acid–base workup. It can also be reused without further purification, for two further cycles without loss of yield and enantioselectivity of the product **4b** (entries 2 and 3). Other 1,3-dicarbonyl compounds such as keto-thioesters were proved to be suitable donors for this reaction (entries 5–7). Tandem CA-E products were obtained in high yields and ees, with diastereomeric ratios of approximately 1 : 1. Interestingly, when 2-acetylcyclopentanone **3g** was subjected to this reaction, high enantioselectivity was also observed (entry 8).

Several allylic bromides of different ring sizes were prepared and investigated to determine the scope of the reaction (Table 3). Allylic chloride **5a** was much easier to handle than the corresponding allylic bromide, which was unstable under the reaction conditions and had led to many side products. The reactions between **5a–c** and **3a** were promoted with **1d** and

Table 2 Reaction between 2-(bromomethyl)cyclopent-2-enone and 1,3-dicarbonyl compounds in the presence of **1d**

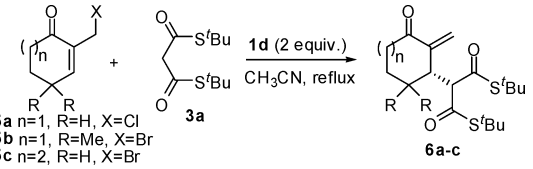


2 **3b-g** **4b-g**

Entry	**3** [R^1, R^2]	Product	Time/h	Yield (%)[a]	ee (%)[b]
1	**3b** [R^1 = R^2 = ]	**4b**	16	83	94
2[c]	**3b**	**4b**	21	74	94
3[d]	**3b**	**4b**	21	87	95
4[e]	**3c** [R^1 = R^2 = ]	**4c**	44	77	97
5	**3d** [Ph, S^{t}Bu]	**4d**	26	91	94, 94
6	**3e** [4-MeOC$_6$H$_4$, S^{t}Bu]	**4e**	23	89	98, 95
7	**3f** [Me, S^{t}Bu]	**4f**	43	76	94, 94
8	**3g** 	**4g**	29	60	98, 95

[a] Isolated yield. [b] Chiral HPLC. [c] Recovered **1d**, 2nd cycle. [d] Recovered **1d**, 3rd cycle. [e] Reaction in CH_2Cl_2.

Table 3 Reaction between activated allylic bromides **5a–c** and *S*,*S*′-di-*tert*-butyl dithiomalonate in the presence of **1d**



5a n=1, R=H, X=Cl
5b n=1, R=Me, X=Br
5c n=2, R=H, X=Br

3a **6a-c**

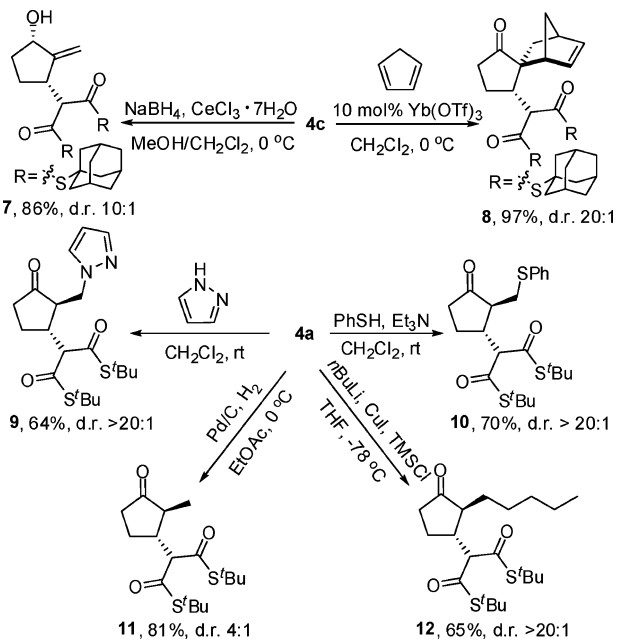
Entry	Substrate	Product	Time/h	Yield (%)[a]	ee (%)[b]
1	**5a**	**6a**	11	40	74
2	**5b**	**6b**	20	37	88
3[c]	**5c**	**6c**	29	46	94

[a] Isolated yield. [b] Chiral HPLC. [c] Reaction at room temperature.

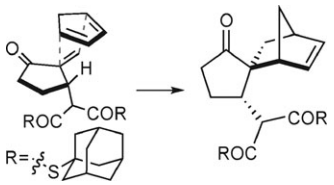
gave slightly lower levels of enantioselectivities than **2**. These reactions were much slower and yields were much lower when they were conducted at room temperature. Increasing reaction temperature improved the reaction rate without affecting the enantioselectivity. Under reflux conditions and with 2 equivalents of **1d**, we were able to improve the yield to a moderate level. The reaction of cycloheptenone **5c** was still carried out at room temperature as product **6c** was found to be unstable at elevated temperature. The double addition product, derived from the addition of a second 1,3-dicarbonyl donor onto **6a–c**, was found to be a major side product in these reactions.

To demonstrate the usefulness of this reaction, the tandem CA-E products were further modified to generate a variety of interesting compounds **7–12** *via* simple transformations (Scheme 1). Chiral allylic alcohol **7** was obtained with a diastereomeric ratio 10 : 1 when product **4c** was subjected to Luche reduction conditions.[11] A solvent mixture of $MeOH/CH_2Cl_2$ 1 : 1 was used, as **4c** was only partially soluble in MeOH.

Lewis acid catalysed Diels–Alder reaction between **4c** and cyclopentadiene can lead to chiral spiro-compounds such as **8**.[12] Such a spiro framework can be found in natural products such



Scheme 1 Stereoselective synthesis of a diverse range of compounds, **7–12**.



Scheme 2 Approach of cyclopentadiene to **4c** in the Diels–Alder reaction.

as artemisolide,[13] which is an inhibitor of IκB kinase β. It was observed that the *exo* adduct[14] **8** is preferred, indicating secondary orbital interactions between the carbonyls of dithiomalonate and the developing π bond of cyclopentadiene (Scheme 2).

The α,β-unsaturated moiety of the tandem CA-E product **4a** was suitably set up for conjugate addition reactions. Hetero-Michael reactions using thiol[15] or amine[16] as the nucleophile gave products with high diastereoselectivites (d.r. > 20 : 1). An α-methyl ketone **11** was generated with a moderate diastereomeric ratio (4 : 1) *via* a palladium catalysed hydrogenation.[17] Conjugate addition reaction with Gilman's reagent[18] provided adduct **12** with excellent diastereomeric ratio (>20 : 1). The relative and absolute stereochemistry of products **7–12** were assigned by ^{1}H NMR spectrum[19] and comparision with literature values.[20] The assignment was further confirmed by single crystal X-ray analyses of compounds **8**, **11** and **12**. (see ref. 23 and ESI‡).

We are keenly aware that the key weakness in this methodolgy is the high amount of CPS required, albeit that they were recoverable. Studies are on-going to make this reaction even more synthetically useful. The replacement of Br in the allylic bromides by CPS to form an ammonium salt[21] is a fairly rapid reaction. However, CPS is a weak base which is not effective in promoting the conjugate addition of the 1,3-dicarbonyl donors. The use of stronger organic bases such as TBD[22] as additives may promote the reaction and allow a catalytic amount of CPS to be used. We have also prepared a polystyrene-supported chiral pyrrolidinyl sulfonamide (PS-CPS) from chiral diamine and polystyrene-bonded sulfonyl chloride. We will determine the effectiveness of this approach to improve the ease of recovery of the CPS.

In conclusion, we have developed a tandem conjugate addition–elimination reaction between activated allylic bromide and various 1,3-dicarbonyl compounds. The reaction was promoted by CPS which were easily prepared from their corresponding amino alcohols. Stereoselective synthesis of several enantiomerically pure compounds were also presented.

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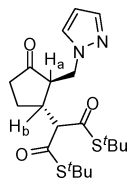

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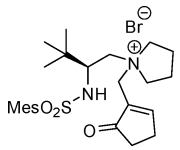

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23 **Crystal data for compounds 8**, **11**, **12** and ref. 21, CCDC reference numbers 692929–692932. **Crystal data of 8**: $C_{34}H_{44}O_3S_2$, M = 564.81, monoclinic, a = 18.7796(12), b = 13.0947(8), c = 11.9738(7) Å^3, β = 94.651(2)°, T = 296(2) K, space group $P2(1)/c$, Z = 4, 19592 refelctions measured, 6730 unique (R_{int} = 0.0577). $R1$ = 0.0666. The final $wR(F_2)$ was 0.1418. **Crystal data of 11**: $C_{17}H_{28}O_3S_2$, M = 344.51, triclinic, a = 9.7296(18), b = 11.309(2), c = 11.780(2) Å^3, α = 65.152(4)°, β = 68.166(4)°, γ = 64.564(4)°. T = 295(2) K, space group $P1$, Z = 2, 11 759 refelctions measured, 7994 unique (R_{int} = 0.0335). R1 = 0.0860. The final $wR(F_2)$ was 0.1925. Flack parameter was 0.17(11). **Crystal data of 12**: $C_{21}H_{36}O_3S_2$, M = 400.62, monoclinic, a = 18.8390(19), b = 12.6378(14), c = 10.2009(10) Å^3, β = 95.756(3)°. T = 223(2) K, space group Cc, Z = 4, 8 416 refelctions measured, 4012 unique (R_{int} = 0.0523). R1 = 0.0595. The final $wR(F_2)$ was 0.1237. **Crystal data of** ref. 21: $C_{26}H_{41}BrCl_2N_2O_3S$, M = 612.48, orthorhombic, a = 8.1010(7), b = 12.7221(10), c = 28.619(2) Å^3, T = 223(2) K, space group $P2(1)2(1)2(1)$, Z = 4, 20732 refelctions measured, 6762 unique (R_{int} = 0.0662). $R1$ = 0.0579. The final $wR(F_2)$ was 0.1430. Flack parameter was 0.008(11).

