ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Z. Gao and S. P. Fletcher, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC05433E.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

Journal Name

COMMUNICATION

Asymmetric Conjugate Addition of Alkylzirconium Reagents to α,β -Unsaturated Thioesters: Access to fragrances and acyclic stereochemical arrays

Zhenbo Gao and Stephen P. Fletcher*^aReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Copper-catalyzed asymmetric conjugate addition of alkylzirconium species to α,β -unsaturated thioesters is reported. A variety of functionalized alkyl nucleophiles were introduced with yields around 70% and ee's over 92%. The method was applied to the straightforward syntheses of the commercially important fragrances phenoxanol (both enantiomers 97% ee), and hydroxycitronellal (98% ee). The 1,4-addition products can be converted to enantiomerically enriched linear building blocks bearing a terminal functional group. Formation of further α,β -unsaturated thioesters provides an iterative route for the stereocontrolled synthesis of functionalized acyclic arrays and we demonstrate almost complete catalyst control in the formation of additional stereocentres.

Intensive research on asymmetric conjugate addition (ACA) of organometallic reagents has lead to useful procedures for the addition of alkyl groups¹. We have previously described Cu-catalysed asymmetric addition of alkylzirconium species generated *in situ* from terminal or internal olefins² which function as primary alkyl nucleophiles³. These procedures allow asymmetric construction of tertiary stereogenic centres by addition to cyclic⁴ and acyclic enones⁵, the formation of cyclic⁶ and acyclic quaternary centres⁷ by addition to β -substituted enones (scheme 1a), and asymmetric allylic alkylations⁸ to give enantiomerically enriched cyclic alkenes. With the exception of one report of addition to unsaturated lactones⁹, the products of these ACAs are cyclic or acyclic ketones which are difficult to differentiate in further transformations and this limits the building blocks that can be accessed through these procedures. While it should be possible to use intermediate Zr-enolates to differentiate the α -CH₂ groups, we¹⁰ and the Šebesta group¹¹ have both found it difficult to develop high yielding procedures.

Here we report ACA of alkylzirconium species to unsaturated thioesters with high yield and excellent stereocontrol. The products readily undergo C-S bond cleavage to provide enantioenriched linear building blocks. The procedure tolerates various functional groups and is applied to the synthesis of two commercially used fragrances. The method

Scheme 1 a) Previous work on ACA of alkyl zirconium species to enones provides ketones b) This work, hydrosilylation of alkenes / ACA to α,β -unsaturated thioesters gives chiral products with an easily differentiated functional group and allows synthesis of functionalized acyclic stereochemical arrays.

can be used in iterative procedures where further α,β -unsaturated thioesters undergo ACA to give additional stereogenic centres with almost complete catalyst control.

Asymmetric addition of alkyl nucleophiles to α,β -unsaturated aldehydes, esters and thioesters are high value transformations as enantiopure β -substituted carboxylic acid derivatives have enormous synthetic utility. While a great many non-enantioselective procedures have been developed and used in synthesis, there are only a few catalytic enantioselective methods, and these are limited to the addition of simple alkyl nucleophiles. The Loh group¹² used Grignard reagents to form stereogenic centres by ACA to esters, while the Minnaard/Feringa¹³ and Alexakis¹⁴ groups built tertiary centres from α,β -unsaturated thioesters and aldehydes respectively.

^a Department of Chemistry, University of Oxford. Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA (UK). E-mail: stephen.fletcher@chem.ox.ac.uk

† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

In the Cu-catalyzed ACA of alkylzirconium species, cyclic and acyclic electrophiles require different ligand families to obtain high ee, and based on procedures which allowed highly enantioselective ACAs to linear enones^{5, 7}, we examined a variety of α,β -unsaturated carboxylic acid derivatives (not shown). Esters give excellent enantioselectivities but low yields (up to 37% yield, 95% ee) due to the intermediate enolate undergoing subsequent reactions with starting material, a process that we were unable to prevent. Additionally, reactions with α,β -unsaturated aldehydes only gave modest results (up to 47% yield and 62% ee). However unsaturated thioesters were found to give good yields and very high ee's after some optimization.

Table 1 Reaction conditions for hydrometallation –ACA asymmetric to α,β -unsaturated thioester **2a**

Entry	Solvent	Ligand	Conversion [%] ^[1]	ee [%] ^[2]
1	Et ₂ O	A	46	91
2	Et ₂ O	B	tiny	83
3	Et ₂ O	C	45	92
4	Et ₂ O	D	53	92
5	DCM	D	61	96
6	Et ₂ O/DCM	D	78	97
7 ^[3]	Et ₂ O/DCM	D	77	98
8 ^[4]	Et ₂ O/DCM	D	86	97
9 ^[4,5]	Et ₂ O/DCM	D	98	97
10 ^[3,4]	Et ₂ O/DCM	D	93	98
11 ^[3,4,5]	Et ₂ O/DCM	D	98	98
12 ^[3,5,6]	Et ₂ O/DCM	D	66	91

Reaction conditions: Hydrosilylation is performed on alkene before ACA. alkene (2.5 eq.), [Cp₂ZrHCl] (2 eq.), enone (1 eq.), copper (10 mol%), ligand (10 mol%), silver (11 mol%), TMSCl (5 eq.), room temperature 15 hours [1] Calculated by HPLC or NMR. [2] Enantiomeric excess was determined by HPLC [3] ice bath [4] 20 mol% catalyst [5] 40 h reaction [6] 1mmol scale reaction using 5 mol% catalyst

We found that the combination of copper (I) triflate and ligand **A** in the presence of TMSCl afforded **3a** with 91% ee (Table 1, Entry 1). After trialling several similar ligands found **D** gave **3a** with better results (Entries 2–4). A combination of Et₂O/DCM (1/1) provided 78% conversion with 97% ee. We found that the yield and ee can be further increased by cooling the reaction to 0 °C, increasing the catalyst loading to 20 mol%, and the reaction time from overnight to 40 h (Entries 7–11). By combining all of these variations, we observe 98% conversion (85% isolated yield) and 98% ee. Throughout this work we chose to use 20 mol% of our readily available catalyst to slightly improve the results, however it is not necessary to use this catalyst loading (*c.f.* Table 1, Entries 6 and 8). We also show that using 5 mol% catalyst (Entry 12, 66% conversion,

91% ee) can give good results and demonstrate (*vide infra*) that preparative scale (~1 g) reactions are easily carried out using 10 mol% catalyst.

We examined various β -substituted α,β -unsaturated thioesters. *n*-Pentyl substituted **2b** almost performed as well as model substrate **2a** (Table 2, Entries 1 and 2). We found that *trans*- α,β -unsaturated thioesters provided much better results than *cis*-electrophiles (*c.f.* **2c** and **2d**, Entries 3 and 4). It may be that the lower ee with *cis*-**2d** is partially due to double bond isomerization during ACA as a reaction using *cis*-**2d** quenched after 15 hours gave *R*-**3d** with 25% yield and 78% ee and the recovered thioester had a *trans/cis* (**2c** to **2d**) ratio of 1:19. The use of (hetero) aromatic β -substituted substrates gave moderate yields (Entries 5 and 6) with the ee's decreased substantially.

The scope of the reaction was investigated using substrates **2a** and **2c** with different zirconium species, especially those containing functional groups. While styrenes are sometimes difficult substrates in alkyl zirconocene additions here the yield and enantioselectivity are high (75%, 97% ee, Table 3, Entry 1). Both 2-bromo styrene and 4-methoxy styrene performed well using our method (Entries 2 and 3) giving ee's over 97%. Alkenes bearing protected alcohols (Entries 4 and 9), unsaturated C-C bonds (Entries 5 and 6), halogens (Entries 7 and 8) and bulky vinylcyclohexane, all gave >92% ee and most products were obtained with >96% ee.

Table 2 Scope of acyclic α,β -unsaturated thioesters

Entry	Substrate	Product	Yield ^[1] ee ^[2]
1 ^[3]	2a	3a	85% 98%ee
2 ^[3]	2b	3b	73% 97%ee
3 ^[4]	2c	3c	80% 97%ee
4 ^[4]	2d	(R)-3c	47% 73%ee
5 ^[4]	2e	3d	63% 71%ee
6 ^[4]	2f	3e	60% 66%ee

Reaction conditions: Hydrosilylation is performed on alkene before ACA. alkene (2.5 eq.), [Cp₂ZrHCl] (2 eq.), enone (1 eq.), copper (20 mol%), ligand (20 mol%), silver (22 mol%), TMSCl (5 eq.) [1] Yield of isolated product. [2] Enantiomeric excess was determined by HPLC. [3] But-3-en-1-ylbenzene was used. [4] Ethylene was used.

We decided to test our approach in the synthesis of some commercially used fragrances where the enantiomers are known to

show different characteristics. We first made the phenoxanols, which have a rosy fragrance and are widely used under various brand names¹⁵ (Scheme 2) from styrene via ACA and then LiAlH₄ reduction. This sequence gave overall yields around 70% for each enantiomer (both 97% ee). We next synthesized (*R*)-hydroxycitronellal¹⁶ (Scheme 2, bottom), which is a perfume ingredient and more expensive than the *S*-enantiomer. Commercially available 2-methylpent-4-en-2-ol was subjected to benzyl protection, ACA, DIBAL reduction and then deprotection to give the fragrance with an overall yield of 62% in 98% ee.

Table 3 Scope of alkenes

Reaction conditions: Hydrozirconation is performed on alkene before ACA. alkene (2.5 eq.), [Cp ₂ ZrHCl] (2 eq.), enone (1 eq.), copper (20 mol%), ligand (20 mol%), silver (22 mol%), TMSCl (5 eq.) [1] Yield of isolated product. [2] Enantiomeric excess was determined by HPLC. [3] α,β-unsaturated thioester 2d was used instead of 2a .		Reaction conditions: Hydrozirconation is performed on alkene before ACA. alkene (2.5 eq.), [Cp ₂ ZrHCl] (2 eq.), enone (1 eq.), copper (20 mol%), ligand (20 mol%), silver (22 mol%), TMSCl (5 eq.) [1] Yield of isolated product. [2] Enantiomeric excess was determined by HPLC. [3] α,β-unsaturated thioester 2d was used instead of 2a .	
Entry	Substrate	Product	Yield ^[1] ee ^[2]
1			75% 97%ee
2			70% 99%ee
3			64% 97%ee
4			75% 98%ee
5			73% 93%ee
6 ^[3]			64% 92%ee
7 ^[3]			62% 97%ee
8 ^[3]			74% 97%ee
9 ^[3]			74% 96%ee
10 ^[3]			83% 97%ee

Reaction conditions: Hydrozirconation is performed on alkene before ACA. alkene (2.5 eq.), [Cp₂ZrHCl] (2 eq.), enone (1 eq.), copper (20 mol%), ligand (20 mol%), silver (22 mol%), TMSCl (5 eq.) [1] Yield of isolated product. [2] Enantiomeric excess was determined by HPLC. [3] α,β-unsaturated thioester **2d** was used instead of **2a**.

The broad range of deoxypropionate containing natural products has promoted the development of many methods for their stereocontrolled synthesis^{13, 17}. However, most of these are limited to the introduction of simple alkyl groups when forming stereocentres. The present method allows

incorporation of several functional groups, which may open a door to more complex “deoxypropionate” units and complement existing methods for iterative synthesis. We therefore examined an iterative route for the stereocontrolled synthesis of 1,3-acyclic arrays where nucleophiles containing important functional groups (an aryl bromide, a protected alcohol, and an alkyl bromide, Scheme 3) were added in sequence.

Scheme 2 Synthesis of phenoxanol (top) and *R*-hydroxycitronellal (bottom)

Scheme 3 Gram-scale asymmetric conjugate addition with 10% catalyst and an asymmetric iterative catalytic route for the synthesis of highly functionalized “deoxypropionate”

This provided the opportunity to examine the ACA on a preparative scale. On a gram scale using 10 mol% catalyst, alkene **1f** and α, β-unsaturated thioester **2a**, we obtained good results (1.03 g **3i**, 70% yield, 96% ee) similar to those on a small-scale with 20% catalyst (75% yield, 98% ee). Product **3i**

was then subjected to DIBAL reduction and a Horner–Wadsworth–Emmons reaction (HWE) to give α,β -unsaturated thioester **5b**. ACA using (*S*)-**D** gave *syn*-thioester **5c** as a 97.5:2.5 mixture of diastereomers and 59% overall yield for the sequence, while the use of (*R*)-**D** gave *anti*-**5d** with a d.r. of 98:2. Further conversion of **5d** to Michael acceptor **5e** allowed formation of a third stereogenic centre via the copper catalysed addition of a Br-containing alkyl chain with a diastereometric ratio of 98:2. This work demonstrates that the formation of new stereogenic centres in these acyclic arrays operates under almost complete ligand control, and that the method is tolerant to the presence of important functional groups that could allow the construction even more complex molecules.

In conclusion, we have established a new Cu-catalysed ACA to enantioselectively generate β -stereogenic centres in acyclic carboxylic acid derivatives. A range of α,β -unsaturated thioesters can be used but the best yields and ee's are obtained when forming tri-*n*-alkyl substituted products. The method tolerates halides, benzyl and silyl ethers, arenes, as well as C-C double and triple bonds without compromising enantioselectivity. The fragrances phenoxanol (97% ee) and hydroxycitronellal (98% ee) were easily made in good yield and preliminary experiments show the reaction can be scaled to 1.0 g with 10% catalyst loading. This method also enables a catalytic asymmetric iterative approach for the synthesis of acyclic 1,3-stereochemical arrays.

ZG thanks the China Scholarship Council (CSC) for financial support. SF acknowledges funding from the EPSRC (EP/N022246/1).

Notes and references

- (a) S. R. Harutyunyan, T. d. Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824–2852; (b) A. Alexakis, J. E. Bačckvall, N. Krause, O. Pa'mies and M. Die'guez, *Chem. Rev.*, 2008, **108**, 2796–2823; (c) A. Alexakis, N. Krause and S. Woodward, *Copper-Catalyzed Asymmetric Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014; (d) S. R. Harutyunyan, in *Progress in Enantioselective Cu(I)-catalyzed Formation of Stereogenic Centers*, Springer, Switzerland, 2016, vol. 58, pp. 1–2.
- L. Mola, M. Sidera and S. P. Fletcher, *Aust. J. Chem.*, 2015, **68**, 401–403.
- (a) R. M. Maksymowicz, A. J. Bissette and S. P. Fletcher, *Chem. Eur. J.*, 2015, **21**, 5668–5678; (b) K. Garrec and S. P. Fletcher, *Org. Lett.*, 2016, **18**, 3814–3817.
- (a) R. M. Maksymowicz, P. M. Roth and S. P. Fletcher, *Nat. Chem.*, 2012, **4**, 649–654; (b) R. M. Maksymowicz, P. M. Roth, A. L. Thompson and S. P. Fletcher, *Chem. Commun.*, 2013, **49**, 4211–4213.
- P. M. Roth and S. P. Fletcher, *Org. Lett.*, 2015, **17**, 912–915.
- (a) M. Sidera, P. M. Roth, R. M. Maksymowicz and S. P. Fletcher, *Angew. Chem. Int. Ed.*, 2013, **52**, 7995–7999; (b) P. M. Roth, M. Sidera, R. M. Maksymowicz and S. P. Fletcher, *Nat. Protoc.*, 2014, **9**, 104–111.
- Z. Gao and S. P. Fletcher, *Chem. Sci.*, 2017, **8**, 641–646.
- (a) H. You, E. Rideau, M. Sidera and S. P. Fletcher, *Nature*, 2015, **517**, 351–355; (b) E. Rideau, H. You, M. Sidera, T. D. W. Claridge and S. P. Fletcher, *J. Am. Chem. Soc.*, 2017, **139**, 5614–5624.
- E. E. Maciver, R. M. Maksymowicz, N. Wilkinson, P. M. Roth and S. P. Fletcher, *Org. Lett.*, 2014, **16**, 3288–3291.
- Unpublished work
- R. Šebesta, I. Némethová and Z. Sorádová, *Synthesis*, 2017, **49**, 2461–2469.
- S. Y. Wang and T. P. Loh, *Chem. Commun.*, 2010, **46**, 8694–8703.
- R. D. Mazery, M. Pullez, F. Lo'pez, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2005, **127**, 9966–9967.
- A. Alexakis, S. Goncalves-Contal, L. Gremaud, L. Palais and L. Babel, *Synthesis*, 2016, **48**, 3301–3308.
- W. M. Akhtar, C. B. Cheong, J. R. Frost, K. E. Christensen, N. G. Stevenson and T. J. Donohoe, *J. Am. Chem. Soc.*, 2017, **139**, 2577–2580.
- T. Yamamoto, in *Current Topics in Flavours and Fragrances: Towards a New Millennium of Discovery*, ed. K. A. D. Swift, Springer Netherlands, Dordrecht, 1999, DOI: 10.1007/978-94-011-4022-5_3, pp. 33–58.
- (a) S. Hanessian, Y. Yang, S. Giroux, V. Mascitti, J. Ma and F. Raepel, *J. Am. Chem. Soc.*, 2003, **125**, 13784–13792; (b) P. Demel, M. Keller and B. Breit, *Chem. Eur. J.*, 2006, **12**, 6669–6683; (c) B. t. Horst, B. L. Feringa and A. J. Minnaard, *Org. Lett.*, 2007, **9**, 3013–3015; (d) B. ter Horst, B. L. Feringa and A. J. Minnaard, *Chem. Commun.*, 2007, DOI: 10.1039/b612593j, 489–491; (e) Y. Schmidt and B. Breit, *Org. Lett.*, 2009, **11**, 4767–4769; (f) T. den Hartog, D. Jan van Dijken, A. J. Minnaard and B. L. Feringa, *Tetrahedron: Asymmetry*, 2010, **21**, 1574–1584; (g) S. Xu, A. Oda, T. Bobinski, H. Li, Y. Matsueda and E. Negishi, *Angew. Chem. Int. Ed.*, 2015, **54**, 9319–9322; (h) S. Drissi-Amraoui, T. E. Schmid, J. Lauberteaux, C. Crévisy, O. Baslé, R. M. de Figueiredo, S. Halbert, H. Gérard, M. Mauduit and J.-M. Campagne, *Advanced Synthesis & Catalysis*, 2016, **358**, 2519–2540; (i) S. Xu, H. Li, M. Komiyama, A. Oda and E. I. Negishi, *Chem. Eur. J.*, 2017, **23**, 149–156.

Asymmetric Conjugate Addition of Alkylzirconium Reagents to α , β -Unsaturated Thioesters: Access to fragrances and acyclic stereochemical arrays

Zhenbo Gao and Stephen P. Fletcher*

Department of Chemistry, University of Oxford. Chemistry Research Laboratory,
12 Mansfield Road, Oxford, OX1 3TA (UK).

An asymmetric iterative route for the synthesis of acyclic stereochemical arrays is obtained by addition to α , β -unsaturated thioesters.