Construction of β to carbonyl stereogenic centres by asymmetric 1,4-addition of alkylzirconocenes to dienones and ynones

Received 00th January 20xx,
Accepted 00th January 20xx

Zhenbo Gao and Stephen P. Fletcher*

DOI: 10.1039/x0xx00000x

www.rsc.org/

Copper-catalyzed asymmetric 1,4-addition of alkylzirconium species to linear $\alpha,\beta,\gamma,\delta$ unsaturated dienones and ynones is reported. A variety of alkyl nucleophiles are introduced with good yields and excellent regio- and enantio-selectivities to give tertiary carbon centres bearing multiple functional groups. The method is also applicable to an ynethioate with ee's over 96%.

Asymmetric conjugate addition (ACA) is a powerful method for the construction of stereogenic centres.¹ In the majority of methods used to add alkyl groups, non-stabilized organometallic reagents are used as nucleophiles, which limits on the sophistication of the alkyl unit and functional groups that can be introduced.²

In our previous work³ we developed ACAs of alkylzirconium species, generated in situ from alkenes and Cp_2ZrHCl , which allow highly enantioselective construction of β -chiral centres from cyclic⁴ and noncyclic⁵ enones, α,β -unsaturated lactones⁶ and thioesters⁷ (black in Scheme 1). However, using these methods we were never able to access molecules with vinyl or alkenyl groups attached to the newly formed stereocentre (blue molecules in Scheme 1).

To obtain these unsaturated targets (shown in blue in Scheme 1), and significantly expand the range of molecules that can be accessed using our methods, we examined several approaches. Attempted Cu-catalyzed ACA of alkenylzirconocenes to construct $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^3}$ bonds⁸ always gave unsatisfactory results. For example, using (E)-hept-3-en-2-one and pent-4-yn-1-ylbenzene (not shown) in combination with a series of copper salts and ligands we were unable to observe any enantiocontrol in the products. This manuscript reports an indirect method to prepare these products – asymmetric 1,4-addition to $\alpha,\beta,\gamma,\delta$ -unsaturated substrates to construct chiral centres β to the carbonyl group.

Scheme 1 Previous work and present work on the copper-catalyzed asymmetric conjugate addition of alkyl zirconium species to various Michael acceptors

In metal-catalyzed asymmetric additions to $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds it is necessary to obtain both excellent regio- and enantio-selectivity and while several groups have reported asymmetric additions polyconjugated systems, most describe procedures to obtain 1,6-addition products.

Enantioselective 1,6-additions have been published by Hayashi who reported Rh-catalyzed additions of aryl zincs to dienones,⁹ Ir-catalyzed additions of arylboroxines¹⁰ and Co-catalyzed additions of acetylene derivatives.¹¹ The Alexakis¹², Guénée^{12b}, Crévisy¹³ and Mauduit^{12b,13} groups have developed Cu-catalyzed methods to construct δ chiral centres from dienones and the Feringa¹⁴ and Hoveyda¹⁵ groups reported asymmetric 1-6 additions to dienones. Fillion et al.¹⁶ examined 1,6-addition to Meldrum's acid derivatives and Feng¹⁷ explored Sc-catalyzed asymmetric 1-6 additions of oxindoles to linear dienyl ketones.

^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

Table 1 Scope of dienones

Entry	Substrate	Product	Yield [%] ^a	ee [%] ^b
1			61	97
2			65	96
3			87	92
4			-	-
5 ^c			53	47
6 ^c			70	43
7 ^c			63	86
8 ^d			51	54
9 ^{d,e}			77	95

Reaction conditions: alkene (2.5 eq.), [Cp₂ZrHCl] (2 eq.), DCM (0.2 ml), enone (1 eq.), copper (10 mol%), ligand (10 mol%), silver (11 mol%), TMSCl (5 eq.); ^aYield of isolated product. ^bAbsolute configuration of **3p** known, other products assigned by analogy (see Supporting information); enantiomeric excess was determined by HPLC or SFC. ^c**1f** was used instead of **1i**. ^dEthylene **1j** was used instead of **1i**. ^e20% catalyst loading was used in a combination of DCM and Et₂O (1:1).

We found that ACA of alkylzirconium species to linear $\alpha,\beta,\gamma,\delta$ -unsaturated dienones, ynones, and ynethioates forms new C-C bonds with stereogenic centres β to carbonyl and excellent regio- and enantio-selectivity (Scheme 1). The method produces tertiary stereogenic centres and each substituent can bear a functional group. The reason for the excellent regioselectivity observed here is currently unclear. In contrast

Various dienones and yneones are easily prepared by Horner-Wadsworth-Emmons reactions of α,β -unsaturated aldehydes and phosphonates. Using coupling partners **1a** and **2a** the combination of copper (I) triflate (generated in situ) and ligand **A** in the presence of TMSCl at 0 °C affords **3a** with 70% yield and 90% ee (Table 1, entry 1). Without TMSCl, 35% yield was observed and the ee dropped to 79% ee. We also found that when we decreased the amount of Schwartz reagent to 1.5 eq. the yield of **3a** decreased to 60%, while 96% ee was observed, the reasons for these effects are not clear but mechanistic studies on related systems are underway. Remarkably, under these conditions no 1,6-adduct was observed at all. The scope of the reaction was studied using **2a** and different zirconium

species bearing functional groups. Alkenes featuring unsaturated C-C bonds (entries 2, 3), a protected alcohol (entry 4), a silane (entry 5), halogens (entries 6, 7) all worked well with the exception of diene **1c**. We found a styrene derivatives could be added in 60% yield and 90% ee, although here some 1,6-adduct was observed (1,4 to 1,6 ratio ~20:1) (entry 8), however in this case **2b** was the starting dienone and it might be that a terminal aromatic ring on the polyene promotes selectivity in favour of complete 1,4-addition.

To further investigate, we examine different dienones using our previous conditions and alkene **1i** (Table 2). Alkyl substituted dienones **2b** and **2c** (entries 1, 2) both afforded 1,4-products with over 60 % yield and 96% ee although a small amount of 1,6 adducts were also observed (1,4 to 1,6 ratio ~20:1). When the bulkier dimethyl substituted dienone **2d** was tested, no 1,6 adduct was obtained (entry 3). With dienone **2e** no reaction was observed overnight and **2e** was recovered. Several dienones with different substitutes on the aromatic rings (entries 5-7) were examined with a loss of enantiocontrol seen with electron donating aromatics and good results with an electron withdrawing group to give **3o** in 86% ee. With substrate **2i**, where a phenyl group replaces the carbonyl methyl group, only 51% yield with 54% ee was observed (entry 8). However, dithioate **2j** gave very good result (77% yield, 95% ee, entry 9), and the thioester group could be transformed into a range of carbonyl derivatives.

The absolute configuration of **3p** was obtained by comparison of optical rotation data with the literature^{19a}, similarly the absolute configuration of **5a** (see below and supporting information) is known. All other stereochemical assignments in this manuscript are made by analogy to **3p** and **5a**.

We also explored if we could reduce the amount of catalyst used in the coupling of **1i** and **2c**. When the catalyst loading was decreased from 10% to 2.5%, the yield and ee were not affected at all (table 3, entries 1-3). 84% ee was observed when 1.2% catalyst was used but ee dropped significantly with 0.5% catalyst (6% ee, entry 5).

Table 3 Catalyst loading study with dienone **2c**

Entry	Catalyst loading [%]	Yield [%] ^a	ee [%] ^b
1	10.0	65	96
2	5.0	63	96
3	2.5	64	96
4	1.2	60	84
5	0.5	63	6

^a Yield of isolated product. ^b Enantiomeric excess was determined by HPLC.

We next examined linear $\alpha,\beta,\gamma,\delta$ -unsaturated substrates featuring triple bonds, ynenones and ynethioates, to test the generality of our method (Table 4). Using alkene **1j** and the

same conditions as above gave **5a** in 70% yield with 94% ee (entry 1). Vinylcyclohexane **1a** was introduced with both good yield and ee (87%, 95% ee, entry 2) and alkenes bearing unsaturated C-C bonds (entries 3, 4), protected alcohols (entry

Table 4 Additions to ynenones and ynethioates

<p> $\text{[Cp}_2\text{ZrHCl]} \text{ DCM;}$ $\text{CuCl (10 mol\%), AgOTf (11 mol\%)}$ $\text{Ligand A (10 mol\%)}$ $\xrightarrow[\text{Et}_2\text{O, ice bath, overnight}]{\text{TMSCl (5.0 eq)}}$ </p>					
Entry	Substrate	Product	Yield [%] ^a	ee [%] ^b	
1		5a	70	94	
2		5b	87	95	
3		5c	84	96	
4		5d	69	92	
5		5e	66	94	
6		5f	75	94	
7		5g	76	96	
8c		5h	66	97	
9c		5i	75	96	

Reaction conditions: alkene (2.5 eq.), $[\text{Cp}_2\text{ZrHCl}]$ (2 eq.), DCM (0.2 ml), enone (1 eq.), copper (10 mol %), ligand (10 mol %), silver (11 mol %), TMSCl (5 eq.) ^a Yield of isolated product. ^b Absolute configuration of **5a** known, other assignments by analogy (see Supporting information); enantiomeric excess was determined by HPLC or SFC. ^c 20 % catalyst loading was used with a mixture of DCM and Et_2O (1:1) as solvent.

5), silanes (entry 6) and halogens (entry 7) could all be installed in around 70% yield with at least 92% ee.

A ynethioate was prepared and tested and, in accordance with previous work, unsaturated thioesters are less reactive than enones making reactions slower.⁷ Increasing the catalyst loading from 10% to 20%, and using a mixture of solvents for these additions (1:1 DCM and Et_2O), allowed alkenes to be introduced in around 70% yield with 96% ee (entries 8, 9).

We can lower the catalyst loading with ynenones. Examining the addition of **1b** to **4a** both the yield and ee were sustained when reducing the catalyst loading from 10% to 1.2 % (table 5, entries 1-4), but serious loss of ee was at 0.5 % loading (table 5, entry 5).

In conclusion, we have established a robust method to construct stereogenic centres β to carbonyl groups by ACAs to linear $\alpha,\beta,\gamma,\delta$ -unsaturated dienones, ynenones and ynethionates. Good yield as well as regio- and enantioselectivity are observed. The method tolerates halides, silyl ethers, arenes, silanes, and C-C double bonds in the nucleophilic alkylzirconium species. Catalyst loading may be decreased to 2.5 % for dienones and 1.2 % for ynenones without much loss in yield or ee. As the products can contain three useful functional groups we believe this new system could be useful for the asymmetric synthesis of target compounds.

Table 5 Catalyst loading study on ynenone **4a**

Entry	Catalyst loading [%]	Yield [%] ^a	ee [%] ^b
1	10.0	75	96
2	5.0	80	95
3	2.5	75	95
4	1.2	79	92
5	0.5	71	36

^aYield of isolated product. ^bEnantiomeric excess was determined by HPLC.

ZG thanks the China Scholarship Council (CSC) and SPF thanks the EPSRC (UK) for financial support.

Notes and references

- (a) A. Alexakis, N. Krause and S. Woodward, *Copper-Catalyzed Asymmetric Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2014; (b) S. R. Harutyunyan, in *Progress in Enantioselective Cu(I)-catalyzed Formation of Stereogenic Centers*, Springer, Switzerland, 2016, vol. 58, pp. 1-2.
- (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. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796-2823.
- (a) P. M. Roth, M. Sidera, R. M. Maksymowicz and S. P. Fletcher, *Nat. Protoc.*, 2014, **9**, 104-111; (b) R. M. Maksymowicz, A. J. Bissette and S. P. Fletcher, *Chem. Eur. J.*, 2015, **21**, 5668-5678; (c) 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; (c) M. Sidera, P. M. Roth, R. M. Maksymowicz and S. P. Fletcher, *Angew. Chem. Int. Ed.*, 2013, **52**, 7995-7999; (d) D. Caprioglio and S. P. Fletcher, *Chem. Commun.*, 2015, **51**, 14866-14868.
- (a) P. M. Roth and S. P. Fletcher, *Org. Lett.*, 2015, **17**, 912-915; (b) Z. Gao and S. P. Fletcher, *Chem. Sci.*, 2017, **8**, 641-646.
- E. E. Maciver, R. M. Maksymowicz, N. Wilkinson, P. M. Roth and S. P. Fletcher, *Org. Lett.*, 2014, **16**, 3288-3291.
- Z. Gao and S. P. Fletcher, *Chem. Commun.*, 2017, **53**, 10216-10219.
- (a) S. Oi, T. Sato and Y. Inoue, *Tetrahedron Letters*, 2004, **45**, 5051-5055; (b) K. C. Nicolaou, W. Tang, P. Dagneau and R. Faraoni, *Angew. Chem. Int. Ed.*, 2005, **44**, 3874-3879; (c) M. Sidera and S. P. Fletcher, *Chem. Commun.*, 2015, **51**, 5044-5047.
- T. Hayashi, S. Yamamoto and N. Tokunaga, *Angew. Chem. Int. Ed.*, 2005, **44**, 4224-4227.
- T. Nishimura, A. Noishiki and T. Hayashi, *Chem. Commun.*, 2012, **48**, 973-975.
- T. Sawano, A. Ashouri, T. Nishimura and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 18936-18939.
- (a) H. Henon, M. Mauduit and A. Alexakis, *Angew. Chem. Int. Ed.*, 2008, **47**, 9122-9124. (b) M. Tissot, D. Poggiali, H. Henon, D. Muller, L. Guenee, M. Mauduit and A. Alexakis, *Chem. Eur. J.*, 2012, **18**, 8731-8747.
- M. Magrez-Chiquet, M. S. Morin, J. Wencel-Delord, S. Drissi Amraoui, O. Basle, A. Alexakis, C. Crevisy and M. Mauduit, *Chem. Eur. J.*, 2013, **19**, 13663-13667.
- (a) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard and B. L. Feringa, *Angew. Chem. Int. Ed.*, 2008, **47**, 398-401; (b) T. den Hartog, Y. Huang, M. Fañanás-Mastral, A. Meuwese, A. Rudolph, M. Pérez, A. J. Minnaard and B. L. Feringa, *ACS Catal.*, 2014, **5**, 560-574.
- F. Meng, X. Li, S. Torker, Y. Shi, X. Shen and A. H. Hoveyda, *Nature*, 2016, **537**, 387-393.
- (a) E. Fillion, A. Wilsily and E. T. Liao, *Tetrahedron: Asymmetry*, 2006, **17**, 2957-2959. (b) S. Chen, L. Wu, Q. Shao, G. Yang and W. Zhang, *Chem. Commun.*, 2018, **54**, DOI: <http://dx.doi.org/10.1039/C8CC00493E>
- Z. Wang, T. Kang, Q. Yao, J. Ji, X. Liu, L. Lin and X. Feng, *Chem. Eur. J.*, 2015, **21**, 7709-7712.
- T. den Hartog, D. Jan van Dijken, A. J. Minnaard and B. L. Feringa, *Tetrahedron: Asymmetry*, 2010, **21**, 1574-1584.
- (a) Z. Ma, F. Xie, H. Yu, Y. Zhang, X. Wu and W. Zhang, *Chem. Commun.*, 2013, **49**, 5292-5294; (b) X. Wu, F. Xie, Z. Ling, L. Tang and W. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 2510-2518.
- M. Tissot and A. Alexakis, *Chem. Eur. J.*, 2013, **19**, 11352-11363.
- S. Okada, K. Arayama, R. Murayama, T. Ishizuka, K. Hara, N. Hirone, T. Hata and H. Urabe, *Angew. Chem. Int. Ed.*, 2008, **47**, 6860-6864.
- (a) A. Masarwa, D. Didier, T. Zabrodski, M. Schinkel, L. Ackermann and I. Marek, *Nature*, 2014, **505**, 199-203; (b) A. Vasseur, L. Perrin, O. Eisenstein and I. Marek, *Chem. Sci.*, 2015, **6**, 2770-2776; (c) J. Bruffaerts, D. Pierrot and I. Marek, *Org. Biomol. Chem.*, 2016, **14**, 10325-10330; (d) A. Vasseur and I. Marek, *Nat. Protoc.*, 2017, **12**, 74-87.
- (a) S. Oi, A. Taira, Y. Honma and Y. Inoue, *Org. Lett.*, 2003, **5**, 97-99. (b) A. Alexakis, V. Albrow, K. Biswas, M. d'Augustin, O. Prieto and S. Woodward, *Chem. Commun.*, 2005, **3**, 2843. (c) V. E. Albrow, A. J. Blake, R. Fryatt, C. Wilson and S. Woodward, *European J. Org. Chem.*, 2006, 2549-2557. (d) R. Shintani, Y. Ichikawa, T. Hayashi, J. Chen, Y. Nakao and T. Hiayama, *Org. Lett.*, 2007, **9**, 4643-4645. (e) T. Nishimura, T. Katoh, K. Takatsu, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2007, **129**, 14158-14159. (f) T. Nishimura, X. X. Guo, N. Uchiyama, T. Katoh and T. Hayashi, *J. Am. Chem. Soc.*, 2008, **130**, 1576-1577.