C–C Coupling Hot Paper

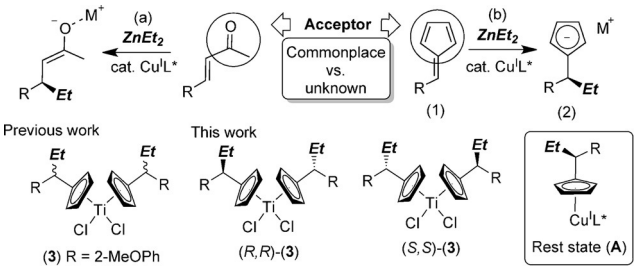
International Edition: DOI: 10.1002/anie.201508034
German Edition: DOI: 10.1002/ange.201508034

Asymmetric Pentafulvene Carbometalation—Access to Enantiopure Titanocene Dichlorides of Biological Relevance

Melchior Cini, Tracey D. Bradshaw,* Simon Woodward,* and William Lewis*

Abstract: *Unprecedented asymmetric copper-catalyzed addition of $ZnEt_2$ ($ZnBu_2$) to the exocyclic C=C bond of pentafulvenes C_5H_4(=CHAr) (Ar = 2-MeOPh and related species) results in enantiomerically enriched (up to 93:7 e.r.) cyclopentadienyl ligands ($C_5H_4CHEtAr$; abbreviated Cp^R). Copper catalyst promotion with both chiral phosphoramidite ligands and a phosphate additive is vital in realizing both acceptable enantioselectivities and reaction rates. Enantiomeric $Cp^R{}_2TiCl_2$ complexes have been prepared; the (S,S) isomer is twice as active towards pancreatic, breast, and colon cancer cell lines as its (R,R) enantiomer at 24 h.*

Asymmetric copper-catalyzed 1,4-addition reactions of organozinc reagents, especially $ZnEt_2$, to enones (e.g., ArCH=CHAc) have become commonplace in the last 10 years (Scheme 1 a).[1] Although they contain an equally powerful anion-accepting group (C_5H_4), the equivalent copper-catalyzed enantioselective carbozincation of pentafulvenes **1** is unknown (Scheme 1 b). Such methodology could, if realized, provide rapid access to enantioenriched substituted cyclopentadienyl ligands **2** that have many applications in synthesis, catalysis,[2] and biology.[3] To give just one specific example, titanocene dichloride **3**, which is an active anticancer agent in micromolar quantities,[3] and presently known only as a mixture of stereoisomers, would become available as single enantiomers, thus facilitating biological screening and potentially allow clinical trials.



Scheme 1. Common Cu^I-catalyzed asymmetric 1,4-addition (a) vs. unknown carbozincation (b) reactions, and applications.

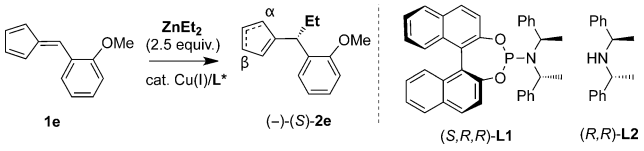
A limited number of stereoselective addition reactions of organometallic reagents to pentafulvenes are known,[4] but all these examples involve stoichiometric chiral additives, including those of Hayashi using **1a** ($R = NMe_2$) and 120 mol% ArLi/(−)-sparteine (63:37 to 96:4 e.r.), Mintz's hydride transfer from *n*BuLi to **1b** (using exocyclic =CPhMe moieties and 100 mol% (−)-proline, e.r. < 59:41), Togni's diasteriose-lective addition of MeLi to the (*R*) enantiomer of **1c** ($R = N(Me)CHcC_6H_{11}$) (90:10 to 94:6 d.r.), and related work by Otero using **1d** (R = (−)-myrtenyl) (d.r. > 99:1). Apart from these examples, only nonstereoselective or achiral addition reactions to fulvenes have been reported (and these are limited to Me and sp^2 C-nucleophiles).[5] The lack of catalytic methodology is due, in part, to the stability of cyclopentadienide-bound kinetic products (see the putative rest state **A**). We found that such rest states could apparently be transmetalated with Grignard reagents to allow the closure of catalytic cycles and effective pentafulvene carbomagnesiation.[3] Unfortunately, Cu^IL^* catalysis using RMgBr provided only racemic products in our own studies (a library of 13 ligands).[3] We predicted that, because of their higher covalency, organozinc-derived copper catalysts would maximize the chances of attaining the desired enantioselective carbocupration. However, the lack of any reported Cu^I catalyst for ZnR_2 enantioselective C=C addition reactions[1] strongly suggested that intermediates related to **A** were very stable and that poor catalyst turnover would have to be overcome.

First trials were conducted using $ZnEt_2$ and pentafulvene **1e** as an assay to determine the e.r. values of the product **2e** is greatly simplified by rapid exchange of the [1,5]-sigmatropic α/β tautomers during GC analysis on a chiral support above 100 °C. From an initial ligand library (see the Supporting Information), phosphoramidite **L1** in the presence of Cu^I precursors was shown to be the highest enantioselective lead (Table 1). As predicted, the reaction suffered from very poor activity and conditions leading to the formation of the Lewis acidic cuprates (runs 1 vs. 2–6) were needed for even partial turnover. Higher loadings (runs 3 and 6) favored significant enantioselectivity and a marginal increase in yield. Additionally, we discovered that MTBE was the optimal solvent and highly purified phosphoramidite **L1** is required as its degradation product **L2** engenders significant ligand acceleration[6] but with minimal enantioselectivity (run 8). While AlR_3 reagents are known to cleave phosphoramidites

[*] Dr. M. Cini, Prof. Dr. S. Woodward, Dr. W. Lewis
School of Chemistry, University of Nottingham, University Park
Nottingham NG7 2RD (UK)
E-mail: simon.woodward@nottingham.ac.uk
Dr. M. Cini, Prof. Dr. T. D. Bradshaw
School of Pharmacy, Centre for Biomolecular Sciences
University of Nottingham, University Park
Nottingham NG7 2RD (UK)
E-mail: cinimelchior@gmail.com
tracey.bradshaw@nottingham.ac.uk

Supporting information for this article (including all synthetic and catalytic procedures, characterization data for all compounds, NMR spectra, biological evaluations, and X-ray crystallographic data for (*R*,*R*)- and (*S*,*S*)-**3**) is available on the WWW under http://dx.doi.org/10.1002/anie.201508034.

Table 1: Cu^{I} phosphoramidite promoted $ZnEt_2$ addition to pentafulvene **1e**.[a]

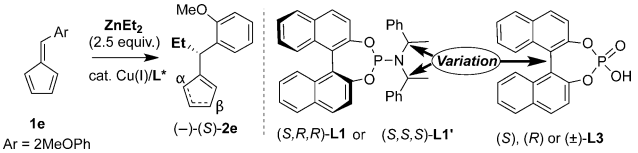


1e (–)-(*S*)-**2e** (*S*,*R*,*R*)-**L1** (*R*,*R*)-**L2**

Run	Cu source ([mol%])	L* ([mol%])	Conditions	**2e** [%][b]	e.r. (**2e**)[b]
1	Cu(TC)[c] (5)	**L1** (10)	0°C, toluene	2	50:50
2	$Cu(OTf)_2$ (5)	**L1** (10)	0°C, toluene	6	58:42
3	$Cu(OTf)_2$ (25)	**L1** (50)	0°C, toluene	16	71:29
4	$Cu(OTf)_2$ (15)	**L1** (30)	25°C, toluene	10	64:36
5	$Cu(OTf)_2$ (15)	**L1** (30)	25°C, MTBE[c]	20	88:12
6	$Cu(OTf)_2$ (20)	**L1** (40)	25°C, MTBE	24	89:11
7	$Cu(OTf)_2$ (20)	**L1′**[c] (40)	25°C, MTBE	25	63:37
8	$Cu(OTf)_2$ (15)	**L2** (30)	25°C, MTBE	76	51:49

[a] Cu source and **L*** in solvent (2.0 mL) stirred for 1 h followed addition of by **1e** (0.5 mmol). After 10 min, $ZnEt_2$ (2.5 equiv) added dropwise and the mixture stirred (16 h). [b] Yield and e.r. value determined by GC analysis on a chiral CP-Chirasil-DEXCB column against internal standard. [c] TC = 2-thiophenecarboxylate; MTEB = 2-methoxy-2-methylpropane. **L1′** is the (*S*,*S*,*S*)-diastereomer of **L1** (see also Table 2).

Table 2: Additive and ligand matching in copper-catalyzed $ZnEt_2$ addition to pentafulvene **1e**.[a]



1e Ar = 2MeOPh (–)-(*S*)-**2e** (*S*,*R*,*R*)-**L1** or (*S*,*S*,*S*)-**L1′** (*S*), (*R*) or (±)-**L3**

Entry	$Cu(OTf)_2$ ([mol%])	L* ([mol]%)	Additive ([mol%])	Yield **2e** [%][b]	e.r. (**2e**)[b]
1	20	(*S*,*R*,*R*)-**L1** (40)	–	24	89:11
2	20	(*S*,*R*,*R*)-**L1** (30)	(*S*)-**L3** (10)	1	86:14
3	20	(*S*,*R*,*R*)-**L1** (30)	(*R*)-**L3** (10)	2	86:14
4	20	(*S*,*S*,*S*)-**L1′** (40)	–	24	60:40
5	20	(*S*,*S*,*S*)-**L1′** (30)	(*S*)-**L3** (10)	34	90:10
6	20	(*S*,*S*,*S*)-**L1′** (30)	(*R*)-**L3** (10)	81	87:13
7	20	(*S*,*S*,*S*)-**L1′** (30)	(±)-**L3** (10)	58	90:10
8	12	(*S*,*S*,*S*)-**L1′** (18)	(*S*)-**L3** (13)	36	88:12
9	10	(*S*,*S*,*S*)-**L1′** (15)	(*R*)-**L3** (10)	81	85:15
10	12	(*S*,*S*,*S*)-**L1′** (18)	(±)-**L3** (13)	66	88:12

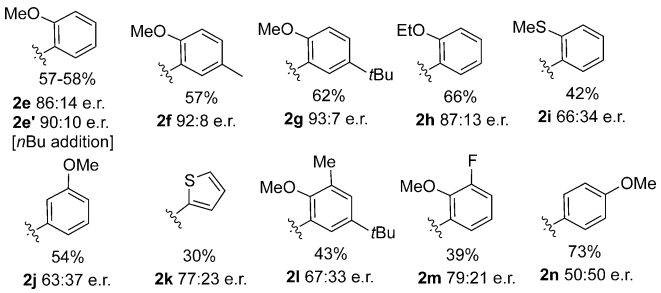
[a] Cu source **L*** and additive in MTBE (1.2 mL) stirred for 1 h, followed by addition of **1e** (0.3 mmol) in MTBE (0.6 mL). After 10 min, $ZnEt_2$ (2.5 equiv) added dropwise and the mixture stirred (16 h). [b] Yield and e.r. value determined by GC analysis on a chiral CP-Chirasil-DEX CB column against tridecane as internal standard. "Variation" in the scheme indicates change of *R*/*S* stereochemistry.

in low-polarity solvents,[7] this behavior is not normally an issue with ZnR_2; we could detect no **L1** degradation at the end of 16 h runs.

Other phosphoramidite ligands provided a range of e.r. values but no significant increase in activity ,and non-phosphoramidite ligand classes were devoid of any enantioselectivity (see the Supporting Information). As electron-deficient $Cu(OTf)_2$ was our most effective precursor (its derived cuprates are known to favor fast additions in copper catalysis[1]), we sought a related additive that might improve or mimic the of behavior of $Cu(OTf)_2$. Bridging ligands are known to play a critical role in organizing selective transition states in asymmetric copper(I) catalysis[8] but are seldom, if ever, modified to chiral units for copper-catalyzed asymmetric catalysis. To our delight, use of the simple commercially available phosphoric acid **L3** had a profound effect on the rate of the carbozincation, and, to a more limited extent, its enantioselectivity (Table 2).

It is clear that **L3** is accommodated into the catalyst and that it affects the rate of turnover—mismatched with the (*S*,*R*,*R*)-**L1** catalyst, but matched with (*S*,*S*,*S*)-**L1′** for (*R*)-**L3** (runs 1 vs. 2–3 and 4 vs. 6 and 9). As the e.r. values were not strongly affected, we trialed the low-cost (±)-**L3**; to our satisfaction it could provide acceptable catalysis at lower loadings (runs 7 vs. 10). A small library of phosphoric acid additives were then tested (see the Supporting Information) but (±)-**L3** was still the best coadditive. The hypothesis that use of (*S*,*S*,*S*)-**L1′**/(±)-**L3** results in the formation of (–)-(*S*)-**2e** was validated by formation of the titanocene dichloride **3** and subsequent X-ray crystallographic analysis to confirm that the (*R*,*R*) stereoisomer was formed. We believe that both the triflate and phosphate **L3** are present in the activated catalyst as Cu(**L3**)$_2$ sources alone are ineffective when combined with **L1′**. Addition of $ZnBu_2$ to **1e** (under conditions of run 10) proceeded analogously to provide the butyl analogue **2e′** with 90:10 e.r. As we assumed that the methoxy group within **1e** acted as a directing group to the chiral catalyst, we tested this hypothesis using other 6-substituted pentafulvene starting materials containing donor groups on aryl or heteroaryl rings, using the conditions of Table 2, run 10 (Scheme 2). Use of substrates with 5-alkyl substituents (**2f** and **2g**), as well as with an ethoxy substituent (**2h**) led to an increase in the enantioselectivity of the reaction. The requirement of a proximal coordinating group was confirmed as vital: Ar = 2-MeOPh (**2e**) gave 86:14 e.r.; Ar = 3-MeOPh (**2j**) provided 63:37 e.r., whilst Ar = 4-MeOPh (**2n**) led to racemic addition. The methoxy group in **2n** is apparently too far away for favorable coordination in the enantioselective transition state. These conclusions were supported by thienyl (**2k**) which gave only a modest e.r. value, and by related modifications of the OMe to alternative donor groups (see the Supporting Information). Based on the configuration determined for **2e**, an (*S*) configuration for the major enantiomers attained from (*S*,*S*,*S*)-**L1** has been tentatively assigned for **2e′**–**m**.

The utility of the cyclopentadienes (**2**) was demonstrated by the preparation of both enantiomers of **3** through



Scheme 2. Scope of catalytic cupration of fulvenes (**1**) as a function of 6-aryl unit.

complexation of (*R*)- and (*S*)-**2e** to $TiCl_4$.[3] Rapid quantitative deprotonation of (*S*)-**2e** by *n*BuLi (1.1 equiv) in Et_2O at 0 °C led to the formation of the lithium-substituted cyclopentadienide. Transmetalation with titanium tetrachloride in THF at reflux for 16 h led to the formation of the enantioenriched (*R*,*R*)-**3**. The synthesis of (*S*,*S*)-**3** was carried out in an analogous way using (*R*)-**2e**. After recrystallization enantiomerically pure samples of (*S*,*S*)- and (*R*,*R*)-**3** were obtained containing, at worst, traces of the achiral *meso* diastereomer (see the Supporting Information). The parent titanocene dichloride Cp_2TiCl_2 ($Cp = C_5H_5$) is a clinically trialed anticancer agent with lower in vivo tissue toxicity than the more commonly encountered Pt-based drugs (cisplatin, carboplatin). Substituted titanocenes $Cp^R{}_2TiCl_2$ ($Cp^R = C_5H_4R$; R = a wide range of substituents) are much more cytotoxic than the parent,[5a,b,9] but the mechanism(s) of action of these agents remains poorly defined—excessive cellular uptake of Cp-free "Ti^{4+}" being the most often cited proposal.[10] The antiproliferative activities of the enantiopure titanocenes (*R*,*R*)-**3**, (*S*,*S*)-**3**, in comparison to the stereoisomeric mixture (*rac*/*meso*)-**3**, and cisplatin were evaluated in vitro at 24 h against the carcinoma cell lines: HCT-116 (colorectal), MiaPaCa-2 (pancreatic), and MDA-MB-468 (breast). A 24 h time period was selected as real-time microscopy studies indicate cancer cell death reached a maximum by 4–6 h, and activity was moderated after 24 h. The values given in Table 3 show that

Table 3: Stereoisomer-dependent in vitro growth inhibition by **3** vs. cisplatin.[a]

Cell line	(*R*,*R*)-(**3**)	(*S*,*S*)-(**3**)	(*rac*/*meso*)-(**3**)[b]	cisplatin
Mia PaCa-2	42.5 ± 0.5	19.9 ± 3.5	32.3 ± 2.8	35.4 ± 1.4
MDA-MB-468	22.8 ± 2.8	11.5 ± 1.2	23.6 ± 0.4	7.4 ± 2.8
HCT-116	31.3 ± 1.6	14.8 ± 1.7	31.6 ± 3.9	34.9 ± 3.0

[a] Cell growth inhibition after 24 determined by MTT assay (GI_{50} in μM); GI_{50} values are represented as mean standard error of mean (SEM) of at least three independent experiments ($n = 4$ per experiment). [b] 1:1:1:1 mixture of *R*,*R*/*S*,*S*/*R*,*S*/*S*,*R*.

statistical ($P < 0.05$) differential biological activity is observed in cancer cell lines for the stereoisomers of **3**. Additionally, compared to cisplatin, (*S*,*S*)-**3** shows more than twice the activity against colon carcinoma, and almost twice the activity in pancreatic carcinoma. On the other hand, cisplatin is more active than (*S*,*S*)-**3** in breast carcinoma.

The stereoisomer-dependent activity of **3** can only be in accord with hydrolysis to "Ti^{4+}" species if such processes are biologically mediated. Hydrolysis of the parent Cp_2TiCl_2 has been proposed to be transferrin-controlled, thus fulfilling this requirement.[10] However, recent studies have shown poor inhibition of A549 lung cancer cell growth by Cp_2TiCl_2 either in the presence or absence of transferrin or Ti-transferrin itself.[11] Other protein chaperones might well offer mechanism(s) for the uptake of ligated titanium species into cells, leading to mechanisms of action dependent on initial titanium ligation, as has been recently shown for the case of $TiCl_2(C_5H_4CH_2C_6H_4\text{-}4\text{-}OMe)_2$ versus salen-based titanium species.[12]

In conclusion, the first examples of copper-catalyzed asymmetric carbozincation of pentafulvenes have been demonstrated. This reaction allows access to a range of enantioenriched substituted cyclopentadienes and their metal complexes. Such species are attracting increasing attention for use in a wide range of applications.[2] While the enantioselectivities and yields of the present system are modest, the use of dual phosphoamidite/phosphite copper catalysis provides a new tool for successful asymmetric carbocupration in what has been a very fallow area.[1,13]

Acknowledgements

We thank the University of Nottingham for a studentship and the support of the Edith Johnson Bequest (M. Cini). We thank A. Kuruppu and D. McLean for their assistance with the biological studies.

Keywords: asymmetric catalysis · carbometalation · C—C coupling · copper · ligand effects

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14179–14182
Angew. Chem. **2015**, *127*, 14385–14388

[1] Overview of copper-catalyzed asymmetric processes: *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), Wiley-VCH, Weinheim, **2014**, Chapters 2 and 10.
[2] Overviews of substituted chiral cyclopentadienyls: a) R. L. Halterman, *Chem. Rev.* **1992**, *92*, 965–994; b) H. H. Brintzinger, D. Fisher, R. Mulhaupt, B. Reiger, R. M. Waymouth, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1143–1170; *Angew. Chem.* **1995**, *107*, 1255–1283; c) O. Vassylyev, A. Panarello, J. G. Khinast, *Molecules* **2005**, *10*, 587–619; d) J.-B. Sortais, C. Darcel, *ChemCatChem* **2013**, *5*, 1067–1068.
[3] M. Cini, T. D. Bradshaw, W. Lewis, S. Woodward, *Eur. J. Org. Chem.* **2013**, 3997–4007.
[4] a) T. Suzuka, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2002**, *67*, 3355–3359; b) H. C. L. Abbenhuis, U. Burckhardt, V. Gramlich, A. Togni, A. Albinati, B. Müllers, *Organometallics* **1994**, *13*, 4481–4493; c) E. A. Mintz, PCT Int. Appl., **1992**, WO1992012112A1; d) M. Honrado, A. Otero, J. Fernández-Baeza, L. F. Sánchez-Barba, A. Lara-Sánchez, J. Tejeda, M. P. Carrión, J. Martínez-Ferrer, A. Garcés, A. M. Rodríguez, *Organometallics* **2013**, *32*, 3437–3440.
[5] Nonstereoselective additions to pentafulvenes: a) M. Hogan, J. Cotter, J. Claffey, B. Gleeson, D. Wallis, D. O'Shea, M. Tacke, *Helv. Chim. Acta* **2008**, *91*, 1787–1797; b) M. Hogan, J. Claffey, C. Pampillón, R. W. G. Watson, M. Tacke, *Organometallics* **2007**,

26, 2501 – 2506; c) E. Kirillov, N. Marquet, M. Bader, A. Razavi, V. Belia, F. Hampel, T. Roisnel, J. A. Gladysz, J.-F. Carpentier, *Organometallics* **2011**, *30*, 263 – 272; d) G. E. Herberich, U. Englert, T. Wirth, *Eur. J. Inorg. Chem.* **2005**, 4924 – 4935. Typically, C-nucleophiles are limited to methyl or sp^2 aryl/heteroaryl systems; with alkyl ($\geq C_2$) organometallics, extensive β-hydride transfer results (e.g. ref. [4c]). This is not the case in our system.

[6] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070; *Angew. Chem.* **1995**, *107*, 1159 – 1171.

[7] C. Bournaud, C. Falciola, T. Lecourt, S. Rosset, A. Alexakis, L. Micouin, *Org. Lett.* **2006**, *8*, 3581 – 3584.

[8] a) S. Woodward in *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), Wiley-VCH, Weinheim, **2014**, Chapter 1; b) P.-F. Larsson, P.-O. Norrby, S. Woodward in *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), Wiley-VCH, Weinheim, **2014**, Chapter 12.

[9] U. Olszewski, A. Deally, M. Tacke, G. Hamilton, *Anti-Cancer Agents Med. Chem.* **2010**, *10*, 302 – 311.

[10] K. M. Buettner, A. M. Valentine, *Chem. Rev.* **2012**, *112*, 1863 – 1881.

[11] A. D. Tinoco, H. R. Thomas, C. D. Incarvito, A. Saghatelian, A. M. Valentine, *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 5016 – 5021.

[12] a) J. Schur, C. M. Manna, A. Deally, R. W. Köster, M. Tacke, E. Y. Tshuvab, I. Ott, *Chem. Commun.* **2013**, *49*, 4785 – 4787; b) E. Y. Tshuva, J. A. Ashenhurst, *Eur. J. Inorg. Chem.* **2009**, 2203 – 2218.

[13] Even in the widest sense (carbometalation of any prochiral C=C unit), successful asymmetric catalytic systems are rare and frequently require use of reactive endocyclic alkenes: a) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2000**, *122*, 978 – 979; b) K. Kramer, P. Leong, M. Lautens, *Org. Lett.* **2011**, *13*, 819 – 821; c) M. Lautens, S. Hiebert, *J. Am. Chem. Soc.* **2004**, *126*, 1437 – 1447. Asymmetric alkene carboalumination (85:15 to 98:2 e.r.) is the most developed reaction: d) E. Negishi, *ARKIVOC* **2011**, 34 – 53.

Received: August 27, 2015
Published online: October 12, 2015

