Asymmetric Pentafulvene Carbometallation – Access to Enantiopure Titanocene Dichlorides of Biological Relevance

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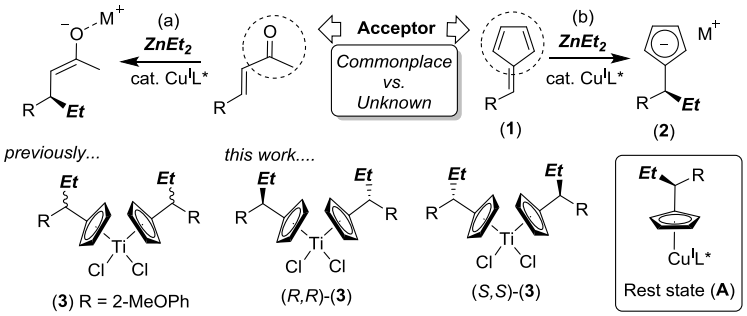
Abstract: *Unprecedented asymmetric copper-catalysed addition of $ZnEt_2$ ($ZnBu_2$) to the exocyclic C=C bond of pentafulvenes C_5H_4(=CHAr) (Ar = 2-MeOPh and related species) yields enantiomerically enriched (up to 93:7 er) cyclopentadienyl ligands [$C_5H_4CHEtAr$; abbreviated Cp^R]. Copper catalyst promotion with both chiral phosphoramidite ligands and a phosphate additive is vital in realising both acceptable enantioselectivities and reaction rates. Demonstrating the utility of these chiral cyclopentadienyl ligands 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-catalysed 1,4-additions of organozincs, especially $ZnEt_2$, to enones (*e.g.* ArCH=CHAc) have become commonplace in the last 10 years (Scheme 1a).[1] Although they contain an equally powerful anion accepting group (C_5H_4), equivalent copper-catalysed enantioselective carbocupration of pentafulvenes **1** is unknown (Scheme 1b). Such methodology could, if realised, provide rapid access to enantio-enriched substituted cyclopentadienyl ligands **2** having many applications in synthesis, catalysis[2] and biology.[3] To give just one specific example, the micromolar active anti-cancer titanocene dichloride **3** (presently known only as a mixture of stereoisomers)[3] would become available as single enantiomers, facilitating biological screening and potentially access to clinical trial candidates in time.

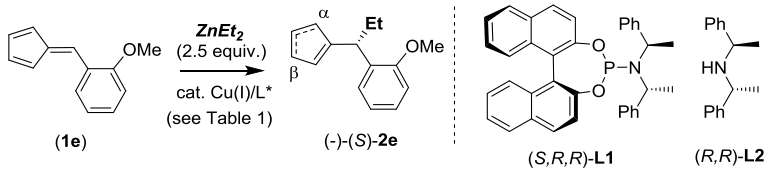


Scheme 1. Exemplary common Cu(I)-catalysed asymmetric 1,4-addition *vs*. unknown carbozination and applications.

A limited number of stereoselective additions of organometallics to pentafulvenes are known[4] but all are stoichiometric in chiral additive including: those of Hayashi using **1a** (R = NMe_2) and 120 mol-% ArLi/(-)-sparteine (*er* 63:37 to 96:4), Mintz's hydride transfer from *n*BuLi to **1b** (using exocyclic =CPhMe and 100 mol-% (-)-proline, *er* < 59:41), Togni's diasterioselective addition of MeLi to the (*R*) enantiomer of **1c** (R = $CHcC_6H_{11}$) (*dr* 90:10 to 94:6) and related work by Otero using **1d** (R = (-)-myrtenyl) (*dr* >99:1). Aside from these, only non-stereoselective or achiral additions to fulvenes are 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, *cf*. the putative rest state (**A**). Recently, we found such rest states could apparently be transmetallated with Grignard reagents allowing closure of catalytic cycles and effective pentafulvene carbomagnesiation.[3] Unfortunately, Cu(I)L* catalysis using RMgBr provided only racemic products in our own studies (library of 13 ligands).[3] We predicted, due to their higher covalency, organozinc-derived copper catalysts would maximise the chances of attaining the desired enantioselective carbocupration. However, the lack of any published Cu(I) catalyst for ZnR_2 enantioselective C=C addition[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 *er* assay of the product **2e** is greatly simplified by rapid exchange of the [1,5]-sigmatropic α/β tautomers during chiral GC analysis above 100 °C. From an initial ligand library (Supporting Information), phosphoramidite **L1** in the presence of Cu(I) precursors was attained as 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 (Run 1 *vs*. 2-6) were needed for even partial turnover. Higher loadings (Runs 3 and 6) favoured 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 while its degradation product **L2** engenders significant ligand acceleration[6] it does so with minimal enantioselectivity (Run 8). While AlR_3 reagents are known to cleave phosphoramidites in low polarity solvents[7] this is not normally an issue with ZnR_2 reagents and we could detect no **L1** degradation at the end of 16 h runs.

Table 1. Cu(I)-phosphoramidite promoted $ZnEt_2$ additions to pentafulvene **1e**.[a]

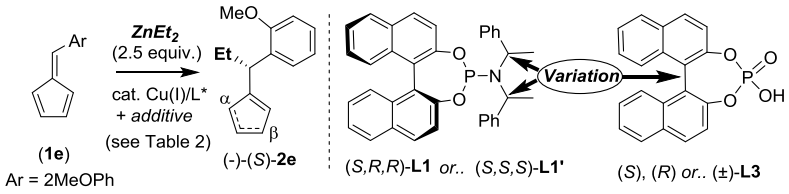


Run	Cu-source (mol-%)	**L*** (mol-%)	Conditions	**2e**/%[b]	*er* (**2e**)[b]
1	Cu(TC) (5)	**L1** (10)	0 °C, toluene	2	50:50
2	$Cu(OTf)_2$ (5)	**L1** (10)	0 °C, toluene	6	58:42
3	$Cu(OTf)_2$ (25)	**L1** (50)	0 °C, toluene	16	71:29
4	$Cu(OTf)_2$ (15)	**L1** (30)	25 °C, toluene	10	64:36
5	$Cu(OTf)_2$ (15)	**L1** (30)	25 °C, MTBE	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 by **1e** (0.5 mmol). After 10 min $ZnEt_2$ (2.5 equiv.) added dropwise and the mixture stirred (16 h). [b] Yield and *er* by chiral GC analysis on a CP-Chirasil-DEXCB column against internal standard. [c] (*S,S,S*)-diastereomer of **L1**.

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

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

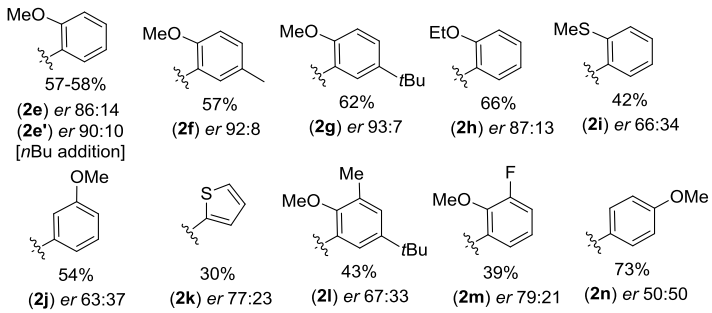


Entry	$Cu(OTf)_2$ (mol-%)	L* (mol-%)	Additive (mol-%)	Yield **2e** (%)[b]	*er* (**2e**)[b]
1	20	(*S,R,R*)- **L1** (40)	-	24	89:11
2	20	(*S,R,R*)- **L1** (30)	(*S*)- **L3** (10)	1	86:14
3	20	(*S,R,R*)- **L1** (30)	(*R*)- **L3** (10)	2	86:14
4	20	(*S,S,S*)- **L1'** (40)	-	24	60:40
5	20	(*S,S,S*)- **L1'** (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 **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 *er* by chiral GC on a CP-Chirasil-DEX CB column against tridecane as internal standard.

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 *er* values were not strongly affected we also trialled 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 (Supporting Information) but simple (±)-**L3** was still the best co-additive. The correlation that (*S,S,S*)-**L1'**/(±)-**L3** provides (-)-(*S*)-**2e** was attained by formation of the titanocene dichloride **3** (see later) and subsequent crystallographic confirmation that the (*R,R*) stereoisomer was formed. We believe that both the triflate and phosphate **L3** are present in the

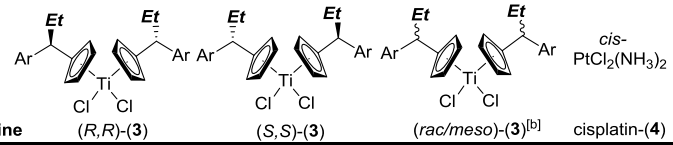
activated catalyst as Cu(**L3**)$_2$ sources alone are ineffective when combined with **L1'**. Addition of $ZnBu_2$ to **1e** (under conditions of run 10) proceeded analogously providing the butyl analogue **2e'** with an *er* of 90:10. As we assumed that the methoxy group within **1e** acted as a directing 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). Substrates **2f** and **2g** having 5-alkyl substituents together with **2h** bearing an ethoxy substituent, 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 *er* 86:14; Ar = 3-MeOPh (**2j**) provided *er* 63:37, whilst Ar = 4-MeOPh (**2n**) led to racemic addition. The methoxy group in **2n** is apparently too far away for favourable coordination in the enatantioselective transition state. These conclusions were supported by thienyl (**2k**) which gave only a modest *er*, and by related modifications of the OMe to alternative donor groups (see Supporting Information). Based on the correlation attained for **2e** an (*S*) configuration for the major enantiomers attained from (*S,S,S*)-**L1** has been tentatively assigned for **2e'-m**.



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

Finally, the utility of the cyclopentadienes (**2**) was demonstrated by the preparation of both enantiomers of **3** through complexation of (*R*)- and (*S*)-**2e** to $TiCl_4$ using a literature approach.[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 which was then cannula filtered, dried and weighed under vacuum. Transmetallation with titanium tetrachloride in refluxing THF for 16 h led to the formation of the enantio-enriched (*R,R*)-**3**. 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 (Supporting Information). The parent titanocene dichloride Cp_2TiCl_2 (Cp = C_5H_5) is a clinically-trialled anti-cancer agent of 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 **4** 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 was maximised by *ca*. 4-6 h and activity was moderated after 24 h. As can be seen in Scheme 3 statistical ($P<0.05$) differential biological activity was observed in cancer cell lines for the stereoisomers of **3**. Additionally, compared to cisplatin,

(*S,S*)-**3** shows a >2-fold more activity against colon carcinoma, and almost twice the activity as cisplatin in pancreatic carcinoma. On the other hand, cisplatin is more active than (*S,S*)-**3** in breast carcinoma.



Cell line	(*R,R*)-(**3**)	(*S,S*)-(**3**)	(*rac/meso*)-(**3**)[b]	*cis*-$PtCl_2(NH_3)_2$
Mia PaCa-2	42.5 ± 0.5[a]	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] GI_{50} values in μM at 24 h; Ar = 2-MeOPh. [b] 1:1:1:1 mixture of *R,R*:*S,S*:*R,S*:*S,R* (**3**).

Scheme 3. Stereoisomer-dependent *in vitro* ~~cytotoxicity~~ growth inhibition for (**3**) *vs*. cisplatin (**4**). Cell growth inhibition after 24 h 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).

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, 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 chaperons might well offer mechanism(s) for uptake of ligated titanium species into cells leading to mechanisms of action dependant on initial titanium ligation, as has been recently shown for the case of $TiCl_2(C_5H_4CH_2C_6H_4$-4-OMe$)_2$ *vs*. salen-based titanium species.[12]

In conclusion the first examples of copper-~~catalysed~~ catalyzed asymmetric carbocuprate of pentafulvenes have been demonstrated. This allows access to a range of enantioenriched substituted cyclopentadienes and their metal complexes. Such species are attracting increasing contemporary 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]

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Experimental All synthetic and catalytic procedures, characterization data for all compounds copies of the NMR spectra, biological evaluations and summary X-ray crystallographic data for (*R,R*)- and (*S,S*)-**3** are given in the Supporting Information.

Acknowledgements

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Keywords: Asymmetric catalysis • C-C coupling • Carbometallation • Ligand effects • Copper

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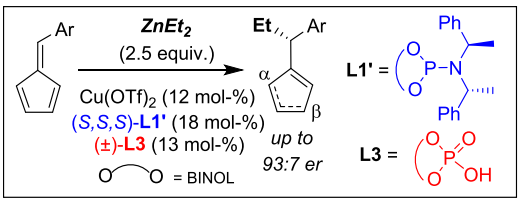

Combined use of phosphoramidite- phosphate ligand systems allows demanding catalytic asymmetric carbozincation of pentafulvenes to be realised for the first time. Derived titanocene dichlorides are useful biological probes.