Click Chemistry

Induction of Planar Chirality Using Asymmetric Click Chemistry by a Novel Desymmetrisation of 1,3-Bisalkynyl Ferrocenes[‡]

Adam J. Wright,[a] David L. Hughes,[a] Phillip C. Bulman Page,[a] and
G. Richard Stephenson*[a]

Abstract: The new asymmetric click CuAAC reaction is used for the first time to induce asymmetry in planar chiral compounds. There are only three classes of stereogenicity (atom-centred, axial and planar), and these results are therefore of fundamental importance as well as practical significance, providing access to chiral ferrocenes at near enantiopurity. Here, we report asymmetric induction (AI) and kinetic resolution (KR) studies on a novel library of prochiral 1,2,3-trisubstituted bis-alkynylferrocenes, obtained by diiodination, derivatisation (in-

cluding reduction and etherification), double Sonogashira coupling and finally transesterification, azidation or silylation. Desymmetrisation using chiral ligands to modify the CuAAC reaction proceeds in up to 60 % yield and >99.5 % ee, yielding planar chiral ferrocenes. The absolute configuration of two of the preferred products was proved by chemical correlation and related to the entire series by circular dichroism spectroscopy (CD).

1. Introduction

Thousands of papers have been published on the copper-catalysed azide-alkyne cycloaddition (CuAAC) click reactions,[1] but only eleven[2] (one of them ours[2a]), report examples of asymmetric "click" chemistry in which a chiral ligand is used to influence the stereochemistry of desymmetrisation reactions of prochiral diazides[2b] and dialkynes[2a,2c–2f,2i,2h] or in kinetic resolutions.[2g,2j,2k] We now provide the first example of a novel induction of planar chirality, achieving ees as high as 99.5 %. Previously-reported applications of asymmetric click chemistry have addressed only carbon-centred[2a–2c,2f–2k] and axial[2d–2e] stereogenicity, and until our work on this topic, the third fundamental class of molecular stereogenicity,[3] the stereogenic plane,[4] has been unexplored. The results reported here fill this gap and complete the range of types of enantiopure structures that can be addressed using the new asymmetric "click" approach. Planar chiral multiply-substituted ferrocenes are an important class of molecules,[5] and in recent years they have come into prominence as scaffolds for chiral ligands that now find widespread use in asymmetric catalysis.[6] While there are already many important examples of preparations of non-race-

mic substituted ferrocenes in the literature, most rely on classic directing groups such as oxazolines,[7a] acetals[7b] and Ugi's amine.[7c] Examples of desymmetrisation approaches are far rarer, but include a series of asymmetric C-H activation reactions,[8a–8d] a lithiation using a chiral amine base[8e] and a two-step asymmetric esterification process.[8f] Our work, reported here, adds a novel alternative to the range of methods that can be employed to access enantiopure planar chiral compounds.

2. Results and Discussion

2.1. Choice of Prochiral Substrates

Because of the ready availability of the starting material, our work on the asymmetric click chemistry of prochiral ferrocenes began with a study of 1,2-diethynylferrocene,[9] but this gave almost entirely the achiral bis-triazole product, and only very low yields of the required mono-triazole. This acceleration of the second click reaction relative to first one is suspected be a consequence of coordination of the catalytic copper to the first triazole.[10] To be useful as a method of asymmetric synthesis, the copper catalysed reaction of the second alkyne must be slower than that of the stereochemically preferred initial site of reaction. To address this issue, we turned to a new series of trisubstituted 1,3-bis-alkynes, in which a central functional group was present to separate the two enantiotopic alkynes and shut down any intramolecular assistance to the second click step. In these circumstances, the remaining alkyne after the initial desymmetrisation should be mismatched with respect to the stereogenicity of the controlling ligand, leading to a slower cycloaddition reaction. Furthermore, with this class of substrate, the nature of the central group can be varied to open

ChemPubSoc
Europe

EurJOC
European Journal
of Organic Chemistry

Full Paper

the way for studies (for examples, see Scheme 1) of the scope of the reaction.
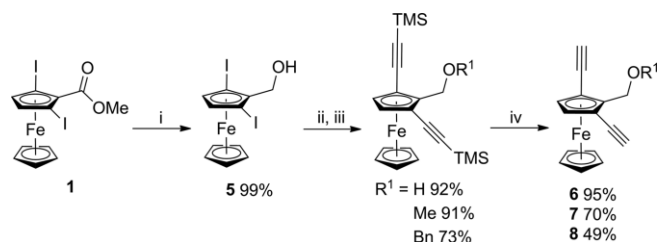
Scheme 1. Examples of the synthesis of alcohol and ether derivatives; i) DIBAL-H, THF, 0 °C to r.t., 10 min; ii) NaH, THF, 0 °C to r.t., 20 min, MeI/BnBr, 16 h; iii) TMS acetylene, bis(triphenylphosphane)palladium(II) chloride, CuI, triethylamine, 45 °C, 16 h; iv) KF, methanol, r.t., 16 h.

We report here asymmetric induction (AI) and kinetic resolution (KR) experiments on a library of such trisubstituted bis-alkynylferrocenes, using a representative selection of chiral ligands prominent in asymmetric reactions chosen because of their importance in other asymmetric "click" methodologies,[2] affording planar chiral ferrocenes with up to 60 % yield and >99.5 % ee. The synthesis of one enantiomer, by the application of a conventional directing group approach,[7a] has provided a proof of absolute configuration by chemical correlation, allowing the absolute configuration of the entire series of desymmetrisation products to be determined by comparison of circular dichroism (CD) spectra. The stereochemical features that control the enantioselectivity of these new asymmetric click reactions, and the influence of KR, which forms achiral bis-triazoles, on the observed levels of stereoselectivity in the mono-triazole products from the asymmetric induction step itself (a "secondary KR effect"), have both been defined in this work.

2.2. Synthesis of Starting Materials and Induction of Asymmetry in Planar Chiral Products

The first trisubstituted bis-alkyne in this series was synthesised from the known[11] methyl 2,5-diiodoferrocenecarboxylate 1 by means of a double Sonogashira coupling with TMS acetylene, followed by desilylation. Desymmetrisation of the resulting compound, methyl 2,5-diethynylferrocenecarboxylate 2, using conditions based on recently established[2c] asymmetric CuAAC "click" reactions [CuICl with (R,R)-Ph-Pybox[12] as the chiral ligand], gave good selectivity for monocycloaddition. Although an initial test using 0.9 equivalents of benzyl azide gave only 16 % ee, the chiral mono-triazole was obtained in a 67 % yield. To investigate the possibility that a secondary KR effect might increase the ee, the reaction was repeated with 1.5 equivalents of the azide; resulting in an improved 31 % ee but a reduced chemical yield (51 %) due to increased formation of the bis-triazole (Scheme 2). This level of ee was sufficient, however, for us to begin a systematic study of differently substituted ferrocenyl 1,3-diynes in which the central (C-2) substituent was varied, using the same asymmetric click conditions in each case (Table 1). These starting materials were obtained (see Supporting Information) by functional group interconversions of the methyl ester. Reduction of 1 to produce 5 gave access to a

series of ethers and 3,3-dimethylbutanoate and benzoyl esters were prepared by double Sonogashira coupling followed by esterification of the alcohol. Ferrocenylmethyl azides were also prepared, but attempted intramolecular CuAAC reactions gave poor results. Successful CuAAC reactions were achieved, however, by using bis-alkynes that were synthesised from 1 by double Sonogashira coupling then hydrolysis and esterification (3), and by double attack with a methyl Grignard reagent (4). These gave contrasting results (a switch in enantioselectivity, Table 1; for assignments of absolute configurations, vide infra). We next examined the less hindered alcohol derivative 6, obtained from 5 by double Sonogashira coupling and desilylation, and the related series of ethers (compounds 7–10). These later examples all showed the same sense of enantioselectivity as that obtained with the first substrate (2).
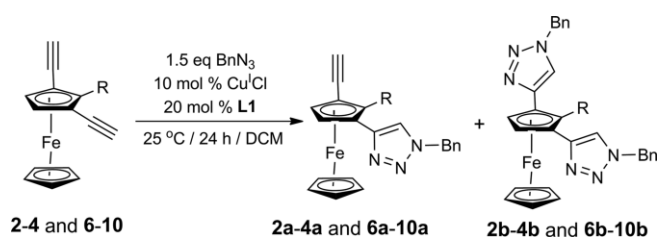
Scheme 2. The substrate screening conditions for the desymmetrisation of bis-alkynylferrocenes (for R, see Table 1).

Table 1. Desymmetrisation of dialkynylferrocenes (Scheme 2) using CuICl and (R,R)-Ph-Pybox, with 1.5 equiv. of benzyl azide.

Structure	R Group	Mono-triazole yield / %	e.e. / %	Starting material yield / %	Bis-triazole yield / %
2	O, OMe	51	31	17	30
3	O, OBn	34	38	1	47
4	OH	19	29[b]	27	46
6	OH	42	97	---	49
7	OMe	47	52	---	49
8	OBn	51	42	8	32
9	OTMS	20[a]	24	23	35[a]
10	OTBDPS	60	79	12	10

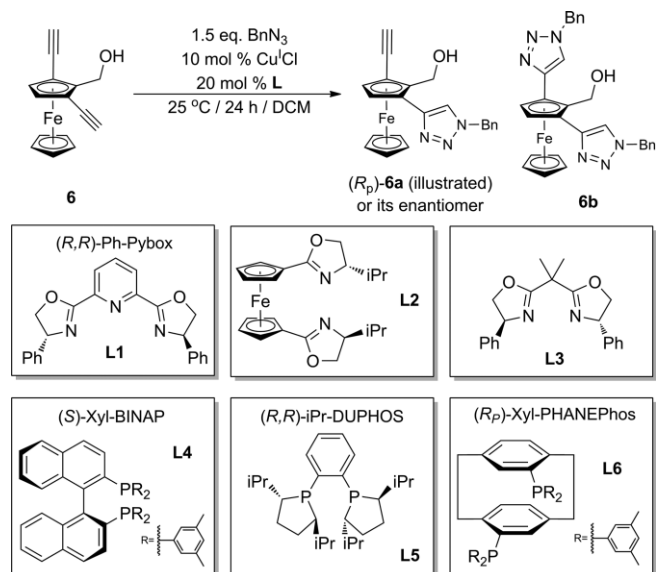[a] TMS deprotected product. [b] Gave the opposite enantiomer to the one that is drawn in Scheme 2.

The asymmetric CuAAC click reaction using alcohol 6 gave a hugely improved 97 % ee and an acceptable 42 % yield of the

ChemPubSoc
Europe

EurJOC
European Journal
of Organic Chemistry

Full Paper

mono-triazole product. Ethers **7** and **8** gave slightly better conversion, but at the cost of a considerable reduction in *ee* when compared to the desymmetrisation of **6**.

Further functionalisation of **6** with TMS to form **9** gave only moderate results. Using *tert*-butyldiphenylsilyl chloride (TBDPSCl) gave bis-alkyne **10**, which after desymmetrisation produced the highest yield of a mono-triazole, 60 %. This reaction also gave a high enough *ee* to prove that a true desymmetrisation must be taking place, since the combination of 79 % *ee* and 60 % chemical yield cannot arise from a non-selective first cycloaddition reaction followed by a highly efficient KR of the resulting near-racemic monotriazole.

2.3. Ligand Screen

After this initial investigation of the influence of different central substituents, we tested a number of ligands that have been shown to be effective in previously published asymmetric click reactions,[2] using our most efficient example, **6**, as the substrate (Scheme 3, and Table 2). The ligand screen produced a range of yields and *ee*s. All the ligands were effective to some extent in promoting the desymmetrisation of **6**, except for **L4,** which produced copper complexes that were not sufficiently catalytically active to consume all the starting material, nor did it generate a good *ee*. This survey includes three N-coordinating

and three P-coordinating ligands, all commercially available. **L3** gave the product (*R*$_P$)-**6a** in almost enantiopure form, but in the lowest chemical yield. In contrast, **L6** gave a high *ee* of the *S*$_P$ enantiomer, as well as a good conversion.

2.4. Possibility That Kinetic Resolution Might Be Influencing Apparent Stereoselectivity

Since the formation of the bis-triazole **6b** is also catalysed by copper bound to the chiral ligand, the possibility that this might influence the apparent enantioselectivity of the desymmetrisation reaction (a secondary KR effect) was probed using a racemic sample of **6** in standard KR experiments (Scheme 4) comparing ligands **L1** and **L6**. An authentic sample of rac-**6a** was synthesised from **6** through a CuAAC reaction catalysed by the very bulky rac-BINAP (to prevent conversion into the unwanted bis-product **6b**).
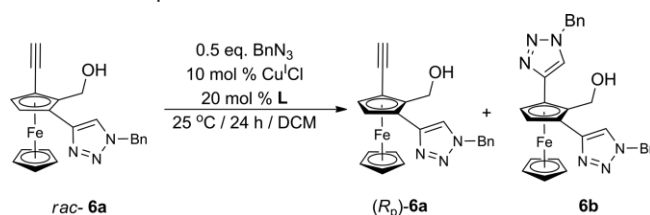
Scheme 4. The KR of *rac*-**6a**, (the results are presented in Table 3).

The results (Table 3) show that high levels of stereoselectivity may be occurring in the initial desymmetrisation step because in both cases the chiral recognition in the KR process is poor. In the case of **L6**, the KR operates in the opposite sense to the asymmetric induction: the asymmetric induction gives an *S*$_P$ product as the major enantiomer (vide supra), but the KR gives an *R*$_P$ product.

Table 3. Results of the KR reactions (Scheme 4) using Cu^{I}Cl and 0.5 equiv. of benzyl azide.

Ligand	**6a** yield / %	*ee* / %	**6b** yield / %
L1	54	32	12
L6	53	7	18

Based on these findings, the influence of the secondary KR effect was then directly demonstrated by performing a series

Scheme 3. The ligand screening conditions for the desymmetrisation of **6** (R = CH$_2$OH; the results are presented in Table 2).

Table 2. Results of the ligand screening reactions (Scheme 3), using Cu^{I}Cl and 1.5 equiv. of benzyl azide.

Ligand	**6a** yield	*ee* / %	**6** yield / %	**6b** yield / %	Azide consumed / %
L1	42	97[a]	–	49	93
L2	30	27[a]	–	46	80
L3	11	>99.5[a]	–	67	>99
L4	34	8[a]	39	–	23
L5	53	43[b]	–	20	63
L6	32	97[b]	–	49	90

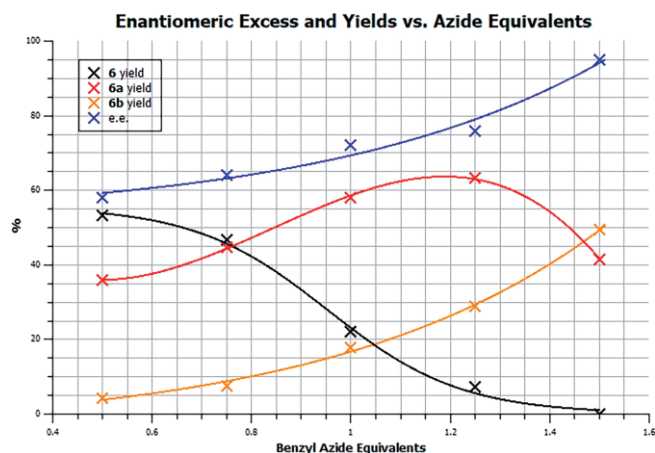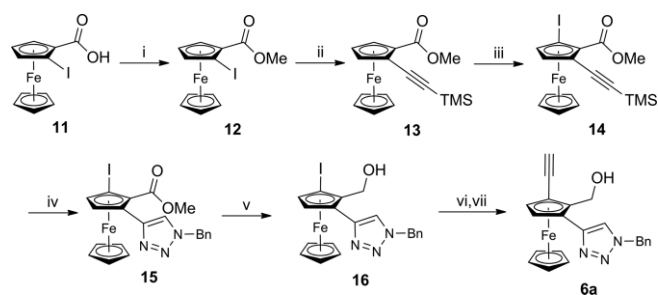[a] *R*$_P$ major enantiomer. [b] *S*$_P$ major enantiomer.

Figure 1. Trends in the yields of products and *ee* of **6a** against the equivalents of benzyl azide used (this data is presented in the Supporting Information).

of desymmetrisation reactions of compound **6**, using ligand **L1** and employing differing quantities of azide. The results reveal that the KR effect is synergistic with the initial asymmetric induction, as the *ee* of **6a** increases with increasing amount of azide (and the consequent increase in the yield of **6b**). This effect is illustrated in Figure 1, which plots the observed *ee* of **6a**, the residual starting material **6**, and the yields of both **6a** and **6b**, against the amount of benzyl azide used in the reaction.

2.5. Determination of Absolute Configuration of the Preferred Product of Asymmetric Induction

The absolute configuration of the *mono*-triazole products of the asymmetric click reactions was determined by chemical correlation (Scheme 5) based on the synthesis of an authentic sample of the R_p enantiomer of **6a** starting from a ferrocenyl carboxylic acid (S_p)-**11** of known absolute configuration.[7a] The required starting material (S_p)-**11** was prepared in four steps following a literature procedure[13] that used a chiral oxazoline directing group,[7a] making (S_p)-**11** available in high *ee*. Our conversion of

(S_p)-**11** into (R_p)-**6a** was performed by esterification, Sonogashira coupling and iodination of the resulting alkyne. Desilylation and a CuAAC click reaction under standard (achiral) conditions was followed by a further Sonogashira reaction and a second desilylation. Crystallisation of the intermediate (R_p)-**14** allowed access to the final product in enantiopure form, and the absolute configuration was confirmed unequivocally by X-ray crystallography (Figure 2).
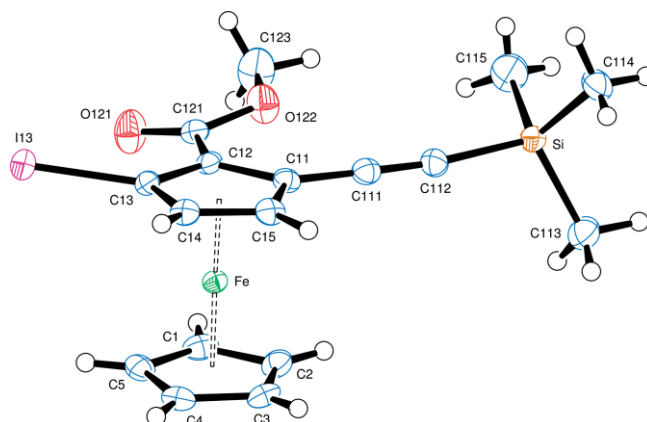

Figure 2. ORTEP diagram for the crystal structure of (R_p)-**14**; CCDC deposition number 1934870 (thermal ellipsoids are drawn at the 50 % probability level).

The CD curve for (R_p)-**6a** (Figure 3, black trace) shows a strong characteristic[14] negative band at 486 nm. The CD curves for the products with alternative central functionality (**2–4** and **7–10**) were also recorded. With one exception, all showed similar negative band maxima in the range 437–486 nm, establishing that all were in the same configurational series (i.e. that the faster reacting enantiotopic alkyne was consistently pro-R_p in all these cases). The one exception (**4a**, which had a strong positive band at 478 nm, magenta trace) was examined in more detail by the preparation of an authentic sample from (R_p)-**15** in two steps (see Supporting Information). This confirmed that this product was indeed (S_p)-**4a**, and that with the very bulky central substituent (CMe_2OH), the enantioselectivity of the

Scheme 5. Synthesis of one of enantiomer **6a** in a known absolute configuration: i) acetyl chloride, MeOH, 40 °C, 16 h; ii) TMS acetylene, bis(triphenylphosphane)palladium(II) chloride, CuᴵI, triethylamine, 45 °C, 16 h; iii) nBuLi, 2,2,6,6-tetramethylpiperidine, ZnCl₂(TMEDA), THF, 0 °C, 2 h, then 1,2-diiodoethane, r.t., 16 h; iv) TBAF, THF, r.t., 20 min, then benzyl azide, CuᴵI, r.t., 16 h; v) DIBAL-H, THF, 0 °C to r.t., 10 min; vi) TMS acetylene, bis(triphenylphosphane)palladium(II) chloride, CuᴵI, triethylamine, 45 °C, 16 h; vii) KF, DCM/MeOH, r.t., 16 h.
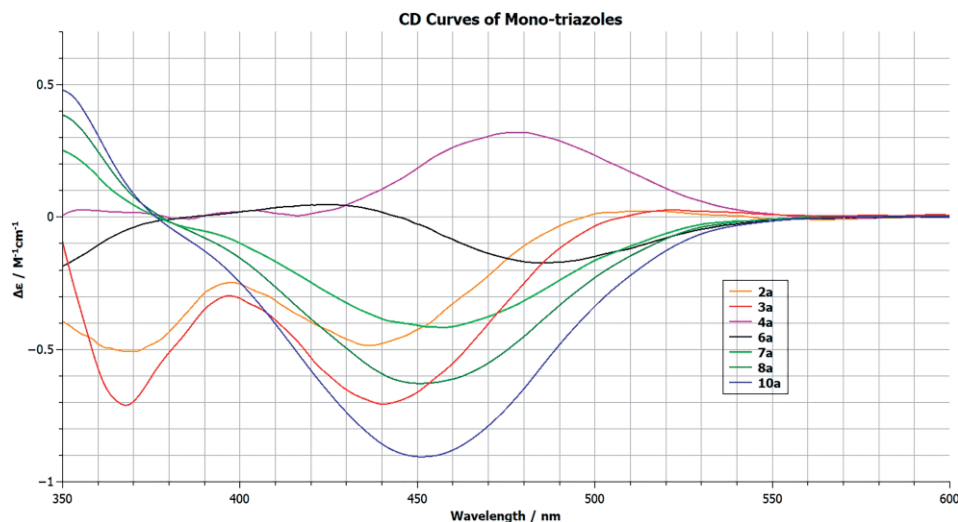

Figure 3. The circular dichroism curves of the mono-triazoles used to correlate the absolute configurations.

ChemPubSoc
Europe

EurJOC
European Journal
of Organic Chemistry

Full Paper

asymmetric click reaction is reversed to favour the pro-S_p pathway.

3. Conclusions

We have shown the first examples of the use of the new asymmetric click reaction to induce planar chirality, giving monotriazole-substituted alkynylferrocenes in high enantiomeric excesses in the cases of three of the ligands studied (**L1**, **L3** and **L6**). The preferred sense of asymmetric induction and the contribution of secondary KR effects to the overall enantiomeric excesses of the isolated products have been identified. Conditions for efficient chiral recognition in the desymmetrisation reaction itself have been demonstrated.

CCDC 1934870 (for (R_p)-**14**), and 1934883 (for **19**, see Supporting Information for structure **19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Experimental Section

Representative procedure for the asymmetric CuAAC click reaction

Copper(I) chloride (10 mol-%) and (R,R)-Ph-Pybox (**L1**, 20 mol-%) were stirred in anhydrous dichloromethane (0.1 M) for 10 min. A solution of the *bis*-alkyne (1 equiv.) in anhydrous dichloromethane (0.1 M) was added. Benzyl azide was added and the reaction mixture was stirred at 25 °C for 24 h. Distilled water was added, and the reaction mixture was extracted three times with dichloromethane. Combined organic phases were dried with sodium sulfate, filtered and the solvent was removed in vacuo. The products were separated by column chromatography (see Supporting Information).

[1] a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708; c) V. V. Fokin, *CuAAC. The quintessential click reaction* (Eds.: K. Ding, L.-X. Dai), in *Organic Chemistry*, Wiley-VCH Verlag GmbH & Co., Weinheim, **2012**, pp 247–277; for a recent update, see:; d) E. Haldón, M. C. Nicasio, P. J. Pérez, *Org. Biomol. Chem.* **2015**, *13*, 9528–9550.

[2] a) G. R. Stephenson, J. P. Buttress, D. Deschamps, M. Lancelot, J. P. Martin, A. I. G. Sheldon, C. Alayrac, A.-C. Gaumont, P. C. Bulman Page, *Synlett* **2013**, *24*, 2723–2729; b) J. Meng, V. V. Fokin, M. G. Finn, *Tetrahedron Lett.*

[2] **2005**, *46*, 4543–4546; c) F. Zhou, C. Tan, J. Tang, Y.-Y. Zhang, W.-M. Gao, H.-H. Wu, Y.-H. Yu, J. Zhou, *J. Am. Chem. Soc.* **2013**, *135*, 10994–1099; d) T. Osako, Y. Uozumi, *Org. Lett.* **2014**, *16*, 5866–5869; e) T. Osako, Y. Uozumi, *Synlett* **2015**, *26*, 1475–1479; f) T. Song, L. Li, W. Zhou, Z.-J. Zheng, Y. Deng, Z. Xu, L.-W. Xu, *Chem. Eur. J.* **2015**, *21*, 554–558; g) J. S. Fossey, B. R. Buckley, W. D. G. Brittain, *Chem. Commun.* **2015**, *51*, 17217–17220; h) M. Y. Chen, Z. J. Zheng, Z. Xu, Y. M. Cui, L. W. Xu, *RSC Adv.* **2016**, *6*, 58698–58708; i) M.-Y. Chen, Z. Xu, L. Chen, T. Song, Z.-J. Zheng, J. Cao, Y. M. Cui, L. W. Xu, *ChemCatChem* **2018**, *10*, 280–286; j) E.-C. Liu, J. J. Topczewski, *J. Am. Chem. Soc.* **2019**, *141*, 5135–5138; k) J. R. Alexander, A. A. Ott, J. J. Topczewski, *Org. Lett.* **2019**, *21*, 4355–4358; for a review, see: l) W. D. G. Brittain, B. R. Buckley, J. S. Fossey, *ACS Catal.* **2016**, *6*, 3629–3636.

[3] a) E. Eliel, S. Wilen, L. Mander, *Stereochemistry of Organic Compounds*, John Wiley and Sons, Inc, New York, **1994**; see also; b) K. Blaha, O. Cervinka, *Chemicke Listy* **1967**, *61*, 897–924; c) L. D. Barron, *BioSystems* **1987**, *20*, 7–14; d) J. Gal J. *Molecular Chirality: Language, History, and Significance* (Ed.: V. Schurig), in *Differentiation of Enantiomers I. Topics in Current Chemistry*, Springer, Cham **2013**, vol. 340; e) B. Testa, *Other stereogenic elements: axes of chirality, planes of chirality, helicity, and (E,Z)-diastereoisomerism* (Eds.: B. Testa, J. Caldwell, M. V. Kisakuerek), in *Organic Stereochemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2014**, pp. 61–85.

[4] For the origin of the term "planar chirality", see: R. S. Cahn, C. Ingold, V. Prelog, *Angew. Chem. Int. Ed. Engl.* **1966**, *4*, 385–415; *Angew. Chem.* **1966**, *78*, 413.

[5] a) J.-C. Zhu, D.-X. Cui, Y.-D. Li, R. Jiang, W.-P. Chen, P.-A. Wang, *ChemCatChem* **2018**, *10*, 907–919; b) R. Yasue, Y. Kazuhiro, *Chem. Eur. J.* **2018**, *24*, 18575–18586.

[6] a) L.-X. Dai, X.-L. Hou, W.-P. Deng, S.-L. Yo, Y.-G. Zhou, *Pure Appl. Chem.* **1999**, *71*, 1401–1405; b) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, X.-L. Hou, *Acc. Chem. Res.* **2003**, *36*, 659–667; c) R. G. Arrayás, J. Adrio, J. C. Carretero, *Angew. Chem. Int. Ed.* **2006**, *45*, 7674–7715; *Angew. Chem.* **2006**, *118*, 7836; d) T. J. Colacot, *Chem. Rev.* **2003**, *103*, 3101–3118.

[7] a) T. Sammakia, H. A. Latham, D. R. Schaad, *J. Org. Chem.* **1995**, *60*, 10–11; b) O. Riant, O. Samuel, H. B. Kagan, *J. Am. Chem. Soc.* **1993**, *115*, 5835–5836; c) D. Marquarding, P. Hoffmann, I. Ugi, G. Gokel, H. Klusacek, *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393.

[8] a) D. W. Gao, Y.-C. Shi, Q. Gu, Z.-L. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2013**, *135*, 86–89; b) D. W. Gao, Q. Yin, Q. Gu, S.-L. You, *J. Am. Chem. Soc.* **2014**, *136*, 4841–4844; c) D. W. Gao, Y. Gu, S. B. Wang, Q. Gu, S.-L. You, *Organometallics* **2016**, *35*, 3227–3233; d) S. Siegel, H. Schmalz, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2456–2458; *Angew. Chem.* **1997**, *109*, 2569; e) G. Dayaker, D. Tilly, F. Chevallier, G. Hilmersson, P. C. Gros, F. Mongin, *Eur. J. Org. Chem.* **2012**, *2012*, 6051–6057; f) C. Valderas, L. Casarrubios, M. C. De, M. A. Sierra, *Tetrahedron Lett.* **2017**, *58*, 326–328.

[9] W. Steffen, M. Laskoski, G. Collins, U. H. F. Bunz, *J. Organomet. Chem.* **2001**, *630*, 132–138.

[10] a) V. O. Rodionov, S. I. Presolski, S. Gardinier, Y.-H. Lim, M. G. Finn, *J. Am. Chem. Soc,* **2007**, *129*, 12696–12704; b) X. You, Z. Wei, *Transit. Met. Chem.* **2014**, *39*, 675–680; c) B. Choubey, L. Radhakrishna, J. T. Mague, M. S. Balakrishna, *Inorg. Chem.* **2016**, *55*, 8514–8526.

[11] G. Dayaker, A. Sreeshailam, F. Chevallier, T. Roisnel, P. R. Krishna, F. Mongin, *Chem. Commun.* **2010**, *46*, 2862–2864.

[12] M. Panera, J. Díez, I. Merino, E. Rubio, M. P. Gamasa, *Inorg. Chem.* **2009**, *48*, 11147–11160.

[13] R. Kuwano, T. Uemura, M. Saitoh, Y. Ito, *Tetrahedron: Asymmetry* **2004**, *15*, 2263–2271.

[14] CD bands in this part of the spectrum have been shown to be indicative of chirality in push-pull disubstituted ferocenes and ferrocenyl peptides, see:; a) I. Janowska, J. Zakrzewski, *Tetrahedron: Asymmetry* **2003**, *14*, 3271–3273; b) V. Kovač, M. C. Semenčić, I. Kodrin, S. Roca, V. Rapić, *Tetrahedron* **2013**, *69*, 10497–10506; c) M. Kovačević, I. Kodrin, M. Cetina, I. Kmetič, T. Murati, M. Č. Semenčić, S. Rocad, L. Barišić, *Dalton Trans.* **2015**, *44*, 16405–16420.