Enantioselective and Regioselective Copper-Catalyzed Borocyanation of 1-Aryl-1,3-Butadienes

Tao Jia,^{†,‡} Marshall J. Smith,[†] Alexander P. Pulis,[†] Gregory J. P. Perry[†] and David, J. Procter^{*,†}

[†]School of Chemistry, University of Manchester, Oxford Rd, Manchester, M13 9PL (UK)

[‡]College of Chemistry and Materials Science, Sichuan Normal University, Chengdu, 610068 (P. R. China)

ABSTRACT: A multicomponent copper-catalyzed enantio- and regioselective borocyanation of 1-aryl-1,3-butadienes has been developed. The method provides access to functionalized allylic nitriles in up to 90% yield and 94% *ee* and thus overcomes some of the long-standing problems associated with the enantioselective insertion of cyano groups into unsaturated organic molecules. Both boron and cyano functionalities can be used as handles for selective manipulation.

KEYWORDS: copper, 1,3-dienes, borylation, asymmetric catalysis, cyanation

Incorporating cyano groups into unsaturated hydrocarbons using transition metal catalysis is established as a highly vital process.¹ The importance of such procedures is best illustrated by the industrial production of adiponitrile,² a key precursor to nylon-6,6, that is currently produced on a >2 million metric ton scale each year by a nickel-catalyzed hydrocyanation of butadiene (the most simple 1,3-diene).³ Intense investigation into this reaction has contributed to some of the fundamental principles of organometallic chemistry.⁴ It is clear that the cyanation of 1,3-dienes is an attractive route for the construction of useful molecules, however, the application of this methodology in complex organic synthesis has stalled due to a lack of enantioselective methods.⁵

Synthetic strategies involving the addition of copper hydride (Cu–H) or copper-boryl (Cu–B) complexes across C=C double bonds, followed by reaction of the resultant organocopper species with electrophiles, have seen great development in recent years.^{6,7} In particular, the copper-catalyzed borofunctionalization of dienes is an attractive route for the rapid build-up of molecular complexity from simple reagents using an inexpensive, non-toxic catalyst.^{8,9} However, there are challenges associated with the borofunctionalization of dienes (Scheme 1); for example, ensuring the Cu–B species (**I**) reacts with a particular substrate (chemoselectivity, *i*)¹⁰ and in a specific fashion (regioselectivity, *ii*). Furthermore, if borofunctionalization is to show its full synthetic utility the development of enantioselective processes are necessary (Scheme 1, step *iii*).

Scheme 1. The challenges in Cu-catalyzed borofunctionalizations of dienes: chemo-, regio- and enantioselectivity.

Scheme 2. A. Rare examples of the enantioselective copper-catalyzed borofunctionalization of dienes. B. Proposed enantioselective copper-catalyzed borocyanation of dienes

Despite these challenges, the first examples of 1,3-diene borofunctionalization have surfaced over the past few years. In 2016, the groups of Hoveyda,¹¹ and Liao and Cao¹² reported the enantioselective carboboration of butadiene, isoprene and other 1,3-dienes (Scheme 2A, *i*). In these cases, the *in situ* generated allyl-Cu species (*cf* Scheme 1, **III**) were trapped with a carbon electrophile (either an enoate or an imine). More recently, Brown and co-workers have developed a similar methodology that uses isoquinolines as imine equivalents,¹³ and have also revealed an approach to the enantioselective arylboration of cyclic arylbutadienes (Scheme 2A, *ii*).¹⁴ Their procedure merges two catalytic cycles: a copper cycle for incorporating boron functionality and a palladium cycle to promote arylation. These three reports demonstrate the current state-of-the-art in enantioselective borofunctionalizations of dienes and go some way to revealing the potential of copper-catalyzed multifunctionalizations.

Continuing our work on copper catalyzed functionalizations of unsaturated hydrocarbons, we were keen to develop an enantioselective method for the borocyanation of 1,3-dienes (Scheme 2B).^{8c,15} If successful, this procedure would yield enantioenriched products bearing both cyano and boron groups, which are ideal for further functionalization. Progress has been made in the field of copper-catalyzed borocyanation,⁷ including recent reports by ourselves^{8c} and Meng *et al.*^{8d} on the borocyanation of 1,3-dienes. However, methods for the enantioselective borocyanation of dienes have not been reported.¹⁶ We believe that the procedure described herein not only represents an interesting example of copper-catalyzed borofunctionalization, but also provides a significant advance in the wider area of enantioselective cyanation of unsaturated hydrocarbons.

We began our investigation by attempting the copper-catalyzed borocyanation of 1-phenyl-1,3-butadiene **1a** with B₂(pin)₂ **2** and the cyanating agent **3** (Table 1).^{17,18} Our previous studies revealed that phosphine ligands can promote regioselective borocyanation.^{8c} Therefore, (*R*)-BINAP **L1** was initially tested (Table 1, Entry 1). This provided a good overall yield of product, however, the regioselectivity of the reaction was poor giving a roughly 50:50 mixture of regioisomers **4a** and **5a**. Despite this, the enantioselectivity of the procedure (45% *ee* for **4a**) was encouraging. A similar C₂-symmetric bidentate phosphine, (*R*)-SEGPHOS **L2**, was also tested, but provided similar yields, regioselectivity and enantioselectivity (Table 1, entry 2). During the 1990's, the groups of Williams, Pfaltz and Helmchen developed a class of non-symmetric chiral phosphinooxazoline (PHOX) ligands.¹⁹ These ligands were found to give superior enantioselectivities and regioselectivities in palladium-catalyzed allylic substitution reactions that proceed via L_nPd-allyl intermediates. We questioned whether PHOX ligands would also prove useful in borocyanations proceeding via L_nCu-allyl intermediates. Interestingly, PHOX ligands have been little used in copper-catalyzed borofunctionalizations of unsaturated bonds.²⁰ Our initial result indeed revealed that PHOX ligand **L3** could impart complete regioselectivity, however, this came at the detriment of enantioselectivity (6% *ee*, Table 1, Entry 3). This demonstrated the challenge of controlling both the regioselectivity and the enantioselectivity of borofunctionalization processes. We then replaced the pendent group at the stereogenic center of the oxazoline ring and found that the ligand substituted with a bulky ^tBu group, **L5**, provided a significant increase in enantioselectivity (54% *ee*, Table 1, Entry 5). Likewise, changing the aryl substituents on the phosphorus atom also allowed us to tune the regio- and enantioselectivity of the reaction (Table 1 Entries 6, 7). Ultimately, ligand **L7**, which features aryl substituents bearing electron-withdrawing groups, was revealed to be the ligand of choice in this process (Table 1, Entry 7). By changing the copper source to CuTc (copper(I) thiophene-2-carboxylate) and the solvent to Et₂O a significant increase in yield and enantioselectivity was observed (Table 1, Entry 9). Finally, by lowering the temperature to 0 °C and inverting the equivalents of diene **1** to cyanating agent **3**, the product could be isolated in a high yield of 83% as a single regioisomer and with excellent enantioselectivity (91% *ee*, Table 1, Entry 12).²¹ The reaction was also performed on a 5 mmol scale using reduced loadings (5 mol %) of catalyst and ligand to show the potential of this procedure for large scale production (Table 1 entry 15). Additional experiments revealed that K₃PO₄ was also a suitable base for this transformation (Table 1, entry 13).

Interestingly, butoxide salts, which are usually the base of choice in similar borofunctionalizations, provided the product with only moderate enantioselectivity (Table 1, entry 14). We believe this is due to the strong butoxide base deprotonating the product and leading to racemization. We have therefore developed a unique system for copper catalyzed borofunctionalizations that uses a base strong enough to activate the boron reagent, but mild enough to avoid racemization.

Table 1. Optimisation of the copper-catalyzed regio- and enantioselective borocyanation of 1,3-dienes.^a

Entry	[Cu] cat.	Ligand	Solvent	Yield (%) 4a/5a	4a (% ee)
1	CuBr(SMe ₂)	L1	THF	33/30	45
2	CuBr(SMe ₂)	L2	THF	32/32	39
3	CuBr(SMe ₂)	L3	THF	71/–	6
4	CuBr(SMe ₂)	L4	THF	59/–	30
5	CuBr(SMe ₂)	L5	THF	57/3	54
6	CuBr(SMe ₂)	L6	THF	42/–	71
7	CuBr(SMe ₂)	L7	THF	58/–	79
8	CuCl	L7	THF	65/–	80
9	CuTc	L7	THF	62/–	83
10	CuTc	L7	Et ₂ O	80/–	88
11 ^b	CuTc	L7	Et ₂ O	60/–	91
12 ^c	CuTc	L7	Et ₂ O	85/– (83) ^d	91
13 ^{c,e}	CuTc	L7	Et ₂ O	90/– (85) ^d	91
14 ^{c,f}	CuTc	L7	Et ₂ O	84	60
15 ^g	CuTc	L7	Et ₂ O	70 (64) ^d	83

^a Reaction conditions: Diene **1** (0.2 mmol), B₂pin₂ **2** (0.4 mmol), cyanating agent **3** (0.26 mmol), Cu cat. (0.02 mmol), Ligand (0.02 mmol), K₂CO₃ (0.24 mmol), solvent (4.0 mL), rt, 16 h. ^b Reaction run at 0 °C. ^c Diene **1** (0.4 mmol), B₂pin₂ **2** (0.4 mmol), cyanating agent **3** (0.2 mmol), Cu cat. (0.02 mmol), Ligand (0.02 mmol), K₂CO₃ (0.24 mmol), solvent (4.0 mL), 0 °C, 16 h. ^d Isolated yield of **4a**. ^e K₃PO₄ used as base. ^f KO^tBu used as base. ^g Large scale: diene **1** (10 mmol), B₂pin₂ **2** (10 mmol), cyanating agent **3** (5 mmol), Cu cat. (0.25 mmol), Ligand (0.25 mmol), K₂CO₃ (6 mmol), solvent (100 mL), 0 °C, 16 h.

We then looked to establish the tolerance of the reaction towards substituents on the aryl ring of the butadiene (Scheme 3A).¹⁸ The regioselectivity of the reaction remained very high for all cases described herein – at most, the minor regioisomer **5** was only ever observed in trace amounts (<4 %), unless otherwise stated. Our first observation was that electron-donating substituents lower the yield of the reaction, but that the enantioselectivity of the reaction remains unaffected (**4b**, **4c**). The

lower yield may be due to a less favorable addition of a nucleophilic $L_nCu-Bpin$ species across the $C=C$ bond of a more electron-rich diene.²² Applying the optimized conditions to a range of halogen-substituted arylbutadienes, including bromo-substituted diene **1g**, gave the corresponding products in high

yields and excellent enantioselectivities (**4e-4g**). Other substrates bearing electron-withdrawing substituents, such as trifluoromethyl- (**4h**) and ester-groups (**4i**), were also tested and gave the

Scheme 3. Scope of the copper-catalyzed enantioselective borocyanation of 1-(hetero)arylbutadienes.^a

^a Reactions run on 0.2 mmol and the isolated yields given. Numbers in parentheses are of NMR yields. ^b K_2CO_3 used in place of K_3PO_4 . ^c **4u:5u** = 7:1. **5u** is the minor 4,1-addition product.

corresponding products in high NMR yield, however, a reduction in enantioselectivity was observed in these cases. The procedure was also applicable to a range of *ortho*- (**4j**) and *meta*-substituted (**4k-4m**) arylbutadienes, without significant detriment to the yield or enantioselectivity of the reaction. Finally, both 1- and 2-naphthylbutadienes performed well under the reaction conditions (**4n**, **4o**). Overall, the application of our procedure to a range of substituted arylbutadienes gave the corresponding products with excellent regiocontrol, in good to excellent yields, and with high to excellent enantioselectivity (79–93% ee).

We were also keen to test our procedure on heteroarylbutadienes as this type of substrate has yet to be applied in enantioselective borofunctionalizations (Scheme 3B). We were pleased to find that high yields and excellent enantioselectivities were obtained with benzothiophene (**4p**), benzothiazole (**4q**), furan (**4r**) and thiophene (**4s**) substituted 1,3-butadienes. Although the reaction with quinoline based diene **4t** provided a good yield of the desired product, the enantioselectivity of the procedure was moderate. This reduction in enantiocontrol may be due to the substrate competing with the chiral ligand in binding to the copper catalyst. Although a uracil derived diene gave only moderate yield, the product was formed with excellent enantioselectivity (**4u**). Several multiply-substituted

dienes were also tested (Scheme 4). We were pleased to observe that the reaction conditions were applicable to 1,2-disubstituted dienes, however, both the yield and the enantioselectivity were lowered (**4v**, **4w**, **4x**).

Scheme 4. Scope of the copper-catalyzed enantioselective borocyanation of multiply-substituted dienes.^a

^a Reactions run on 0.2 mmol and the isolated yields given. Numbers in parentheses are of NMR yields. ^b K_2CO_3 used in place of K_3PO_4 . ^c **4y:5y** = 13:1. **5y** is the minor 4,1-addition product.

Scheme 5. A. Tentative stereochemical model; B. Proposed catalytic cycle for the enantioselective borocyanation of dienes; C. Investigating the reaction mechanism through hydroboration; D. The reactivity of *trans*- vs *cis*-dienes.

^a CF₃ groups of ligand have been removed for clarity. ^b Reactions run on 0.02 mmol.

A 1,1-disubstituted diene showed poor reactivity but gave product **4y** with respectable enantiocontrol. The procedure could also be applied to the borocyanation of 1-phenyl-1,3,5-hexatriene (**1z**) to give the diene product in good NMR yield and excellent enantioselectivity (**4z**). This result shows the potential of this methodology for the enantioselective dual functionalization of other polyunsaturated compounds.

A tentative stereochemical model and catalytic cycle for the transformation is presented in Scheme 5. The model invokes steric hindrance in quadrants I, II, and IV that would block the approach of the diene (Scheme 5A). This leaves quadrant III accessible for the diene **1** to approach the Cu–Bpin bond leading to borocupration of the substrate to provide organocopper species **B** (Scheme 5A and 5B, *i*).²³ Preliminary experiments by us (*vide infra*) and others have suggested that isomerization of **B** can lead to the thermodynamically more favorable (*Z*)-allyl copper species **C** (*ii*).^{8b,9q,12,14,23,24} Steps consisting of a stereoselective insertion of the cyanating agent **3** (*iii*), followed by 1,2-elimination to release the copper amide species **E** would lead to the allyl nitrile product **4** (*iv*). On the basis of previous reports, we suggest that reaction of **C** with the cyanating agent **3** proceeds *via* the 6-membered transition structure **D**.^{7c} Finally, the active copper catalyst **A** can be regenerated

through sigma-bond metathesis of species **E** with B₂pin₂.²⁵ Attempts to isolate/observe the intermediate organocopper species **B** and **C** were unsuccessful. However, the corresponding products of hydroboration (**6a** and **7a**) were observed when mixing the diene **1a** with a stoichiometric amount of CuCl, **L5** and B₂pin₂ in the absence of the cyanating agent (Scheme 5C).^{26,27} In line with the observations of Brown,¹⁴ we propose that the minor product **6a** forms from protodemetalation of intermediate **B**, and the major product **7a** from protodemetalation of the (*Z*)-allyl intermediate **C**. Interestingly, when using the *cis*-diene **1a'**, the products **6a** and **7a** were also formed in the same ratios. These results suggest that, in the absence of an electrophile; 1) the dienes **1a** and **1a'** converge to similar intermediates;¹⁴ and 2) the isomerization of **B** and **C** is reversible.²⁸ Due to the preferential formation of the (*Z*)-hydroboration product, and in agreement with previous reports,^{8b,9q,12,14,23,24} we suggest that the cyanating agent **3** reacts with the (*Z*)-allyl species **C** to deliver the product with the observed stereochemistry (Scheme 5B, *iii*).

Interestingly, under the standard reaction conditions, the *cis*-isomer of phenyl-1,3-butadiene (**1a'**) gave the (*E*)-alkene product **4a'** – the opposite enantiomer of product **4a** that is formed using the *trans*-diene **1a** (Scheme 5D, *i*). This again highlights that the *trans*- (**1a**) and *cis*- (**1a'**) isomers of phenyl-1,3-butadiene converge to give a product with the same geometry about the alkene bond, though with opposite configuration at the sp³-carbon bearing the cyano group.²⁹ Finally, the reaction of substrate **8**, which shares features of both **1a** (a *trans*-diene) and **1a'** (a *cis*-diene) led to the product **9** (Scheme 5D, *ii*). The absolute configuration of this product suggests that borocupration occurs preferentially at the *trans*-alkenyl unit, thus implying that *trans*-dienes react faster than *cis* dienes in this process.³⁰ Future studies will allow for a better understanding of the reactivity observed and allow closer comparison to related transition metal-catalyzed processes.

The products obtained from the enantioselective transformation of dienes contain boro-, cyano- and alkenyl functionalities, each of which can be readily manipulated (Scheme 6). For example, the boryl group can be easily transformed into alcohol **10** (*i*). This prepares the molecule for an iodocyclization *via* reaction of the alkene with an iodonium reagent, to give multi-substituted tetrahydrofurans **11a** and **11a'** (*ii*). Alternatively, the alkene can be selectively reduced in the presence of the cyano group to give **12** (*iii*). The nitrile group is also susceptible to hydrolysis or reduction to give amide (**13**) or amine (**14**) containing products (*iv*, *v*). Importantly, no loss of enantiomeric purity was observed in these manipulations.

Scheme 6. Manipulations of borocyanation products.

^a H₂O₂, K₂CO₃ (2.0 eq), THF, –20 °C, 16 h. ^b Pd/C (10 mol %), H₂, MeOH/EtOAc, rt, 16 h. ^c Oxone® (2.0 eq), KI (4.0 eq), MeCN/H₂O, rt, 30 min. ^d NiCl₂ (1.5 eq), NaBH₄ (10.0 eq), Boc₂O

(3.0 eq), MeOH, 0 °C, 2 h. ^e ZnBr₂ (1.0 eq), H₂O/*i*-PrOH, 90 °C, 16 h.

In conclusion, we have reported on the copper-catalyzed enantioselective borocyanation of unsaturated hydrocarbons: 1,3-Dienes undergo 4,3-borocyanation with excellent regio- and enantiocontrol. Preliminary results show the potential application of this methodology to other unsaturated hydrocarbons, such as trienes, and we have demonstrated the high synthetic value of the products through various derivatisations. Further studies on the utility of this rare example of an enantioselective cyanation of an unsaturated feedstock are currently underway.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data are available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

* Email: david.j.procter@manchester.ac.uk Website: www.proctergroupresearch.com Twitter: @GroupProcter

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the EPSRC (Established Career Fellowship to D.J.P.; EP/M005062/1), the Royal Society (Newton International Fellowship to T.J.) and the University of Manchester (Lectureships to A.P.P. and G.J.P.P.). We also thank the X-ray Crystallography Service at the University of Manchester.

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(26) CuCl, KO^tBu and **L5** were used in the stoichiometric reaction in place of CuTc, K₃PO₄/K₂CO₃ and **L7**. During optimisation, it was observed that the use of CuCl, KO^tBu and **L5** led to similar yields and regiocontrol, but lower enantiocontrol, when compared to use of the optimised conditions.

(27) A proton source (e.g. MeOH) was not required to obtain the hydroboration products **6a/7a**. It is likely that adventitious water is responsible for the protonation of the unstable phosphine ligated-Cu-allyl species (**B** and **C**). Previous studies on copper catalysed hydroboration have also observed hydroboration products without the addition of a proton source. See ref 7e and; Lee, Y.; Hoveyda, A. H. Efficient Boron–Copper Additions to Aryl-Substituted Alkenes Promoted by NHC–Based Catalysts. Enantioselective Cu-Catalyzed Hydroboration Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161.

(28) Hydroboration product **6a** can only form from **1a'** if isomerisation can occur between organocopper species **B** and **C**.

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