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The asymmetric synthesis of β-lactams: HETPHOX/Cu(I) mediated synthesis via the Kinugasa reaction

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Abstract—The reactions of nitrones with terminal alkynes, catalysed by a range of HETPHOX ligands afforded β-lactams in moderate to good conversions with ees up to 55%. High levels of diastereoselectivity, dependent on the alkyne, were obtained. For example, the reaction is highly *cis*-diastereoselective with phenylacetylene (>9:1), while an unexpected reversal of diastereoselectivity is observed with the 3,5-trifluoromethyl phenylacetylene, which is highly *trans* selective (1:9) with an ee of 53%. The reaction scope with differently substituted nitrones and phenylacetylenes was also studied.

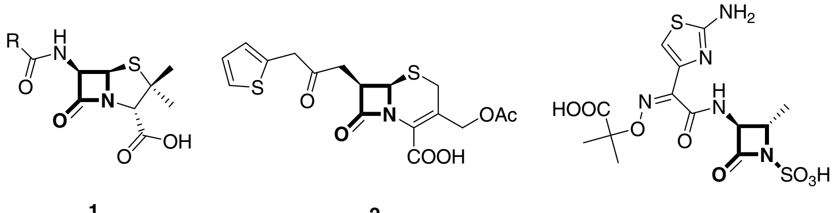
1. Introduction

β-Lactams are one of the best known and most extensively studied class of compounds due to their biological activity.[1] The β-lactam class of drugs have revolutionised treatment in medicine (Fig. 1).[2]

The β-lactam antibiotics such as penicillins **1** and cephalosporins **2** have been in use since the 1940s and are generally synthesised by fermentation processes. The monobactam antibiotics, such as astreonam **3**, are purely synthetic antibiotics, which have been available since the early 1980s. With antibiotic resistance a major problem with existing antibiotics, the synthesis of new and more potent antibiotics is a major focus for synthetic chemists.

As a result the stereoselective synthesis of β-lactams has been investigated by many approaches based on chiral precursors. Of the catalytic enantioselective variants, the most successful is the asymmetric Staudinger reaction of ketenes and imines, which was developed by Lectka.[3] Another catalytic asymmetric approach is the Kinugasa reaction, which was developed in the 1970s.[4] This provides an easy route to β-lactams using the readily available starting materials of *C*,*N*-diphenylnitrone **4**, phenylacetylene **5** and stoichiometric quantities of copper (Scheme 1) and the scope of the reaction has been reviewed recently.[4b]

Ding and Irwin carried out further work on this reaction and were the first to provide a basis for an understanding of the reaction mechanism.[5] In 1995, Miura developed



1 **2** **3**

Figure 1. β-Lactam based antibiotics.

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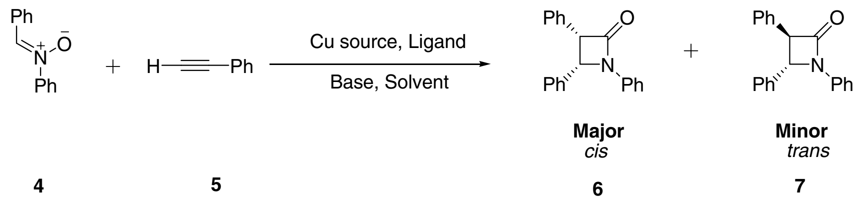


Scheme 1. Kinugasa reaction.

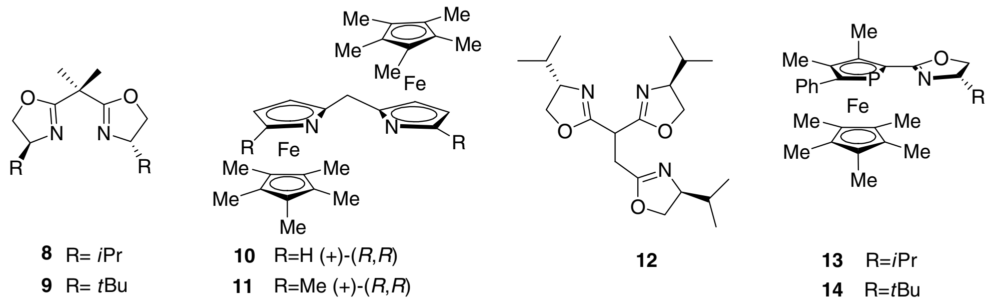


Figure 2. Chiral ligands used in the asymmetric Kinugasa reaction.

the first asymmetric variant of the Kinugasa reaction with CuI and the bisoxazoline ligands **8** and **9** using K_2CO_3 as the base. The reaction of *C*,*N*-diphenylnitrone **4** and phenylacetylene **5** provided *cis*-β-lactam **6** in 57% ee and 30% de (Scheme 1).[6]

In 2002, Fu reported the first completely diastereoselective and enantioselective Kinugasa reaction with CuCl and the C_2 symmetrically bis(azaferrocene) ligands **10** and **11** (Fig. 2).[7] Using ligands **10** and **11**, *cis* β-lactams **6** and **7** were formed in an excellent diastereoselectivity (up to 93%) and enantioselectivity (>92%). Tang recently applied trisoxazoline ligand **12** in the Kinugasa reaction of *C*,*N*-diphenylnitrone **4** and phenylacetylene **5** with a Cu(II) source. The advantage of the Cu(II) source is that the reaction does not need to be carried out under anhydrous conditions.[8] β-Lactams **6** and **7** were obtained in a high *cis*-diastereoselectivity and enantioselectivity (up to 95%). All of the above cases have used N,N ligands whilst P,N ligands have only been applied in the intramolecular version developed by Fu.[9] Ligands **13** and **14** induced ees >85% in this intramolecular variant.

The HETPHOX ligands were developed independently by Tietze and Cozzi who applied these ligands to asymmetric allylic alkylation and imine hydrogenation, respectively.[10,11] We have applied these ligands to both the intermolecular and intramolecular Heck reaction with high enantioselectivities in the reaction of 2,3-dihydrofuran with phenyl triflates (up to 95%).[12,13] These HETPHOX ligands **15–18** (Fig. 3) compare favourably with other P,N ligands in a wide range of asymmetric transformations.[14]

Due to the broad reactivity of metal complexes of HETPHOX ligands **15–18** and in view of Fu's success with P,N ligands **13** and **14**, we wished to investigate the application of the HETPHOX ligands to the catalytic asymmetric Kinugasa reaction. This represents the first application of P,N ligands to the intermolecular Kinugasa reaction.

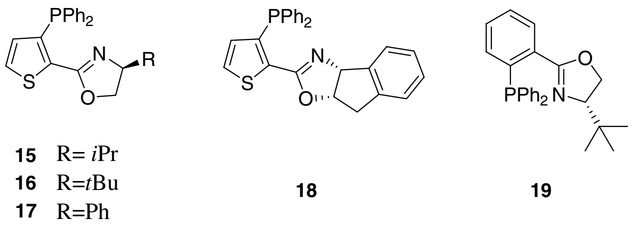


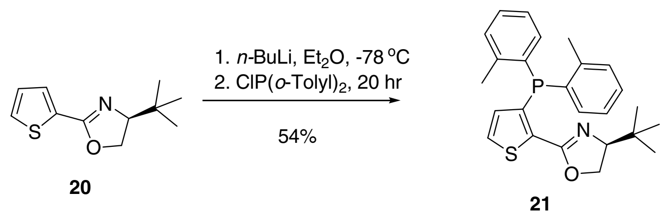
Figure 3. P,N Ligands applied in the intermolecular Kinugasa reaction.

2. Results and discussion

The synthesis of ligands **15–18** has previously been reported by our research group.[12b] The thiophene-oxazoline was synthesised from the condensation of thiophene carbonitrile with the corresponding chiral amino alcohol. The phosphine moiety was introduced by *o*-lithiation followed by quenching with chlorodiphenylphosphine. These ligands are the heterocyclic analogues of Pfaltz PHOX ligand **19**.

Herein, we report the synthesis of a new HETPHOX ligand with an *o*-tolyl substituent on the phosphorus. Its synthesis was carried out as previously described for HETPHOX ligands **15–18** employing *o*-lithiation of **20** followed by quenching with chlorodi-*o*-tolyl phosphine to give the desired HETPHOX ligand **21** in 54% yield (Scheme 2).

The addition of the *o*-tolyl substituent on the phosphine has been shown to have a significant effect on the enantioselectivity obtained in asymmetric catalysis using other ligand classes. For example, Pfaltz synthesised the analogous PHOX ligand **19** with the *o*-tolyl substituted



Scheme 2. Synthesis of *o*-tolyl phosphorus substituted ligand.

phosphorus and found it increased enantioselectivity in a range of catalytic reactions.[15]

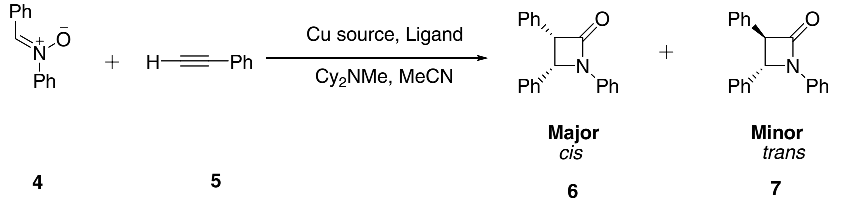
Our initial Kinugasa reaction studies were carried out using the standard test reaction of *C*,*N*-diphenylnitrone **4** with phenylacetylene **5** using HETPHOX ligand **17** and CuCl as catalyst. The base used was *N*,*N*-dicyclohexylmethylamine, which was the base of choice in Fu's work.[8] The reaction was carried out at an ambient temperature for 3 days (Table 1, entry 1), with a conversion of 40% and an enantioselectivity of 12%. The reaction using HETPHOX ligand **17** was screened with both Cu(I) (Table 1, entries 1–5) and Cu(II) (Table 1, entries 7–9) salts. The type of copper salt employed has been shown to have an effect on the diastereoselectivity as well as the enantioselectivity.[5,6]

Of the copper salts examined, CuCl (Table 1, entry 1) gave the best conversion and enantioselectivity. The other Cu(I) salts (Table 1 entries 3–5) showed a high diastereoselectivity (up to 99:1 in the case of CuI), but gave poor conversion and enantioselectivity. By increasing the reaction time to 5 days, the conversion was increased from 40% to 58% (Table 1, entries 1 and 2). When Cu(II) salts were examined, a high diastereoselectivity was observed although low conversion and enantioselectivity were obtained (Table 1, entries 6–8). The generation of the Cu(I) species in situ was also investigated. Sharpless and Carreira successfully have used this method in the Huisgen cycloaddition reaction.[16,17] The reaction was carried out using copper(II) acetate and sodium ascorbate (20 mol %) and although the conversion was high (75%), the enantioselectivity was poor (5%). It was decided from the copper salt screen that CuCl was the copper source to be used in further studies.

The initial copper screen had been carried out using HETPHOX ligand **17** and the enantioselectivity found to be poor (up to 15%). Therefore, a number of other HETPHOX ligands **15**, **16**, **18**, and **21** were examined. For the sake of comparison Pfaltz's PHOX ligand **19** was also tested. The reactions were carried out with *C*,*N*-diphenylnitrone **4** and phenylacetylene **5** using CuCl as the copper source and *N*,*N*-dicyclohexylmethylamine as the base.

The *t*-butyl substituted HETPHOX ligand **16** (Table 1, entry 10) gave the best conversion and enantioselectivity (37%) in this reaction. The isopropyl and phenyl substituted HETPHOX ligands **15** and **17** (Table 1, entries 9 and 2) showed significantly lower conversion and enantioselectivity. When the sterically demanding indanol derived HETPHOX ligand **18** (Table 1, entry 11) was employed, a low enantioselectivity (16%) was observed. The application of *o*-tolyl phosphorus derived *t*-butyl HETPHOX ligand **21** resulted in a decrease in conversion from 73% to 44%, although there was an increase in enantioselectivity to 55% (Table 1, entry 13). The steric crowding around the phosphorus seemed to increase the enantioselectivity

Table 1. Effect of Copper salt and HETPHOX ligand on the asymmetric Kinugasa reaction[a]



Entry	Ligand	Cu source	Time (h)	Conversion[b] (%)	**6**:**7**[c]	ee **6**[d] (%)
1	**17**	CuCl	72	40	89:11	12
2	**17**	CuCl	120	58	91:9	12
3	**17**	CuBr	72	15	93:7	9
4	**17**	CuI	72	8	99:1	15
5	**17**	$(CuOTf)_2 \cdot C_6H_5CH_3$	72	23	87:13	12
6	**17**	$CuCl_2$	72	35	87:13	8
7	**17**	$CuBr_2$	72	15	93:7	9
8	**17**	$Cu(ClO_4)_2 \cdot 6H_2O$	72	58	85:15	4
9	**15**	CuCl	120	43	93:7	16
10	**16**	CuCl	120	73	91:9	37
11	**18**	CuCl	120	72	93:7	16
12	**19**	CuCl	120	85	93:9	22
13	**21**	CuCl	120	44	90:10	55

[a] Reactions were carried out at 15 °C using 12 mol % HETPHOX ligand and 10 mol % Cu source under an anhydrous atmosphere.
[b] Conversion determined by ^1H NMR.
[c] *cis*:*trans* ratio of **6**:**7** determined by ^1H NMR.
[d] Enantiomeric excess determined by chiral HPLC (see Section 4 for conditions).

with a concomitant decrease in conversion. All the HETPHOX ligands **15**–**18** and **21** are highly *cis* selective with diastereoselectivities up to 96:4 (*cis*:*trans*) being obtained.

The reaction employing PHOX ligand **19** gave the highest conversion at 85%, although the enantioselectivity was found to be lower than the corresponding HETPHOX analogue **16** at 22% (Table 1, entry 12). From this screening of the HETPHOX ligands, the most successful ligands were the *t*-butyl derived HETPHOX ligands **16** and **21**. Therefore, *t*-butyl ligand **16** was applied in further investigations. The confirmation of the structure of the *cis* isomer isolated after purification by column chromatography was determined by X-ray crystallography (Fig. 4).

The crystals were grown by slow evaporation from dichloromethane. The analysis of the X-ray crystal structure show that the two phenyl groups at the C-3 and C-4 position are *cis* to each other. The torsion bond angle between the two phenyl rings on C-2 and C-3 is 0.61°. The bond lengths on C-2 and C-3 to the phenyl rings is 1.49 and 1.50 Å, respectively. According to the space group $P2_1/c$ the crystal consists of a racemic mixture.

The effect of solvent was examined using ligand **16** and *N*,*N*-dicyclohexylmethylamine as base. The Kinugasa reaction is generally carried out in polar solvents.[7–9] A range of polar solvents were examined in the reaction of *C*,*N*-diphenylnitrone **4** and phenyl acetylene **5** with CuCl and HETPHOX ligand **16** to give β-lactams **6** and **7**. Acetonitrile was the solvent that gave the highest conversion and enantioselectivity with HETPHOX ligand **16**. For most of the solvents tested, a high *cis* diastereoselectivity was observed. When water was used as the solvent a low conversion of 38% was observed, accompanied by a decrease in diastereoselectivity from 9:1 to 2:1 when compared to acetonitrile.

From these studies, it was observed that the Kinugasa reaction between *C*,*N*-diphenylnitrone **5** and phenylacetylene **6** produced the best results when HETPHOX ligand **16** and CuCl in acetonitrile was employed.

In order to expand upon the scope of the reaction, we wished to study the effects of systematic variation on the aryl groups of both the nitrone and alkyne using the optimised reaction conditions. Therefore, the reaction of five different substituted phenylacetylene derivatives were applied in the reaction (Table 2).

The introduction of the 4-OMe group onto the phenyl ring of acetylene **22** (Table 2, entry 2) led to a decrease in conversion (22%) and a drop in the enantioselectivity of *cis*-isomer **23** to 10%. The diastereoselectivity was found to be almost unchanged (92:8) in comparison to phenylacetylene **5**. 4-Ethynylanisole **22** was less reactive than phenylacetylene and because of this the reaction was carried out over 14 days. When the electron-withdrawing 4-CF_3 phenylacetylene **25** was introduced (Table 2, entry 3), a change was observed in the diastereoselectivity, which dropped from 9:1 (*cis*:*trans*) with phenylacetylene **5** to 3:1 and with a lower ee of 29%. We reasoned that the introduction of a further electron-withdrawing group could cause the reaction to go exclusively *trans* selective. When the reaction was carried out with 3,5-bis(trifluoromethyl)phenylacetylene **28**, this was found to be the case (Table 2, entry 4). The diastereoselection was found to change from 9:1 (*cis*:*trans*) with unsubstituted phenylacetylene **5** to 1:9 (*cis*:*trans* **29**:**30**) with the 3,5-CF_3 substituted phenylacetylene accompanied by an ee of 53% for *trans* isomer **30**. Such a highly *trans* selective Kinugasa reaction has not been previously reported before with substituted phenylacetylenes. The comparison of coupling constants (*J*) for *cis* and *trans* isomers (Fig. 5) demonstrates that the *trans* isomer we prepared had a coupling constant of 2.6 Hz, which is similar to the values reported for other *trans*-β-lactams.[3]

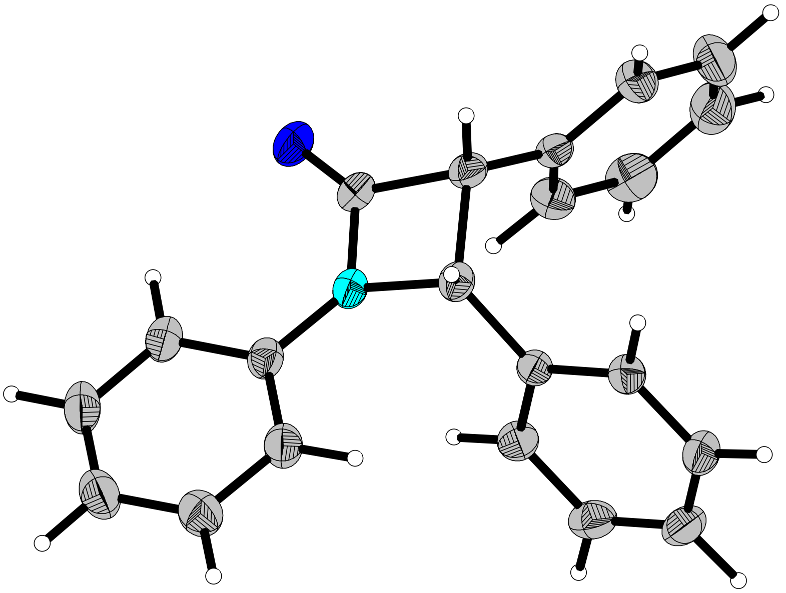
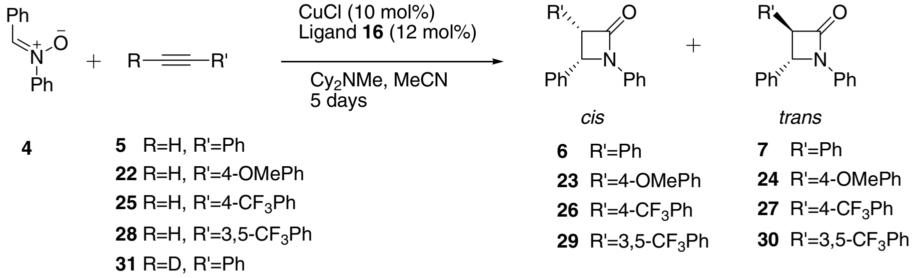


Figure 4. Molecular structure of *cis*-isomer **6** (ORTEP plot).

Table 2. Effect of variation of aryl group on phenylacetylene[a]



Entry	Phenylacetylene	Conversion (%)[b]	Product	*cis*:*trans*[c]	ee (%)[d]
1	**5**	73	**6**, **7**	91:9	37
2	**22**	22[e]	**23**, **24**	92:8	10
3	**25**	80	**26**, **27**	76:24	29
4	**28**	64	**29**, **30**	8:92	53 (*trans*)
5	**31**	38	**6**, **7**	91:9	22

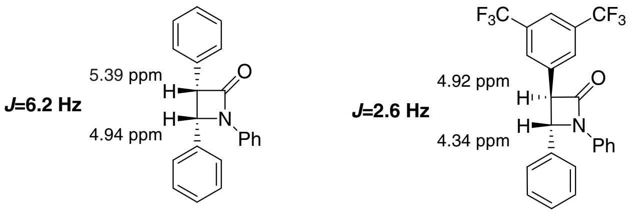
[a] Reactions were carried out at 15 °C using 12 mol % HETPHOX ligand **16** and 10 mol % CuCl under an anhydrous atmosphere.

[b] Conversion determined by ^{1}H NMR.

[c] *cis*:*trans* ratio determined by ^{1}H NMR.

[d] Enantiomeric excess determined by chiral HPLC (see Section 4 for conditions).

[e] Reaction time 14 days.



cis-**6** *trans*-**30**

Figure 5. Diastereoselectivity of β-lactams **6** and **30**.

In order to determine the fate of the acetylenic proton, the reaction was carried out with phenylacetylene-d_1 **31** (Table 2, entry 5), but no deuterium incorporation was observed in the *cis*-isomer. Products **6** and **7** were identical to those prepared using phenylacetylene **5**. The conversion was found to be lower than in the reaction with non-deuterated phenylacetylene and the enantioselectivity of *cis*-isomer **6** was lower at 22%.

As the electronics on phenylacetylene had a large effect on the diastereoselectivity we also wished to determine what effect the change in the electronics of the α-phenyl of *C*,*N*-diphenylnitrone **4** would have on both diastereoselectivity and enantioselectivity (Table 3).

C,*N*-Diarylnitrones **4**, **32**, **35**, **38** and **41** were synthesised according to the procedure of Fu and Davis.[7,18] The 4-OMe phenyl substituted nitrone **32** gave a higher conversion when compared to the unsubstituted *C*,*N*-diphenylnitrone **4** (Table 3, entry 1), though the enantioselectivity of *cis*-isomer **33** decreased to 32%. When 4-CF_3 phenyl substituted nitrone **35** was examined, an increase in the enantioselectivity of *cis*-isomer **36** to 48% compared to 37% with unsubstituted *C*,*N*-diphenylnitrone **4** was observed (Table 3, entry 3). The diastereoselectivity was largely unchanged when electron donating and electron-withdrawing substituents were introduced (Table 3, entries 1–3). The α-position on the nitrone was substituted with a naphthyl group to examine any possible steric effects. 1-Naphthyl substituted nitrone **38** gave a lower enantioselectivity (26%) than *C*,*N*-diphenylnitrone **4** (Table 3, entry 4). When the substituent was changed to a 2-naphthyl group, there was a decrease in conversion, as well as a small increase in enantioselectivity of *cis*-isomer **42** to 41% (Table 3, entry 5). The introduction of electron-donating and electron-withdrawing substituents on the α-phenyl of the nitrone did not have a large effect on the conversion and diastereoselectivity of the reaction.

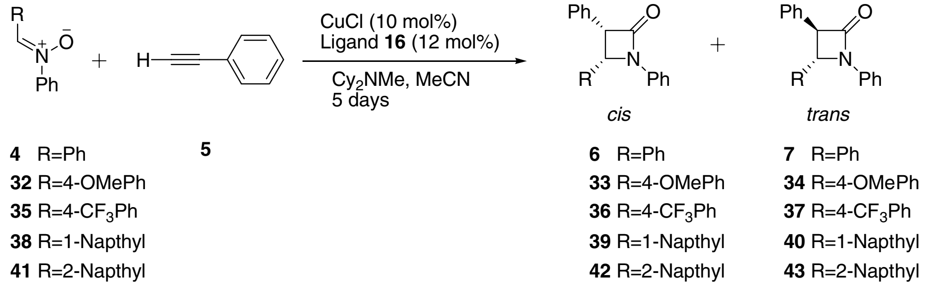
3. Conclusion

We have studied the asymmetric intermolecular Kinugasa reaction using HETPHOX ligands, the first class of P,N ligands employed in this copper-catalysed transformation. A high *cis*-diastereoselection in the reaction of *C*,*N*-diphenylnitrone with phenylacetylene using CuCl was observed with the *t*-butyl substituted HETPHOX ligands. When 3,5-bis(trifluoromethyl)phenylacetylene was employed in the reaction, a reversal of diastereoselectivity was observed. This *trans*-diastereoselectivity has not previously been observed in the asymmetric Kinugasa reaction. The enantioselectivities observed with this ligand class were found to be moderate with the highest enantioselectivity of 55% obtained with the *o*-tolylphosphine derived HETPHOX ligand.

4. Experimental

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Infrared FT spectrometer. Electron impact mass spectra were deter-

Table 3. Effect of change in electronics and sterics on the α-phenyl of *C*,*N*-diphenylnitrone[a]



Entry	Nitrone	Conversion[b] (%)	Product	*cis*:*trans*[c]	ee[d] (%)
1	**4**	73	**5**, **6**	91:9	37
2	**32**	85	**33**, **34**	93:7	32
3	**35**	64	**36**, **37**	87:13	48
4	**38**	78	**39**, **40**	94:6	26
5	**41**	58	**42**, **43**	92:8	41

[a] Reactions were carried out at 15 °C using 12 mol % HETPHOX ligand **16** and 10 mol % CuCl under an anhydrous atmosphere.

[b] Conversion determined by ^{1}H NMR.

[c] *cis*:*trans* ratio determined by ^{1}H NMR.

[d] Enantiomeric excess determined by chiral HPLC (see Section 4 for conditions).

mined on a VG Analytical 770 mass spectrometer with attached INCOS 2400 data system in the EI mode. NMR was recorded on a Varian Inova 300 MHz, Varian NMR System 400 and 600 MHz spectrometers at room temperature in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm). All reactions were carried out under nitrogen atmosphere. Thin-layer chromatography (TLC) was carried out on plastic sheets pre-coated with silica gel 60 F254 (Merck). Column chromatography was performed using Merck Kieselgel 60 (0.040–0.063 mm). HPLC analysis was performed using a Shimadzu LC-2010A liquid chromatograph equipped with a Daicel Chiracel OD column (0.46 cm I.D. × 25 cm). HPLC grade hexane and isopropanol were used as eluting solvents. Anhydrous acetonitrile was supplied from Aldrich. The di-*o*-tolylchlorophosphine was purchased from Strem. All other chemicals were purchased from Aldrich. Ligands **15** to **19** were synthesised according to the literature procedures.[12b] β-Lactams **6**, **23**, **26**, **33** and **36** have been previously synthesised and the stereochemical assignment is based on the comparison of the optical rotation with literature values.[7,9] The experimental details below are given for the major isomers isolated by column chromatography.

4.1. (*S*)-4-*tert*-Butyl-2-[3-(di-*ortho*-tolylphosphino)-2-thienyl]-4,5-dihydro-1,3-oxazole 21

Thiophene-2-oxazoline **20** (0.418 g, 2.0 mmol) was dissolved in dry Et_2O (5 mL) and the resultant solution was cooled to −78 °C. A solution of 2.5 M *n*BuLi in hexane (1.6 mL, 4.0 mmol) was added dropwise and the orange solution was stirred at −78 °C for 30 min. The reaction was warmed up to 0 °C and stirred at this temperature for 30 min. The orange solution was then cooled to −78 °C then di-*o*-tolylchlorophosphine (0.99 g, 4.0 mmol) was added. The reaction was allowed to warm to room temperature over 20 h and quenched with water (10 mL). The phases were separated and the aqueous phase extracted with Et_2O (2 × 5 mL), then the organic layers were combined, dried over Na_2SO_4 and evaporated under reduced pressure to give an orange oil, which was purified by column chromatography (Et_2O–pentane 1:1) to give a white solid. Yield 54%. Mp: 134–136 °C. $[\alpha]_D^{20} = -107$ (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 0.63$ (s, 9H), 2.40 (d, $J = 1.2$ Hz, 3H), 2.46 (d, $J = 1.2$ Hz, 3H), 3.96–4.16 (m, 3H), 6.34 (d, $J = 4.9$ Hz, 1H), 6.76 (m, 2H), 7.06 (m, 2H), 7.17–7.30 (m, 5H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) $\delta = 21.2$, 21.4, 21.5, 21.6, 25.7, 34.1, 69.0, 126.2, 126.3, 127.7, 127.8, 130.1, 130.2, 132.7, 133.1, 133.9, 168.2 ppm. ^{31}P NMR (122 MHz, $CDCl_3$) $\delta = -30.3$ ppm. IR (KBr) $\nu = 1164$, 1238, 1288, 1361, 1419, 1450, 1498, 1632, 2863, 2906, 2950 cm^{-1}. Anal. Calcd for $C_{25}H_{28}NOSP$: C, 71.23; H, 6.70; N, 3.32. Found: C, 71.38; H, 6.9; N, 3.38. LRMS (ES+) calcd for $C_{25}H_{38}NOPS$ 421.2; found $m/z = 422.2$ [M+1].

4.2. General procedure for the synthesis of *C*,*N*-diphenylnitrone 4

Nitrobenzene (6.11 g, 50 mmol), benzaldehyde (6.08 mL, 50 mmol), NH_4Cl (3.47 g, 65 mmol), EtOH (100 mL) and water (100 mL) were added to a 500 mL round-bottomed flask. The reaction mixture was cooled to 0 °C, and zinc powder (6.53 g, 100 mmol) added slowly over 4 h. The mixture was then warmed to room temperature and stirred for 12 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 (50 mL), and the filtrate extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were dried over $MgSO_4$ and concentrated to afford the crude product. This was purified by recrystallisation from dichloromethane and pentane. Off-white solid. Yield 41%. Mp 110–112 °C (lit. Mp 112–113 °C).[18] ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.44$–7.49 (m, 6H), 7.75–7.78 (m, 2H), 7.91 (s, 1H), 8.37–8.40 (m, 2H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) $\delta = 122.0$, 128.9, 129.2, 129.3, 129.4, 129.5, 130.2, 130.9, 131.2, 134.8, 143.3 ppm. IR (KBr) $v = 1548$, 1662, 3050 cm^{-1}; LRMS (ES+) calcd for $C_{13}H_{11}NO$ 197.1; found $m/z = 198.1$ $[M+1]^+$.

The *C*,*N*-diarylnitrones **32**, **35**, **38** and **41** were all synthesised according to the above procedure.

4.3. Synthesis of β-lactams

4.3.1. (3*R*,4*R*)-1,3,4-Triphenyl-2-azetidinone 6. A mixture of copper(I)chloride (2.68 mg, 0.025 mmol) and ligand **16** (12.4 mg, 0.03 mmol) in dry acetonitrile (4 mL) was stirred under a nitrogen atmosphere at ambient temperature for 2 h. The solution was cooled to 0 °C and *N*,*N*-dicyclohexylmethylamine (0.053 mL, 0.25 mmol) was added. After 10 min phenyl acetylene (0.041 mL, 0.375 mmol) was added. The mixture now a yellow colour was stirred for a further 10 min. *C*,*N*-Diphenylnitrone **4** (0.049 g, 0.25 mmol) was added. The reaction was stirred at an ambient temperature under a nitrogen atmosphere for 144 h (5 days). The reaction was passed through a short silica column using dichloromethane as the solvent. The residue was concentrated in vacuo and placed onto a flash column of silica gel (230–400 mesh ASTM). The product was eluted with dichloromethane to yield the title compound. Conversion 73%. Ee 37%, $[\alpha]_D^{20} = +13.0$ (*c* 0.1, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) $\delta = 4.94$ (d, $J = 6.2$ Hz, 1H), 5.39 (d, $J = 6.2$ Hz, 1H), 6.97–7.04 (m, 10H), 7.21 (app. t, 4H), 7.34 (app. d, 2H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$) $\delta = 60.3$, 60.4, 117.2, 124.0, 127.1, 127.9, 128.1, 128.2, 128.9, 129.1, 132.1, 134.4, 137.7, 165.6 ppm. IR (KBr) $v = 1735$ cm^{-1} (C=O), LRMS (ES+) calcd for $C_{21}H_{17}NO$ 299.2; found $m/z = 300.2$ $[M+1]^+$.

4.3.2. (3*R*,4*R*)-3-(4-Methoxyphenyl)-1,4-diphenylazetidin-2-one 23. Off-white solid. Conversion 22%. Ee 10%. $[\alpha]_D^{20} = +6.1$ (*c* 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) $\delta = 3.60$ (s, 3H), 4.88 (d, $J = 5.9$ Hz, 1H), 5.36 (d, $J = 5.9$ Hz, 1H), 6.54 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 7.00–7.06 (m, 2H), 7.19–7.45 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 55.3$, 60.0, 60.7, 113.8, 117.5, 120.3, 124.2, 124.4, 124.8, 127.2 127.4, 128.0, 128.5, 129.0, 129.3, 129.4, 130.2, 132.0, 134.7, 137.9, 166.3 ppm (one C-13 shift missing due to overlap), IR (KBr) $v = 1729$ cm^{-1} (C=O). LRMS (ES+) calcd for $C_{22}H_{19}NO_2$ 229.2; found $m/z = 330.2$ [M+1]. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.02; H, 5.72; N, 4.46.

4.3.3. (3*R*,4*R*)-1,4-Diphenyl-3-(4-(trifluoromethyl)phenyl)-azetidin-2-one 26. White solid. Conversion 80%. Ee 29%. $[\alpha]_D^{20} = +3.2$ (*c* 0.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) $\delta = 5.06$ (d, $J = 6.0$ Hz, 1H), 5.52 (d, $J = 6.0$ Hz, 1H), 7.02–7.13 (m, 6H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.26–7.40 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 59.7$, 60.5, 117.2, 123.7 (q, $J = 256$ Hz), 124.4, 125.2 (q, $J = 3.8$ Hz), 127.5, 127.6, 128.3, 128.7, 129.2, 130.2 (q, $J = 40$ Hz), 131.4, 137.3, 138.7, 142.3, 165.2 ppm. IR (KBr) $v = 1736$ cm^{-1} (C=O). LRMS (ES+) calcd for $C_{22}H_{16}NOF_3$ 367.2; found $m/z = 368.2$ $[M+1]^+$, (ES−) found m/z 366.2 $[M-1]^+$.

4.3.4. (3*R*,4*S*)-3-(3,5-Bis(trifluoromethyl)phenyl)-1,4-diphenylazetidin-2-one 30. White solid. Conversion 64%. Ee 53%, $[\alpha]_D^{20} = +19.0$ (*c* 0.1, $CHCl_3$). Mp 152–154 °C. ^1H NMR ($CDCl_3$, 600 MHz) $\delta = 4.34$ (d, $J = 2.6$ Hz, 1H), 4.92 (d, $J = 2.6$ Hz, 1H), 7.03 (t, $J = 7.3$ Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 2H), 7.27 (d, $J = 7.74$ Hz, 2H), 7.32–7.38 (m, 5H), 7.73 (s, 1H), 7.78 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 600 MHz) $\delta = 63.1$, 64.0, 117.3, 122.0, 122.0, 122.1, 122.2, 124.6, 127.5–127.7 (m), 129.2, 129.3, 129.6, 132.4 (q, $J = 33.7$ Hz), 136.5, 137.0, 137.1, 163.5 ppm, ^{19}F NMR ($CDCl_3$, 282 MHz) $\delta = -63.6$ ppm. IR (KBr) $v = 1741$ cm^{-1} (C=O). LRMS calcd for $C_{23}H_{15}F_6NO$ 435.1; found $m/z = 434.1$ [M−1]. Anal. Calcd for $C_{25}H_{15}F_6NO$: C, 63.45; H, 3.47; N, 3.22. Found: C, 63.75; H, 3.57; N, 3.24.

4.3.5. (3*R*,4*R*)-4-(4-Methoxyphenyl)-1,3-diphenylazetidin-2-one 33. White solid. Conversion 85%. Ee 32%. $[\alpha]_D^{20} = +6.8$ (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) $\delta = 3.67$ (s, 3H), 4.99 (d, $J = 6.3$ Hz, 1H), 5.44 (d, $J = 6.3$ Hz, 1H), 6.65 (dd, $J = 2.1$, 6.6 Hz, 2H), 7.00 (dd, $J = 2.4$, 6.9 Hz, 2H), 7.06–7.14 (m, 6H), 7.24–7.31 (m, 2H), 7.40–7.43 (m, 2H) ppm. IR (KBr) $v = 1726$ cm^{-1} (C=O). LRMS (ES+) calcd for $C_{21}H_{17}NO$ 299.2; found $m/z = 300.2$ $[M+1]^+$.

4.3.6. (3*R*,4*R*)-1,3-Diphenyl-4-(4-(trifluoromethyl)phenyl)-azetidin-2-one 36. White solid. Conversion 64%. Ee 48%, $[\alpha]_D^{20} = +2.8$ (*c* 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 5.03$ (d, $J = 6.0$ Hz, 1H), 5.52 (d, $J = 6.0$ Hz, 1H), 7.07–7.20 (m, 8H), 7.30–7.45 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 59.6$, 60.1, 117.2, 123.8 (q, $J = 256$ Hz), 124.3, 125.0 (q, $J = 3.5$ Hz), 126.8, 128.3, 128.5, 129.2, 129.9 (q, $J = 41$ Hz), 133.8, 136.3, 137.4, 164.6 ppm. IR (KBr) $v = 1755$ cm^{-1} (C=O). LRMS calcd for $C_{22}H_{16}NO$ 367.2; found $m/z = 366.2$ [M−1].

4.3.7. (3*R*,4*R*)-4-(Naphthalen-1-yl)-1,3-diphenylazetidin-2-one 39. Off-white solid. Conversion 78%. Ee 26%, $[\alpha]_D^{20} = +4.2$ (*c* 0.2, $CHCl_3$). Mp 204–205 °C. ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 5.18$ (d, $J = 6.1$ Hz, 1H), 6.20 (d, $J = 6.1$ Hz, 1H), 6.83 (dd, $J = 1.8$, 2.1 Hz, 2H), 6.86–7.54 (m, 18H), 7.59 (d, $J = 8.1$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 1H), 7.96 (d, $J = 8.2$ Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 58.0$, 61.1, 117.6, 122.7, 124.3, 125.0, 125.1, 125.9, 126.2, 127.5, 127.7, 128.4, 129.1, 129.4, 129.6, 130.8, 131.7, 133.5, 138.0, 166.2 ppm. IR (KBr) $v = 1732$ cm^{-1} (C=O). LRMS calcd for $C_{25}H_{19}NO$ 349.1; found $m/z = 350.1$ [M+1]. Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.92; H, 5.67; N, 3.92.

4.3.8. (3*R*,4*R*)-4-(Naphthalen-2-yl)-1,3-diphenylazetidin-2-one 42. Off-white solid. Conversion 58%. Ee 41%. $[\alpha]_D^{20} = +9.1$ (*c* 0.2, $CHCl_3$). Mp 135–137 °C, ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 5.01$ (d, $J = 6.1$ Hz, 1H), 5.54 (d, $J = 6.1$ Hz, 1H), 6.88–7.04 (m, 8H), 7.17–7.21 (m, 2H), 7.31–7.37 (m, 3H), 7.46 (d, $J = 8.5$ Hz, 1H), 7.57–7.63 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 60.6$, 60.8, 117.4, 124.3, 124.6, 126.3, 126.4, 126.9, 127.4, 127.9, 128.0, 128.3, 128.4, 129.0, 129.3, 132.2, 132.4, 138.0, 165.9 ppm. IR (KBr) $v = 1732$ cm^{-1} (C=O). LRMS calcd for $C_{25}H_{19}NO$ 349.1; found $m/z = 350.1$ [M+1]. Anal.

Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.88; H, 5.37; N, 4.12.

4.4. X-ray crystal structure of 6

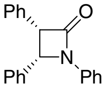
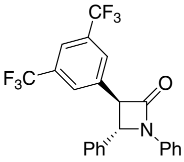
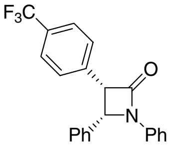
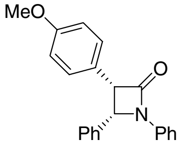
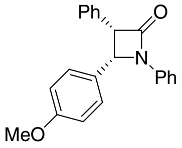
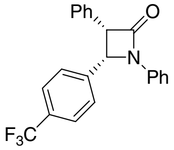
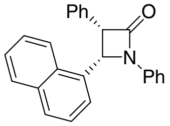
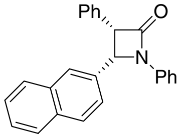
Crystal data were collected at 113 K using a Bruker SMART APEX CCD area detector diffractometer. A full sphere of the reciprocal space was scanned by phi–omega scans. Pseudo-empirical absorption correction based on redundant reflections was performed by the program SADABS. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares on F^2 for all data using SHELXL-97. All hydrogen atoms were located in the difference Fourier map and allowed to refine freely with isotropic temperature factors. Anisotropic temperature factors were used for all non-hydrogen atoms. Monoclinic space group $P2_1/c$. $D_c = 1.245$ Mg/m^3, $Z = 4$, $a = 9.0025(14)$, $b = 8.7315(12)$, $c = 20.666(3)$ Å, $V = 1597.4(4)$ Å^3, Bruker-Nonius Diffractometer, Mo Kα radiation, $\lambda = 0.71073$ Å, $\mu = 0.076$ mm^{-1}. The crystal of **6** for X-ray crystallographic analysis was grown from dichloromethane (linear dimensions $1.00 \times 0.80 \times 0.30$ mm). The numbers of measures and unique reflections are 26,348 and 3150, respectively (Rint = 0.0277). Final R(F) = 0.0381, wR(F2)—0.1002 for 276 parameters and 3150 reflections with $I > 2\sigma(I)$ and the θ range for the data collection was 2.30° to 26.00° (corresponding R values based on all 26,348 reflections are 0.0381 and 0.1002, respectively).[19–21]

CCDC 622862 **6** contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.5. HPLC conditions

These are given in Table 4.

Table 4. Assay conditions for enantiomeric β-lactams (Chiracel OD 1 mL/min, 254 nm)

β-Lactam	Solvent (hexane–IPA)	Major (min)	Minor (min)
	98:2	15.2	48.3
	99:1	6.5	7.3
	95:5	10.6	27.5
	90:10	13.6	21.3
	90:10	9.1	23.5
	95:5	12.0	48.7
	95:5	15.5	44.3
	95:5	18.9	53.5

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