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Chiral tris(oxazoline)/Cu(II) catalyzed coupling of terminal alkynes and nitrones†

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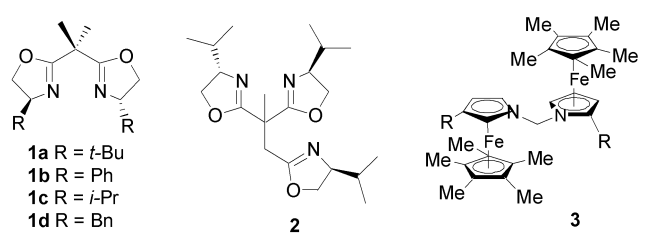
Novel chiral ^{i}Pr-tris(oxazoline)/Cu(ClO$_4$)$_2$·6H$_2$O catalyzed coupling of terminal acetylenes and nitrones to afford *cis*-disubstituted β-lactams is described; the choice of base proves essential to both the diastereoselectivity and the enantioselectivity.

C_2-symmetric chiral bis(oxazoline)–metal complexes have developed into versatile catalysts for numerous asymmetric processes during the last decade.[1] In sharp contrast to the great success of bis(oxazolines), the development and application of tris(oxazolines) are rather limited.[2] In our efforts to develop superior catalysts which are cheap, easy to access, air-stable and water-tolerant, we designed a pseudo C_3-symmetric tris(oxazoline) **2** (Scheme 1) by sidearm approach and found that **2**/Cu(II) was an efficient catalyst for the asymmetric Friedel–Crafts reaction of indole with alkylidene malonate.[3] In this communication, we wish to report the application of ligand **2** in the asymmetric Kinugasa reaction.[4]

The Kinugasa reaction was developed in 1972.[4] Initially, it was performed in dry pyridine using stoichiometric copper acetylide. Later on, Miura *et al*. found that this reaction could be accomplished with the use of terminal alkynes and nitrones directly in the presence of substoichiometric CuI.[5] They also pioneered the asymmetric version but only phenylacetylene was examined. In their study, 57% ee and 35% de were achieved when a mixture of 10 mol% CuI and 20 mol% bis(oxazoline) **1c** was employed. Very recently, Fu and coworkers[6] found that bis(azaferrocenes)/CuCl (Scheme 1) could catalyze the Kinugasa reaction very well to afford the desired products with good to high enantioselectivity for *cis*-isomers (up to 93% ee, *cis*/*trans* up to 95/5).

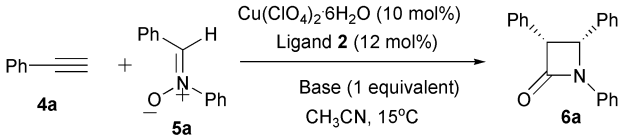
As mentioned above, Cu(I) is always used as the catalyst for Kinugasa reaction.[4–7] And thus, this reaction is performed strictly under nitrogen to mitigate the Glaser oxidative coupling. Fortunately, we found that Cu(ClO$_4$)$_2$·6H$_2$O, instead of sensitive Cu(I) salts, could catalyze this reaction very well in the air. In this case, tris(oxazoline) **2**/Cu(ClO$_4$)$_2$·6H$_2$O provided the desired β-lactam in moderate yield with 63% ee when triethylamine was used as the base under air (entry 1, Table 1) in the absence of reductant.[8]

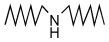
Further studies showed that the amines strongly influenced both the selectivity and the yield. As shown in Table 1, although primary amines, secondary amines and tertiary amines all could promote this reaction, primary amines gave moderate ee, low de and poor yield (entry 12). Tertiary amines provided high diastereoselectivity and moderate enantioselectivity (entries 1–4). Compared with both primary amines and tertiary amines, secondary amines afforded the desired products with better diastereoselectivity and enantioselectiviy (entries 6–11). Obviously, bulkier amines gave better diastereoselection. For example, both 2,2,4,4-tetramethylpyrollidine and diisopropylethylamine gave the *cis*-isomer as the sole product (entries 2, 5). Dicyclohexylamine (entry 11) proved to be the best base in our screened conditions. In this case, the reaction of phenylacetylene **4a** with nitrone **5a** gave 80% ee, comparable to that when **3**/CuCl was used (77% ee).[6] These results suggested that amines might coordinate to the copper center and relay the effect of the chiral ligand. Under the optimized reaction conditions, we next examined the generality of the reaction by employing a variety of structurally different nitrones and alkynes. As shown in Table 2, the electronic character of the α-aryl group on nitrones had almost no effect on the enantioselection (entries 6–10). Whatever electron-deficient or electron-rich α-aryl nitrones were used, all reactions gave good enantioselectivity and diastereoselectivity. Nitrones with an α-furyl group furnished good ee but low diastereoselectivity (entry 9).



Scheme 1

Table 1 Effects of organobases on Kinugasa coupling reaction[a]



Entry	Base	Time/h	*cis*/*trans*[b]	ee (*cis*, %)[c]	Yield (%)[d]
1		18	92/8	63	45
2		17	> 99/1	56	51
3		35	92/8	56	57
4		24	96/4	58	45
5		17	> 99/1	55	54
6		5	86/14	79	55
7		6	86/14	82	61
8		16	90/10	72	61
9		15	90/10	68	52
10		26	94/6	73	62
11		16	93/7	80	63
12		7	83/17	59	39

[a] Reactions were run at 15 °C using 12 mol% ^{i}Pr-tris(oxazoline) and 10 mol% copper salt under air atmosphere on 0.25 mmol scale. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Total isolated yield of *cis*- and *trans*-isomers.

† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b3/b306653c/

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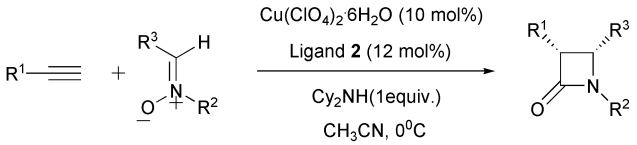
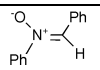
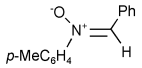
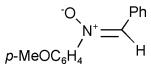
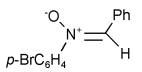
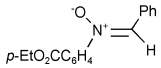
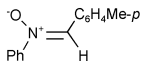
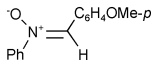
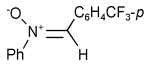
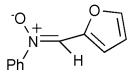
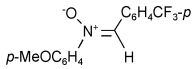
Table 2 Aymmetric synthesis of β-lactams[a]



Alkyne **4a**: R^1= Ph; **4b**: R^1= *p*-$CF_3C_6H_4$; **4c**: R^1= 1-cyclohexenyl

Entry	Alkyne	Nitrone	*cis*/*trans*[b]	ee (*cis*, %)[c]	Yield (%)[d]
1	**4a**		94/6	82	56
2	**4a**		95/5	82	36
3	**4a**		97/3	84	36
4	**4a**		93/7	74	70
5	**4a**		91/9	70	98
6	**4a**		95/5	82	50
7	**4a**		95/5	83	58
8	**4a**		93/7	82	75
9	**4a**		67/33	85	56
10	**4a**		96/4	84	35
11	**4b**		75/25	73	65
12	**4c**		93/7	72	33

[a] Reactions were run at 15 °C using 12 mol% of ^{i}Pr-tris(oxazoline) **2** and 10 mol% of copper salt under air atmosphere on 0.25 mmol scale. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Total isolated yield of *cis*- and *trans*-isomers.

Substituents on the N-bound aromatic group of nitrones influenced both the yield and the selection. Electron-rich ones increased the enantioselectivity but decreased the reactivity (entries 1–3). By contrast, electron-deficient substituents slightly decreased the enantioselectivity and increased the reactivity (entries 4 and 5). Besides arylacetylenes (entries 1–11), alkyl alkyne worked well in this reaction (entry 12). For example, cyclohexenyl acetylene gave also good ee with high diastereoselectivity (entry 12).

In summary, the air-stable and water-tolerant tris(oxazoline) **2**/$Cu(ClO_4)_2·6H_2O$ complex proved a catalyst in the asymmetric Kinugasa reaction. This method provided a facile access to *cis*-β-lactams with good enantioselectivty. Noticeably, the Cu(II) salt proved an efficient catalyst precursor for the first time in the Kinugasa reaction. It is significant that this modification allowed the reaction to run under air atmosphere whereas all documented protocols[4–7] were run under nitrogen. In addition, organic bases were found to influence both the selectivity and the reactivity strongly and this probably provides some information for ligand design to further improve the selectivity and reactivity in this reaction.

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Notes and references

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8 Most recently, Carreira used $Cu(OAc)_2$ instead of Cu(I) to produce copper acetylide in the presence of sodium ascorbate. See: T. F. Knopfel and E. M. Carreira, *J. Am. Chem. Soc.*, 2003, **125**, 6054.