Chiral Tricyclic Lactams

Catalytic Enantioselective Synthesis of β-Lactams: Intramolecular Kinugasa Reactions and Interception of an Intermediate in the Reaction Cascade**

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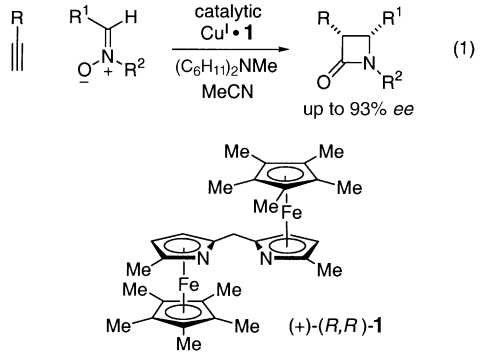
β-Lactams have been intensely investigated as a result of both their biological activity and their utility as synthetic intermediates.[1,2] For example, in the pharmaceutical arena, penicillins and cephalosporins are widely prescribed antibiotics,[1] ezetimibe (zetia) serves as a potent hypocholesterolemic agent,[3] and a β-lactam is employed in the commercial synthesis of the anticancer drug paclitaxel (taxol) to install a β-amino acid derived side chain.[4]

Because of the wide-ranging significance of β-lactams, the development of efficient methods for their enantioselective synthesis is an important objective. A number of noteworthy strategies have been described, almost all of which rely upon the generation of chiral, nonracemic precursors, followed by formation of the four-membered ring.[1,2] In contrast, very few catalytic enantioselective routes to β-lactams from achiral precursors have been reported.[5]

Based on the pioneering work of Kinugasa et al.,[6] Miura et al.,[7] and others,[8] we recently described a copper/bisazaferrocene-catalyzed method for the asymmetric coupling of alkynes with nitrones (the Kinugasa reaction; [Eq. (1)] and Figure 1).[9] This mild approach to the generation of β-lactams is very attractive owing to its convergence, its high functional-group tolerance, and the ready availability and stability of alkynes and nitrones. In our initial study, planar-chiral bisazaferrocene **1** proved to be the most effective ligand among those that we examined.



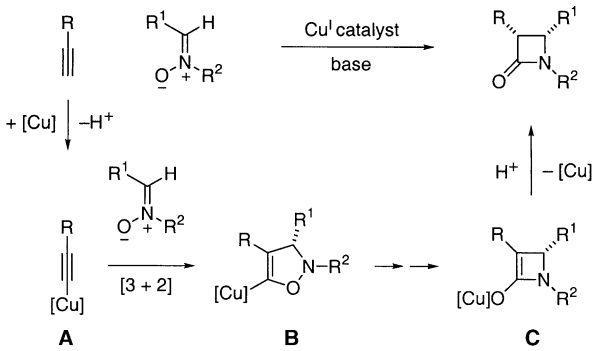


Figure 1. Outline of a possible mechanism for the Kinugasa reaction.

This early investigation explored the generation of monocyclic β-lactams exclusively. Bicyclic and polycyclic β-lactams also constitute important targets, both as endpoints (e.g., penicillins[1] and trinems/tribactams[10]) and as synthetic intermediates.[11] Although, in principle, an intramolecular Kinugasa reaction would provide efficient access to these classes of compounds, to the best of our knowledge no

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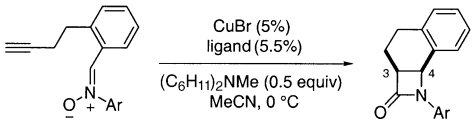
examples of such a process have been reported. We therefore turned our attention to the development of intramolecular Kinugasa reactions, ideally with a chiral catalyst, with a view to preparing enantioenriched bi- and polycyclic β-lactams. Herein we demonstrate that a copper/phosphaferrocene–oxazoline catalyst mediates asymmetric intramolecular Kinugasa reactions to produce two new rings with very good stereoselectivity. Furthermore, we establish that one of the presumed intermediates in the catalytic cycle (**C** in Figure 1) can be intercepted with an electrophile to generate an additional C–C bond and a quaternary stereocenter.

Our initial investigations focused on the intramolecular Kinugasa reaction of alkyne–nitrone **2** (Table 1) to produce

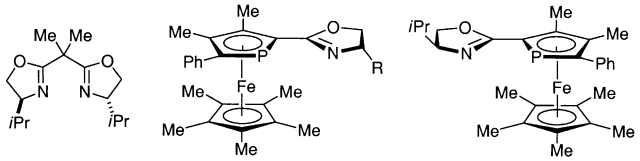
Table 1: Ligand effects for an intramolecular Kinugasa reaction.[a]



2 Ar = *p*-carboethoxyphenyl **3**

Entry	Ligand	*ee* [%]	Configuration	Yield [%]
1	**1**	6	3*S*,4*S*	30
2	**4**	62	3*R*,4*R*	39
3	**5a**	88	3*S*,4*S*	74←
4	**5b**	90	3*S*,4*S*	47
5	**6**	58	3*S*,4*S*	52

[a] All data are the average of two runs.



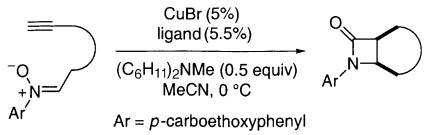
4 **5a**: R = *i*Pr; **5b**: R = *t*Bu **6**

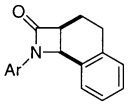
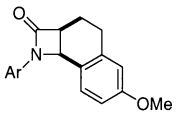
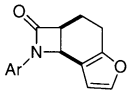
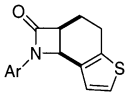
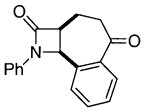
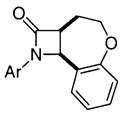
the tricyclic β-lactam framework employed by Merck for the synthesis of melanocortin receptor agonists.[12] Disappointingly, planar-chiral bisazaferrocene **1**, which had been useful for intermolecular processes [Eq. (1)], furnished the desired β-lactam **3** with poor enantioselectivity and in low yield (6% *ee* and 30% yield; Table 1, entry 1). We therefore decided to explore alternative ligand architectures. Chiral bisoxazolines have proved to be effective for a wide variety of transformations, including an array of copper-catalyzed reactions.[13] Unfortunately, the use of bisoxazoline ligand **4** afforded **3** with only moderate stereoselectivity and in modest yield (62% *ee* and 39% yield; Table 1, entry 2).[14]

During the past few years, we have begun to explore the use of a new family of ligands, planar-chiral phosphaferrocene–oxazolines, in asymmetric catalysis (e.g., **5a**, **5b**, and **6** in Table 1).[15] When we applied ligand **5a** in the copper-catalyzed intramolecular Kinugasa reaction of alkyne–nitrone **2**, we were pleased to observe that the desired β-lactam **3** was furnished with markedly improved stereoselectivity and yield (88% *ee* and 74% yield; Table 1, entry 3). Ligand **5b**, in which the *i*Pr group of the oxazoline has been replaced with a *t*Bu group, promoted a similar level of enantioselectivity but a lower yield (90% *ee* and 47% yield; Table 1, entry 4). Finally, phosphaferrocene–oxazoline **5a** is superior to the diastereomeric ligand **6** with respect to both enantioselectivity and yield (Table 1, entry 3 vs. entry 5).[16,17]

Having established that a Cu/phosphaferrocene–oxazoline catalyst not only promotes an intramolecular Kinugasa reaction, but does so with very good enantioselectivity, we explored the application of our method to the synthesis of a range of tricyclic compounds containing a 6,4 or a 7,4 ring system (Table 2).[18] The *i*Pr-substituted ligand **5a** was typically found to be the ligand of choice for the generation of β-lactams fused to a six-membered ring (86–90% *ee*; Table 2, entries 1–3), whereas for seven-membered rings the *t*Bu-substituted analogue **5b** gave superior results (85–91% *ee*; entries 5 and 6).[19]

Table 2: Copper-catalyzed intramolecular Kinugasa reactions in the presence of planar-chiral phosphaferrocene–oxazoline ligands: Enantioselective synthesis of two new rings.[a]

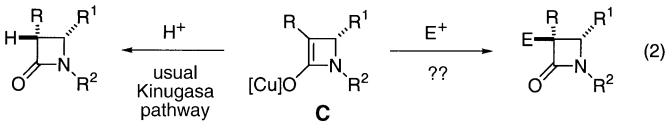


Entry	Product	Ligand	*ee* [%]	Yield [%]
1		**5a**	88	74
2		**5a**	86	60
3[b]		**5a**	90	46
4[b]		**5b**	90	64
5[b]		**5b**	85	53
6		**5b**	91	68

[a] All data are the average of two runs. [b] The reaction was run at room temperature.

The proposed mechanism for the Kinugasa reaction is illustrated in Figure 1.[6–8] It is believed that the terminal alkyne is converted into copper acetylide **A** in the presence of Cu^I and a base (e.g., $(C_6H_{11})_2NMe$),[6] and that **A** participates in a [3+2] dipolar cycloaddition with the nitrone. The resulting heterocycle **B** then rearranges to afford the conjugate base of a β-lactam (enolate **C**).[20] Protonation (e.g., by $[(C_6H_{11})_2NHMe]^+$) furnishes the desired product and releases the copper catalyst.

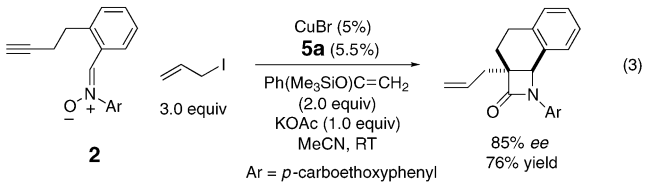
It occurred to us that the utility of the Kinugasa reaction would be further enhanced if we could intercept intermediate **C** by adding an electrophile to the reaction mixture, thereby generating a quaternary stereocenter [Eq. (2)].[21] This is not a



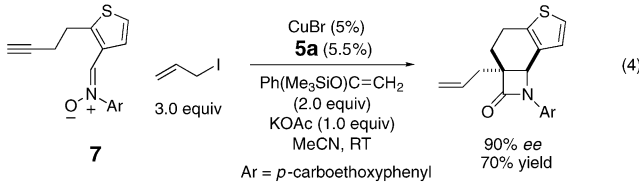
(2)

trivial objective, as energetically favorable proton transfers often proceed with remarkable facility relative to other bond-forming reactions.[22] Indeed, when allyl iodide was added to the reaction mixture under our otherwise standard conditions for the cyclization of alkyne–nitrone **2**, a negligible amount of the α-allylated β-lactam was obtained.

After considerable effort, we were pleased to discover conditions under which the desired α functionalization occurred. In the presence of a mixture of a silyl enol ether and KOAc as the base (rather than $(C_6H_{11})_2NMe$), alkyne–nitrone **2** underwent cyclization followed by α alkylation with good stereoselectivity and in good yield (85% *ee* and 76% yield; Eq. (3)).[23] Similarly, the heterocyclic substrate **7** was efficiently converted into the desired enantioenriched β-lactam (90% *ee* and 70% yield; Eq. (4)). Thus, two carbon–carbon bonds, a carbon–nitrogen bond, two new rings (including a β-lactam), a carbonyl group, and adjacent tertiary and quaternary stereocenters can be generated in a single cyclization–alkylation sequence.



(3)



(4)

In summary, we have demonstrated that an intramolecular Kinugasa reaction can be used to prepare fused tricyclic ring systems efficiently with very good levels of enantioselectivity in the presence of a planar-chiral Cu/phosphaferrocene–oxazoline catalyst. Other ligands, including bisoxazolines and bisazaferrocenes, led to the formation of the desired β-lactam in significantly lower yields and with lower *ee* values. Based on the postulated mechanism for the Kinugasa reaction, we have devised a variant of the process in which a presumed intermediate in the catalytic cycle (an enolate) is intercepted with an electrophile. The viability of this variant provides support for the suggested mechanism and enhances the remarkable utility of the Kinugasa reaction. Additional studies of this and related transformations are underway.

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Keywords: asymmetric catalysis · copper · cyclizations · domino reactions · nitrogen heterocycles

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[6] Their original report describes the stoichiometric reaction of a copper acetylide with a nitrone: M. Kinugasa, S. Hashimoto, *J. Chem. Soc. Chem. Commun.* **1972**, 466–467.

[7] M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999–5004.

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[13] a) For a review of applications of C_2-symmetric bisoxazolines in asymmetric catalysis, see: A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) for some leading references to copper-catalyzed reactions, see: T. Rovis, D. A. Evans, *Prog. Inorg. Chem.* **2001**, *50*, 1–150.

[14] Similarly, in the only study by others of a catalytic asymmetric Kinugasa reaction, Miura et al. found bisoxazoline **4** to be only modestly effective as a chiral ligand for copper-catalyzed intermolecular couplings of alkynes with nitrones (maximum *ee* value: 57%).[7]

[15] a) R. Shintani, M. M.-C. Lo, G. C. Fu, *Org. Lett.* **2000**, *2*, 3695–3697; b) R. Shintani, G. C. Fu, *Org. Lett.* **2002**, *4*, 3699–3702.

[16] The data for ligands **5a** and **6** in Table 1 (entries 3 and 5) indicate that the central chirality of the oxazoline subunit is the dominant stereocontrol element and that the planar chirality of the phosphaferrocene subunit plays a subordinate, although significant, role.

[17] The absolute configuration of the product was determined through X-ray crystallographic analysis of the bis(amide) that is produced upon the reaction of β-lactam **3** with excess 2-bromobenzylamine (see Supporting Information).

[18] Notes for Table 2, entry 1: 1) When CuBr is used, the product is furnished with somewhat higher *ee* values than with CuCl, CuI, Cu(OTf), $Cu(MeCN)_4BF_4$, or Cu(SCN). 2) The course of the coupling is highly dependent on the $(C_6H_{11})_2NMe$/Cu ratio (e.g., a 20:1 ratio leads to a substantial increase in side reactions). 3) The use of bases such as $K_3PO_4{\cdot}H_2O$, K_2CO_3, 1,4-diazabicyclo[2.2.2]octane (dabco), 2,6-lutidine, KF, NEt_3, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and KOH results in an erosion in enantioselectivity and/or yield. 4) The use of MeCN as the solvent gives rise to much cleaner reactions than the use of CH_2Cl_2, THF, dioxane, *N,N*-dimethylformamide (DMF), acetone, or 2-methylbutan-2-ol. 5) Kinugasa reactions of *N*-phenyl and *N*-(4-carboethoxyphenyl)-substituted nitrones lead to β-lactams with similar *ee* values, but couplings of *N*-(4-carboethoxyphenyl)-substituted nitrones generally proceed in somewhat better yield. In the case of an *N*-benzyl- rather than an *N*-(4-carboethoxyphenyl)-substituted nitrone, the *ee* value and the yield of the β-lactam are lower. We have not attempted to optimize these processes. 6) Recrystallization of the β-lactam from Et_2O enhances the *ee* value (> 99% *ee*; 53% recovery).

[19] Ligands **5a** and **5b** promote similar enantioselectivity in the synthesis of 6,4 bicyclic systems (Table 2, entries 1–4). However, the yields are generally higher when **5a** is employed. For the synthesis of 7,4 bicyclic systems (Table 2, entries 5 and 6), comparable yields were observed when ligands **5a** or **5b** were used, but somewhat better *ee* values (up to 15% higher) were observed in the presence of ligand **5b**.

[20] We believe that this proceeds through ring-opening fragmentation to a ketene, followed by recyclization; see: C. Ahn, J. W. Kennington, Jr., P. DeShong, *J. Org. Chem.* **1994**, *59*, 6282–6286.

[21] For a recent review of catalytic asymmetric methods for the generation of quaternary stereocenters, see: E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; see also: J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597.

[22] Another potential complication is the reaction of a nucleophilic Brønsted base (e.g., a tertiary amine) with the electrophile (E^+).

[23] When $KOAc/Ph(Me_3SiO)C{=}CH_2$ is used instead of $(C_6H_{11})_2NMe$, acetophenone is presumably generated, rather than a trialkylammonium salt. Acetophenone is a poor proton donor compared to a trialkylammonium salt.

