

# Mechanism of alkene aziridination in the [(biaryldiimine)Cu<sup>I</sup>] catalyst system; precise substrate orientation *via* two-centre binding†

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The highly enantioselective ( $\leq 98\%$ ) aziridination of cinnamate esters is achieved using the title catalyst system *via* a concerted non-polar mechanism involving ancillary binding of carbonyl group to copper.

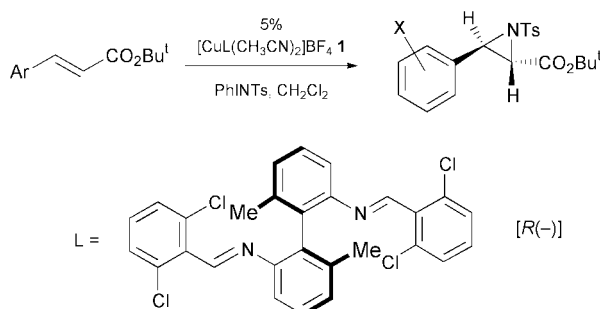
The addition of nitrenes RN: to alkenes is an attractive method for the synthesis of aziridines.<sup>1</sup> Evans' work<sup>2</sup> and particularly the asymmetric variant,<sup>3</sup> has inspired a number of groups to design chiral metal complex systems for this reaction.<sup>4</sup> The standard protocol uses an I<sup>III</sup> iodine such as PhINTs as the source of nitrene and a metal complex (most successfully of Cu) which acts as a transfer catalyst (Fig. 1). An early report provided powerful evidence for the presence of a discrete nitrenoid complex intermediate **I**.<sup>5</sup>

It has been noted that both Cu<sup>I</sup> and Cu<sup>II</sup> act as adequate precatalysts and that UV spectra of the Cu<sup>I</sup> and Cu<sup>II</sup>-derived reaction mixtures are indistinguishable in the Evans system.<sup>2</sup> Mechanistic evidence from Pérez relating to a tris(pyrazolyl)borate catalyst points clearly to Cu<sup>II</sup>.<sup>6</sup> It is becoming clear, however, that the mechanism may be system-dependent; Norrby has very recently described detailed calculations on the Jacobsen system which indicate a route by which a Cu<sup>II</sup> starting complex may enter the Cu<sup>I</sup> manifold.<sup>7</sup> *In situ* UV spectra of our catalysts are consistent with operation in this lower oxidation state.

The Evans and Jacobsen systems appear to be complementary in that the former give excellent enantioselectivity for *trans* disubstituted alkenes,<sup>3</sup> while the latter are most efficient for *cis*.<sup>5</sup> We were thus rather surprised to find that [CuL(CH<sub>3</sub>CN)<sub>2</sub>] **1**, which is a very fast and selective precatalyst for *cis*-disubstituted alkenes,<sup>8</sup> also mediates the rapid aziridination of a range of *trans*-cinnamate esters with excellent enantioselectivity (Scheme 1, Table 1).

Data from competitive kinetic experiments based on eight cinnamate esters gave an excellent straight line Hammett plot, using simple  $\sigma_X$  constants, with slope  $\rho = -0.65$  (Fig. 2). The low negative value of  $\rho$  indicates that the intermediate species is not dipolar, *i.e.* there is little build up of positive charge at the benzylic carbon in the rate- and selectivity-determining nitrene transfer step. Even so, we might expect a deviation from linearity in Fig. 2 for mesomerically electron-donating substituents (*e.g.* OMe), necessitating the use of  $\sigma^+$  constants.<sup>6,9</sup> That this is *not* observed indicates that there is minimal through-conjugation between substituent X and the reaction centre. This

is probably caused by disinclination of the system to become planar (*vide infra*). In any event, the behaviour is very different from that in the Pérez system for which a two-term Hammett-type equation incorporating  $\sigma^+$  and Jackson's  $\sigma^*$  constants<sup>10</sup> was required to fit the data.<sup>6</sup> Finally in this regard we note that the



Scheme 1 Catalytic synthesis of cinnamate esters using **1**.

Table 1 Enantioselective aziridination of cinnamate esters *etc.*

| Entry | X (See Scheme 1) <sup>a</sup> | Yield <sup>b</sup> | ee <sup>c</sup>   |
|-------|-------------------------------|--------------------|-------------------|
| 1     | H                             | 77                 | 89                |
| 2     | 4-MeO                         | 67                 | 93                |
| 3     | 4-Me                          | 82                 | 88                |
| 4     | 3-Me                          | 56                 | 96                |
| 5     | 4-F                           | 45                 | 98                |
| 6     | 4-Cl                          | 89                 | 92                |
| 7     | 4-Br                          | 59                 | 98                |
| 8     | 3-NO <sub>2</sub>             | 32                 | 96                |
| 9     |                               | 99                 | 34 <sup>d</sup>   |
| 10    |                               | 88                 | 28 <sup>d,e</sup> |

<sup>a</sup> Absolute configurations of all cinnamate products were [2S, 3R (-)] as inferred by comparison of relative retention times of the enantiomers with those of entry 1 for which the configuration is known.<sup>3</sup> <sup>b</sup> Isolated yield of pure aziridine. <sup>c</sup> Ee determined by HPLC (Chiralcel OD 15 cm  $\times$  0.46 cm i.d. hexane:propan-2-ol (various ratios)). <sup>d</sup> Ee determined by <sup>1</sup>H NMR using [Eu(hfc)<sub>3</sub>]. <sup>e</sup> *Trans*:*cis* ratio 97:3. <sup>e</sup> Ee given for *trans* product.

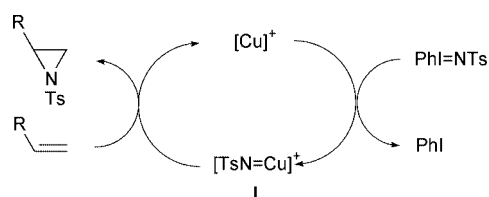


Fig. 1 Cycle for the Cu-catalysed aziridination of alkenes with PhINTs.

† Electronic supplementary information (ESI) available: experimental and theoretical details. See <http://www.rsc.org/suppdata/cc/b1/b101415n/>

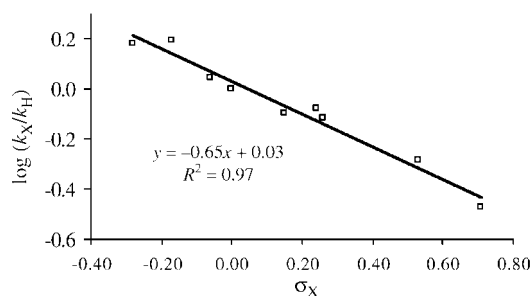
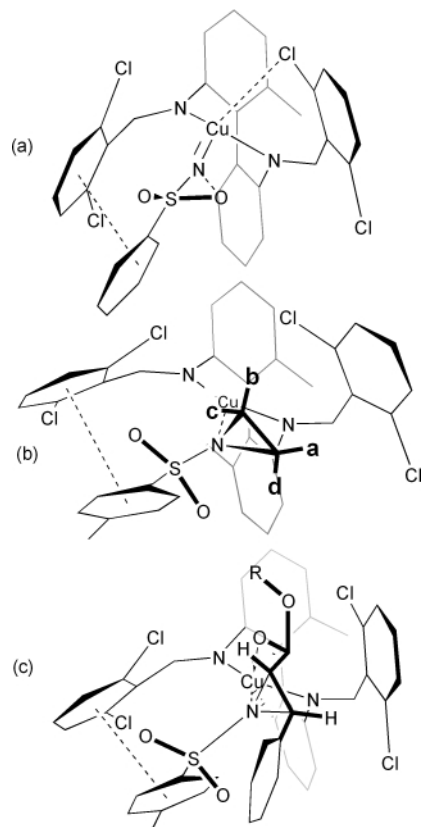


Fig. 2 Hammett plot for the reaction in Scheme 1.



**Fig. 3** Based on calculated (DFT) structures of (a) catalyst [CuL(NTs)] **2**, (b) aziridine complex **3** and (c) cinnamate ester aziridine complex.

presence of significant radical character in our rate- (and selectivity-) determining step is strongly opposed by the absence of detectable levels of *cis* cinnamate aziridines in the product mixtures. Our catalysts clearly operate *via* a concerted mechanism; both C–N bonds are formed at approximately the same time.

Armed with this experimental data we set out to investigate the structure of the relevant catalytic intermediates using Density Functional Theory (DFT).<sup>†</sup> A fully optimised DFT structure of the precatalyst **1** was found to be essentially superimposable on the molecular structure.<sup>8</sup> The proposed catalyst species arising from the removal of the CH<sub>3</sub>CN groups and addition of the nitrene NTs *i.e.* [CuL(NTs)] **2** was minimised successfully. One of two similar structures located<sup>‡</sup> is shown in Fig. 3(a). The tosyl group is oriented such that the arene forms what may be a planar  $\pi$  stacking interaction with one of the dichlorophenyl groups. Interestingly, coordination of one of the sulfonyl O atoms to the nitrene N has occurred, thus forming a three-membered ring.<sup>‡</sup> Although we do not wish to assert that this interaction plays an important part in the catalysis, it does indicate that the N atom is highly electrophilic, as expected from the negative value of  $\rho$  above. The TsN–Cu distance of 1.80 Å in **2** indicates multiple metal–ligand bond character.

Insights into the interactions between the catalyst and alkene were obtained by computing the structure of a complex with ethylene bound to the nitrene N.<sup>7</sup> The aziridine complex [CuL(TsNC<sub>2</sub>H<sub>4</sub>)] **3** thus obtained [Fig. 3(b)] has a TsN→Cu distance of 1.93 Å. The alignment of the alkene fragment in this species is controlled by the chiral ligand *via* the orientation of the tosyl group as described above.

The energetic consequences of adding substituents to the alkene were assessed by optimising the structures for three orientations of styrene bound to N; that with a phenyl group in

site **a** was not considered viable since it is severely hindered by a dichlorophenyl group. The structures with phenyl in sites **b–d** have the same energies within *ca.* 10 kJ mol<sup>–1</sup>, and this is consistent with the modest enantioselectivity for aziridination of this alkene (entry 9). The stereochemical preference for the cinnamate esters is more clear cut however. Placing a –CO<sub>2</sub>Me group in site **b** facilitates coordination of the carbonyl oxygen to the otherwise three-coordinate copper [Fig. 3(c)]; this is not feasible at sites **c** and **d**.<sup>§</sup> The interaction contributes *ca.* 20 kJ mol<sup>–1</sup> to the stability of the structure, and, assuming that this energetic preference is reflected at the transition state for alkene binding (which seems likely given the concerted mechanism) it readily explains the excellent selectivity observed. The absolute sense of asymmetric induction is as predicted by this model.

Two compelling pieces of circumstantial evidence further support our proposed mode of enantioselection. Firstly, the cinnamate phenyl group must be placed in site **d**, and our calculations indicate that its achievement of coplanarity with the alkene unit (and thus through-conjugation, *vide supra*) is hampered by steric effects [Fig. 3(c)]. Secondly, we note that while Evans' bis(oxazoline) system was highly selective for aziridination of both cinnamates and *trans*- $\beta$ -methylstyrene, **1** performed very poorly with the latter (entry 10). With no suitable coordinating group, this alkene shows little preference for either of the two possible diastereomeric orientations, *viz.* Me and Ph at sites **b** and **d**.

Hence the observed enantioselectivity for aziridination of cinnamate esters with precatalyst **1** arises in two-centre binding of the substrate. While being somewhat unexpected, it is related to well documented examples of  $\eta^2$  substrate binding at catalytic metal centres.<sup>11</sup>

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## Notes and references

<sup>†</sup> In contrast, Norrby<sup>7</sup> found that in calculations based on the Jacobsen system,  $\eta^2$ -N,O coordination at Cu of N–SO<sub>2</sub>Me was found throughout. We were unable to locate such a structure here.

<sup>§</sup> In the catalyst structure there is weak dative coordination of an aryl C atom at this site [see Fig. 3(a)].

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