Cuh-mediated hydroamination of styrene

Abstract: A detailed computational exploration of mechanistic intricacies of the copper(I) hydride (CuH)-catalysed hydroamination of styrene with a prototype hydoxylamine ester by a recently reported (dppbz)CuH catalyst (dppbz ≡ {P^P} ≡ 1, 2-bis(diphenylphosphino)benzene) is presented. A variety of plausible mechanistic avenues have been pursued by means of a sophisticated computational methodology, from which a general understanding of the factors controlling hydroamination catalysis emerged.

The catalytically competent {P^P}Cu^I hydride, which is predominantly present as its dimer, involves in irreversible hydrocupration proceeding with complete 2, 1 regioselectivity to form a secondary {P^P}Cu^I benzyl intermediate. Its interception with benzylamine ester produces the branched tertiary amine product and {P^P}Cu^I benzoate upon intramolecular S$_N$2 disruption of the amine electrophile's N-O linkage to precede highly rapid, strongly exergonic C-N bond-forming reductive elimination. The {P^P}Cu^I benzoate corresponds to the catalyst resting state and its conversion back into the {P^P}Cu^I hydride upon transmetalation with a hydrosilane is turnover limiting. The effect of electronic perturbations at the amine electrophile upon the reaction rate for productive hydroamination catalysis and also non-productive reduction of the hydroxylamine ester has been gauged, which unveiled a more fundamental insight into catalytic structure-performance relationships.

Introduction

The catalytic hydroamination (HA) reaction, the direct addition of an N-H bond across an unsaturated carbon-carbon linkage, offers facile access to an

industrially relevant organonitrogen commodity and fine chemicals in a green, waste-free and highly atom-efficient manner. [1] By focusing on late d-block metal catalysis, several distinct mechanistic pathways have been revealed over the years for the hydroamination of alkenes, including the following principal processes: 1) N-H bond activation with subsequent alkene insertion into the metal-NR$_2$ linkage, [2] nucleophilic attack of an amine at a metal-bound alkene, [3] nucleophilic attack of a metal amido species at an activated alkene [4] and amine coordination to be followed by proton transfer onto an activated alkene. [5] Despite the significant progress achieved over the past years the utilisation of these methodologies is still limited by a number of drawbacks. [1] The development of a general approach for regio- and enantioselective hydroamination of a broad range of alkene substrate classes, in particular, remains an important challenge in the context of intermolecular HA.

Recently, the groups of Miura [6] and Buchwald [7a] reported independently a mechanistically distinct approach for styrene HA that involves copper(I) hydride (CuH) as the catalyst together with amine electrophiles and a hydrosilane hydride source to furnish amines in excellent yields and enantio-/regioselectivities under mild conditions. [8] Miura and co-workers disclosed that styrenes react with benzylamine ester reagents in THF at room temperature to afford exclusively branched benzylic tertiary amines in the presence of a (dppbz)CuH catalyst (dppbz ≡ {P^P} ≡ 1, 2-bis(diphenylphosphino)benzene) and a hydrosilane hydride source (Scheme 1). [6] Treatment of the Cu(OAc)$_2$/dppbz starting material with Li(OtBu) and

a reducing agent likely gives rise to {P^P}Cu(O *t*Bu)2, which becomes converted into the catalytically competent {P^P}Cu^I hydride3through transmetalation with silane.

According to plausible mechanistic pathways outlined in Scheme 2 styrene insertion into the Cu-H linkage at3leads to {P^P}Cu^I alkyl4that couples with the benzylamine ester electrophile thereafter to generate amine product P and {P^P}Cu^I benzoate6. Various mechanistic pathways can be envisaged for this transformation,[9] but its precise details remain largely elusive thus far. Transmetalation of6with hydrosilane regenerates the catalytically competent {P^P}Cu^I hydride for another catalyst turnover. The performance of HA catalysis via the productive cycle can be compromised by the well known aptitude of the {P^P}Cu^I hydride to reduce the amine electrophile. This may proceed through various pathways to involve formation of either N-H (one plausible path via a {P^P}Cu^{III} benzoate amido hydride intermediate7is exemplified in Scheme 2) or O-H bonds to afford {P^P}Cu^I benzoate6by consumption of a molar equivalent of the amine electrophile.

Precise knowledge of both the operative mechanism and of catalytic structure-performance relationships are indispensable for the rational design of improved HA catalysts. In light of the fact that precise details of mechanistic intricacies of CuH-mediated vinylarene HA remain largely elusive thus far,[10] a sophisticated computational protocol has been employed as an established and predictive means to study reaction mechanisms and to guide rational catalyst design. The present study

scrutinises rival mechanistic pathways for HA of styrene (1a≡ S) with O -benzoyl- N , N -dimethyl-hydroxylamine (1b≡ A) by a catalytically competent dppbz-ligated Cu ^{I} hydride complex in the presence of prototype trimethylsilane (1c≡ H) as hydride source. No structural simplification (other than replacing O -benzoyl- N , N -diethyl-hydroxylamine and HSiPh $_3$ used in experiment by1band1c, respectively, solely for the purpose of computational efficiency) of any kind has been imposed for any of the key species involved.

The computational methodology employed (highly accurate DLPNO-CCSD(T) in conjunction with basis sets of def2-TZVP quality and a sound treatment of bulk solvent effects) simulated authentic reaction conditions adequately and mechanistic analysis is based on Gibbs free-energy profiles. This computational protocol can confidently be expected to reliably map the energy landscape and this has allowed mechanistic conclusions with substantial predictive value to be drawn.

As detailed herein, our comprehensive mechanistic examination provides support that effective HA catalysis involves irreversible hydrocupration with strict 2, 1 regioselectivity to be followed by generation of the branched tertiary amine product by interception of the thus formed secondary {P^P}Cu ^{I} benzyl nucleophile with amine electrophile. The prevailing pathway sees the first intramolecular S $_N$ 2 displacement of the benzoate leaving group and is followed by highly facile and strongly exergonic C-N bond-generating reductive elimination from a highly reactive, intervening {P^P}Cu ^{III} species. It leads to amine product and {P^P}Cu ^{I} benzoate, the

latter of which corresponds to the catalyst resting state. Its conversion back into the catalytically competent {P^P}Cu[I] hydride is turnover limiting.

Results and Discussion

The aim of the present study is twofold. A first part scrutinises thoroughly all the relevant elementary steps of Scheme 2, with special attention devoted to the several mechanistic avenues that can be invoked regarding the interaction of {P^P}Cu[I] alkyl nucleophile with the amine electrophile and also the productivity-limiting reduction of the amine transfer agent. A second part explores the effect of electronic perturbations at the amine electrophile upon catalyst performance.

{P^P}CuH-mediated HA of styrene with amine electrophile 1b

Catalyst initiation

Effective HA catalysis entails the initial conversion of {P^P}Cu(OtBu)2 into the catalytically competent {P^P}Cu[I] hydride compound. The ability of hydrosilane 1c($\equiv$ H) to affect transmetalation at 2, although being rather unlikely turnover limiting, will influence the performance of HA catalysis, since it determines the amount of catalytically competent {P^P}Cu[I] hydride species available for catalyst turnover.

Hydroxylamine ester 1b (displaying a slight preference for $\ddot{i}\!\!\not{i}\,\ll^1$ -N over $\ddot{i}\!\!\not{i}\,\ll^1$ -O donor ligation) and THF (T) show a comparable aptitude to bind at copper in 2. However, the entropic costs linked with reactant association place the respective adducts 2•A, 2•T higher in free energy relative to the separated

fragments. This gap widens regularly for ever weaker donor molecules as clearly seen in Figure 1 for silane (2•H) adducted species. Furthermore, 2exhibits no propensity toward dimer formation, as all the efforts to localise a dimeric species failed.

After the initial facile, but uphill association of trimethylsilane1cat2, transmetalation evolves through a metathesis-type transition-state (TS) structure (see Figure S1 in the Supporting Information), which decays thereafter into the {P^P}Cu ^{I} hydride complex3through facile liberation of Me $_3$ SiO t Bu. Figure 2 reveals an affordable kinetic barrier (ï $\dagger$ „ G ‡ = 22. 4 kcal mol $^{-1}$ relative to {2+1c}) for conversion of2into the catalytically competent complex3, which is driven by a thermodynamic force of substantial amount.

{P^P}Cu ^{I} hydride compound

Reactant (styrene S, hydroxylamine ester A, hydrosilane H), amine product (P) and THF (T) solvent molecules can associate in various ways at copper in the catalytically competent hydride compound (see Figure S2 in the Supporting Information) to give rise to a multitude of adducted species, all of which are expected to participate in mobile association/dissociation equilibria. [11] Similar to what is found for2, the copper centre can accommodate only a single molecule; [13] its moderate binding enthalpy, however, cannot compensate for the associated entropic costs, thereby rending the various adducted species to be higher in free energy than the respective separated fragments. Amines (A, P) and styrene (benefitting from

coppers ability for backbonding) are found to associate preferably and hence 3•A, 3•S display an energy gap (relative to separated fragments) that is somewhat smaller than for 3•T and 3•H (Figure 3). On the other hand, 3 exhibits a pronounced propensity towards dimer formation with 3dim is favoured by 7. 5 kcal mol^{-1} relative to 3 (Figure 3). Hence, the catalytically competent {P^P}Cu^I hydride is predominantly present as dimer 3dim with relevant adducts 3•S (productive cycle, Scheme 2) and 3•A (non-productive cycle, Scheme 2) are well separated and higher in free energy by more than 12 kcal mol^{-1} (Figure 3).

Styrene insertion into the Cu-H linkage

Following the plausible catalytic scenario in Scheme 2, the productive cycle entails the first generation of {P^P}Cu^I alkyl 4. Alternative regioisomeric pathways for migratory C= C bond insertion into the Cu-H ï♀³-bond commencing from 3•S have been examined. The possible participation of another reactant, amine product or solvent molecule has been probed explicitly, but neither encounter, product or TS structures featuring a stable coordination of a spectator molecule could be located. [13] Common to both pathways for 1, 2 and 2, 1 insertion is the evolution of C-H bond formation through a four-centre planar TS structure describing metal-mediated migratory insertion of the styrene C= C linkage into the polar Cu-H bond, which occurs at distances of 1. 57-1. 65 Å (see Figure S3 in the Supporting Information) for the emerging C-H bond. Following the reaction path further, TS structures decay into primary {P^P}Cu^I alkyl 4b (1, 2 insertion) and secondary {P^P}Cu^I benzyl 4a (2, 1 insertion), respectively.

Effective delocalisation of electron density is known to markedly influence the stability of the polarised TS structure describing the interaction of an electron-rich Cu-H ï∦³-bond with the styrene C= C linkage and also of4, such that the regioselectivity of the hydrocupration is largely dictated on electronic grounds. [14] The °-electron-withdrawing arene functionality at the styrene carbon directly adjacent to the copper centre effects an effective depletion of electron density from the nonsubstituted olefinic CH_2 centre in the TS structure and also assist through hyperconjugative interaction with the stability of4a. Hence it electronically stabilises both the TS structure for 2, 1 insertion and4awhen compared to the species involved in 1, 2 insertion that are devoid of such an opportunity. The located TS and product species (see Figure S3 in the Supporting Information) give no indication that the electronic predisposition towards 2, 1 insertion is likely to be reversed due to favourable {P^P}Cu-arene interactions along the 1, 2 pathway. Thus, 2, 1 insertion is expected to prevail energetically on both kinetic and thermodynamic grounds.

Indeed, Figure 4 reveals that migratory olefin insertion proceeds with complete 2, 1 regioselectivity to afford secondary {P^P}Cu^I benzyl4aby overcoming a barrier of 21. 6 kcal mol^{-1} (ï∦„ G relative to3dim), whereas the 1, 2 pathway remains inaccessible due to higher kinetic demands (ï∦„ ï∦„ $G^{\ddagger}$ = 4. 1 kcal mol^{-1}) and is also disfavoured thermodynamically (ï∦„ ï∦„ G = 4. 4 kcal mol^{-1}). It characterises hydrocupration via the energetically prevalent 2, 1 pathway to be kinetically viable and irreversible. [15]

Amine product generation upon interception of 4 by amine electrophile

The interception of {P^P}Cu ^{I} alkyl4with amine electrophile1bgives rise to the generation of amine product P and releases {P^P}Cu ^{I} benzoate6(Scheme 2). Various mechanistic scenarios are conceivable for this transformation, [9] but, unfortunately, virtually no precise details of the operative mechanism are available. [10] This section intends to fill this gap by thoroughly examining several rival pathways. It includes the cleavage of the hydroxylamine ester N-O linkage via: 1) S_N2 displacement of the benzoate leaving group; 2) intramolecular S_N2 displacement; and 3) oxidative addition across the N-O linkage. This affords transient {P^P}Cu ^{III} intermediate5, from which P and6are likely formed upon C-N bond-forming reductive elimination. The generation of the branched tertiary amine product Pa in a single step through nucleophilic attack of the Cu-C linkage at the positive N(amine) centre with concomitant N-O bond cleavage has been probed as a further plausible mechanistic avenue (dashed arrow in Scheme 2). Given that hydrocupration proceeds with strict 2, 1 regioselectivity, the discussion will focus exclusively on pathways that commence from4a. Notably, rival paths starting from4bare found energetically non-competitive in every case studied. The full account of all the studied pathways can be found in the Supporting Information.

We start with examining N-O bond cleavage of1bby nucleophilic {P^P}Cu ^{I} benzyl4a. Figure 5 collates the free-energy profile of the most accessible pathway for the various mechanistic scenarios examined, whilst structural aspects of key species involved can be found in Figures S4-S9 (see the

Supporting Information). The electrophile1bbinds preferably via its N donor

centre ($\ddot{i} \dagger \ll {}^{1}$ -N) at copper to furnish adducts with the unbound carboxylate

oxygen pointing either towards (4a $_1$ •A) or away (4a $_2$ •A) from the metal,

both of which are higher in free energy than the separated fragments. The

located TS[4a $_2$ •A–5a] structure describes N-O bond cleavage that is

reminiscent of a S $_N$ 2 displacement of the benzoate group, featuring

distances of 1. 72 and 2. 02 Å for vanishing N-O and emerging Cu-N amido

bonds (see Figure S5 in the Supporting Information). Progressing further

along the reaction trajectory, the benzoate group binds eventually at copper

to deliver transient {P^P}Cu ^{III} intermediate5a. The intramolecular process

version commencing from4a $_1$ •A evolves through a five-centre TS[4a $_1$ •A-

5a] that displays similar metrics regarding vanishing N-O and emerging Cu-N

amido bonds, but crucially benefits from an already pre-established Cu-

O(benzoate) contact (see Figure S7 in the Supporting Information). As it

turns out, this contact likely renders4a $_1$ •A→5aintramolecular S $_N$ 2

displacement somewhat favourable kinetically over4a $_2$ •A→5awith both

pathways are indistinguishable on thermodynamic grounds. The TS $_{OA}$ [4a $_2$

•A-5a] shown in Figure 5 (see also Figure S9 in the Supporting Information)

has been located as energetically prevalent three-centre TS structure

describing oxidative addition across the N-O linkage that occurs at distances

of 2. 43 Å and 1. 89/2. 60 Å for vanishing N-O and newly built

Cu-N(amido)/Cu-O bonds, respectively. The condensed free-energy profiles in

Figure 5 reveal that for cleavage of the electrophile's N-O linkage by

{P^P}Cu ^{I} benzyl nucleophile the4a $_1$ •A→5aintramolecular S $_N$ 2 pathway

(ï † „ $G^{\ddagger}$ = 19. 8 kcal mol $^{-1}$ relative to {4a+1b}) prevails kinetically

somewhat over4a $_2$ •A→5a, with oxidative addition proceeding through TS $_{OA}$ [4a $_2$ •A-5a] (ï $\ddagger$ „ $G^{\ddagger}$ = 31. 1 kcal mol $^{-1}$ relative to {4a+1b}) is found substantially more demanding kinetically and hence not accessible. The fine energy balance between the alternative S $_N$ 2-type pathways is likely be influenced by the diphosphine catalyst backbone.

Figure 6 combines the dominant pathway for N-O bond cleavage at amine adduct4a•A with C-N bond-generating reductive elimination at transient {P^P}Cu ^{III} 5ataking place thereafter. Given that benzyl and amido functionalities are already preferably arranged in5ano major structural reorganisation is required prior to traversing TS[5a–6•Pa], which occurs at a distance of 2. 36 Å of the emerging C-N bond (see Figure S11 in the Supporting Information) and decays thereafter into the branched tertiary amine product that is initially bound to {P^P}Cu ^{I} benzoate (6•Pa), but is readily released thereafter. The reductive elimination is found highly facile (ï $\ddagger$ „ $G^{\ddagger}$ = 5. 2 kcal mol $^{-1}$ relative to5a) and driven by a remarkably strong thermodynamic force (Figure 6). Of the two consecutive steps converting {P^P}Cu ^{I} benzyl4ainto amine product Pa and {P^P}Cu ^{I} benzoate6through interception with electrophile1b, the first intramolecular S $_N$ 2 displacement of the benzoate leaving group determines the overall kinetic demands (ï $\ddagger$ „ $G^{\ddagger}$ = 19. 8 kcal mol $^{-1}$ relative to {4a+1b}) with Pa and6are then generated from transient, highly reactive {P^P}Cu ^{III} intermediate5upon rapid and strongly downhill reductive elimination.

Nucleophilic attack of the Cu-C linkage at the positive N centre of the amine electrophile with concomitant N-O cleavage, thereby affording6a+ Pa in a

single step, describes an alternative mechanistic scenario. Despite all our efforts, a precise TS structure associated to this pathway could not be located, but examination by means of a state-of-the-art reaction-path-optimisation (chain-of-state; see the Computational Methodology) method provided a reasonably approximate TS structure. The multicentre TS[4a $_1$ •A-6•Pa] describes concerted N-O bond cleavage (2. 30 Å) together with C-N (2. 54 Å)/Cu-O(2. 37 Å) bond formation, all occurring in the immediate vicinity of the copper centre (see Figure S12 in the Supporting Information). A substantial barrier of approximately 30. 7 kcal mol $^{-1}$ (ï ‡ „ $G^{‡}$ relative to {4a+1b}) has to be overcome (Figure 7), which renders the concerted4a $_1$ •A→6•Pa pathway non-accessible kinetically in the presence of the viable two-step conversion shown in Figure 6. [16]

{P^P}Cu ^{I} benzoate compound

In light of the strong thermodynamic force associated with generating the C-N bond, the {P^P}Cu ^{I} benzoate may become, among others, a candidate for the catalyst resting state. Hence, the aptitude of6to accommodate additional reactant, amine product and THF solvent molecules has been probed in order to clarify its precise identity. In accordance with findings for2and3, a single molecule only can bind at copper at the expense of one of the two Cu-O(carboxylate) linkages, but adduct formation is disfavoured in terms of free energy. Hence the {P^P}Cu ^{I} benzoate is predominantly present as non-adducted form6featuring a ï ‡ « ^{2} -O ligated benzoate functionality (Figure 8).

Regeneration of {P^P}Cu ^{I} hydride from {P^P}Cu ^{I} benzoate

Transmetalation of 6 with trimethylsilane 1c regenerates the catalytically competent {P^P}Cu^I hydride 3 for another catalyst turnover, thereby closing the cycle for productive HA catalysis. Two scenarios have been analysed that are distinguished by which of the carboxylate oxygens at silane adducted 6•H participate in Si-O bond formation. The transfer of silyl onto the oxygen directly bound to Cu evolves through a four-centre metathesis-type TS[6•H-3•OS$_1$] and leads eventually to 3 upon facile liberation of Me$_3$SiOBz. On the other hand, a six-centre TS[6•H-3•OS$_2$] is traversed along an alternative pathway representing silyl transfer onto the unbound carboxylate oxygen (Figure 9 and Figure S13 in the Supporting Information). The enhanced stability of six-centre TS[6•H-3•OS$_2$] versus four-centre TS[6•H-3•OS$_1$] discriminates among the two pathways, which are driven by a thermodynamic force (ï∙„ G = 0. 5 kcal mol^{-1} relative to {6+1c}) of identical magnitude. The assessed barrier of 26. 2 kcal mol^{-1} (ï∙„ $G^‡$ relative to {6+1c}) for the most accessible pathway characterises 6+1c→3+ Me$_3$SiOBz as a kinetically demanding, but viable transformation that is slightly uphill thermodynamically (Figure 9).

Reduction of the benzylamine ester by {P^P}Cu^I hydride

The well known tendency of the catalytically competent {P^P}Cu^I hydride to reduce the amine electrophile under N-H bond formation, hence giving rise to {P^P}Cu^I benzoate, or alternatively via O-H bond formation to afford a {P^P}Cu^I amido can severely compromise the catalyst performance. To this end, several conceivable pathways (some of which are sketched in Scheme 2) have been studied. Whilst focusing on thermodynamic aspects amine

reduction with N-H bond formation via 3+1b→6+ HNMe$_2$ (ï‡„ G = -71. 9 kcal mol^{-1}) appears to be strongly favoured over O-H bond generating 3+1b→{P^P}Cu^{I} (NMe$_2$) + benzoic acid (ï‡„ G = -51. 3 kcal mol^{-1}). The cleavage of the N-O linkage of 1b at amine adduct 3•A does preferably proceed through S$_N$2 displacement of the benzoate leaving group with the intramolecular pathway proved to be somewhat favourable energetically (see Figure S14 in the Supporting Information), whilst oxidative addition of electrophile 1b across the N-O linkage is found substantially more demanding kinetically. All these aspects closely parallel the findings regarding the preferable avenue that leads to generate {P^P}Cu^{III} 5a (see above). Likewise, N-H bond-forming reductive elimination at {P^P}Cu^{III} amido hydride intermediate 7 is highly facile kinetically and strongly downhill as 5a→6a+ Pa is. Unfortunately, all the efforts to localise the associated TS structure have not been successful, but the examination of the reaction path thoroughly by means of a chain-of-state method firmly indicates that reductive amine elimination at 7 has an only marginal barrier, if at all, to overcome, hence it proceeds almost instantaneously. Overall, a smooth, kinetically affordable pathway for undesired 3+1b→6+ HNMe$_2$ conversion has been located that comprises a first intramolecular S$_N$2 cleavage of the N-O bond (ï‡„ $G^{\ddagger}$ = 26. 3 kcal mol^{-1} relative to 3dim, Figure 10), to be followed by highly rapid reductive amine elimination from an intervening and highly reactive {P^P}Cu^{III} intermediate 7, thus reflecting the well-documented aptitude of 3 to engage in performance-limiting reduction of the electrophilic amination reagent. [6, 7]

Further attempts devoted upon locating a proper TS structure for the concerted attack of the nucleophilic Cu-H linkage at the N centre of the amine electrophile to be accompanied with N-O bond disruption has not been successful. However, a reasonably approximate TS (see Figure S15 in the Supporting Information) is seen to be above TS[3 $_1$ •A-7] by another 19. 8 kcal mol $^{-1}$, such that the concerted pathway can confidently be discarded as energetically viable alternative to the operative two-step process.

Proposed catalytic cycle

The mechanistic picture based upon the above thoroughly conducted examination of relevant elementary steps is presented in Scheme 3. An energetically smooth and downhill sequence of steps transforms the starting material into the catalytically competent {P^P}Cu ^{I} hydride3, which is in a mobile equilibrium [11b] with its thermodynamically prevalent dimer3dim. Migratory insertion of the styrene C= C linkage into the Cu-H bond is kinetically facile (ï ‡ „ $G^{\ddagger}$ = 21. 6 kcal mol $^{-1}$ relative to {½3dim+1a}), thermodynamically downhill and proceeds with strict 2, 1 regioselectivity. Hence irreversible hydrocupration is regioselectivity determining and occurs prior to the turnover-limiting step. The interception of the thus generated secondary {P^P}Cu ^{I} benzyl4awith amine electrophile1bproduces the branched tertiary (*Markovnikov*) amine product Pa and {P^P}Cu ^{I} benzoate6. This transformation favours a two-step process comprising the first intramolecular S $_N$ 2 displacement of the benzoate leaving group (ï ‡ „ $G^{\ddagger}$ = 19. 8 kcal mol $^{-1}$ relative to {½3dim+1a+1b}) to furnish transient, highly reactive {P^P}Cu ^{III} intermediate5from which Pa and6are generated upon

highly rapid and strongly downhill reductive elimination. It renders 6 to be the most stable species of the cycle for productive HA catalysis and it thus corresponds to the catalyst resting state. The regeneration of catalytically competent 3 from 6 through transmetalation with hydrosilane 1cis found most demanding, but affordable, kinetically ($ï‡„G^{\ddagger}$ = 26. 2 kcal mol^{-1} relative to {6+1c}) and hence is turnover limiting – its assessed barrier is compatible with reported catalyst performance data. [6] It is worth mentioning that a similar picture regarding hydrocupration and transmetalation steps has emerged from a recent experimental study by the Buchwald group on a DTBM-SEGPHOS-based Cu^{I} catalyst. [7d]

A stepwise pathway closely related to 4a•A→6+ Pa is preferably traversed for the non-productive reduction of amine electrophile by 3. An intramolecular S$_N$2 N-O bond disruption ($ï‡„G^{\ddagger}$ = 26. 3 kcal mol^{-1} relative to {½3dim+1b}) precedes highly facile and strongly downhill reductive amine elimination from intervening, highly reactive {P^P}Cu^{III} intermediate 5a. The assessed small kinetic gap ($ï‡„ï‡„G^{\ddagger}$ = 0. 1 kcal mol^{-1}) between discriminative TS structures for productive and non-productive reaction branches reflects adequately the observed close competition between the two processes, which can lead to compromised catalyst performance for improper chosen amine electrophiles. Furthermore, it provides further confidence into the substantial predictive ability of the herein employed high-level computational methodology. [17]

Effect of the amine electrophile upon catalyst performance

A second part of this study explores the effect of the amine electrophile upon

catalyst performance. To this end, the energy profile for two