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# Computational studies on the copper(II) catalyzed Michael reaction

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**Abstract**

We report computational results on the mechanism of the copper(II) catalyzed Michael addition of enamines formed from β-diketones and amino acids. The results suggest that the enamine gets deprotonated upon coordination to $Cu^{2+}$, and that it occupies three coordination sites of a square planar geometry. The formation of this coordinated aza-enolate is facilitated by basic co-ligands such as acetate which take over the enamine proton. In this rather rigid structure, the former amino acid side chain assumes an angular position which leads to preferred attack of the Michael acceptor from the non-hindered side of the coordination plane and the formation of a preferred enantiomer if one starts from a prochiral diketone. This discrimination becomes effective because the Michael acceptor, although only loosely bound to the complex before carbon-carbon bond formation, attaches itself to a "free" axial position of the copper centre during the reaction.


*Keywords:* Michael reaction; Mechanism; Calculation; B3LYP; Reactive intermediate; Catalysis

## 1. Introduction

The 1,4-addition of β-diketones to enones (Michael addition) is an important C–C bond formation reaction. Modern metal catalyzed variants allow for the use of base-free conditions [1–9]. Enantioselectivity could be achieved starting from (chiral) enamines **3** made from β-diketones **1** and an amino acid derivative **2** which is used as a chiral auxiliary in stoichiometric quantities [10–13](Scheme 1). Although the usefulness of this reaction has widely been demonstrated, experiments have so far contributed only limited insight into mechanistic details [14–20]. In particular, it is not established how the chirality transfer from the auxiliary to the product becomes effective. This situation triggered us to perform quantum chemical calculations to shed some light on the mechanism of this reaction.

The addition of the parent β-diketones **1** to enones **4** is best catalyzed by Fe(III) salts [3]. We have recently presented a combined computational and experimental investigation giving support to a mononuclear active complex as active species in that case [21]. In this case, it is furthermore clear from the outset that the nucleophile approaching the enone is a coordinated enolate, since the free diketone is no nucleophile and the free enolate cannot exist in sufficient concentration in the acidic reaction medium. In the case of the addition of enamines, the situation is more complicated: first, we will assume that the copper catalyzed enamine addition also involves a single copper site. Note that this assumption can hardly be validated by theoretical methods and calls for experimental kinetic studies. Furthermore, there are three different possibilities as far as the nature of the nucleophile is concerned: first, the free enamine is nucleophilic enough to add to enones, such that there will always be a non-catalyzed background reaction [10]. Then there are two scenarios which involve a metal centre, namely that the enone is attacked by a coordinated enamine or by a coordinated aza-enolate. The latter is formed by deprotonation at the enamine nitrogen atom and is obviously a stronger nucleophile. The question is, however, if this species exists in sufficient quantities in the reaction medium to become important in the reaction.

## 2. Computational exploration of different reaction paths

All our computations have been performed for the Michael addition of the enamine **3a** (produced from 2,4-

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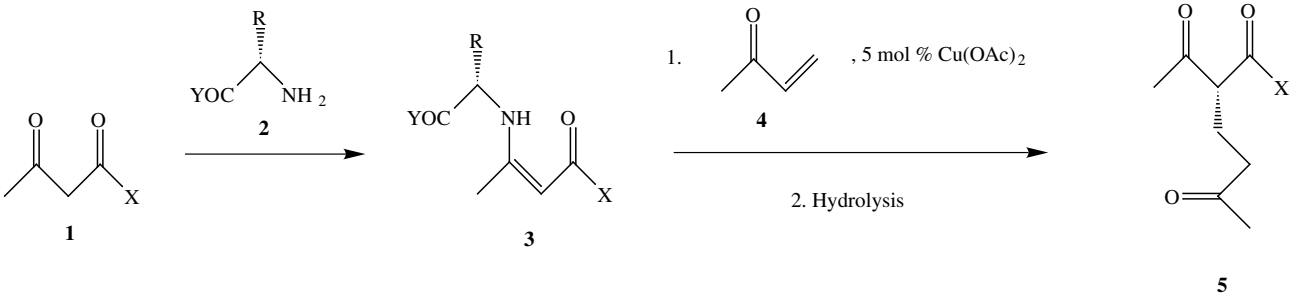



**1a.** X=Me
**2a.** Y=$NMe_2$, R=Me
**3a** . X=Me, R=Me, Y=$NMe_2$

Scheme 1.

pentanedione **1a** and (*S*)-alanine dimethyl amide **2a**) to methyl vinyl ketone **4**. We have investigated the three mechanistic possibilities sketched in the preceding section, namely the metal-free "background" reaction of **3a** with **4**, the Michael addition of **7** to **4**, and the reaction of the copper-coordinated aza-enolate **9** which is produced upon deprotonation at the enamine nitrogen atom (Scheme 2). In this work, our focus is on the elucidation of the reaction mechanism rather than on the calculation of the enantiomeric excess (which makes little sense unless model systems with larger amino acid side chains are used). In all our calculations, the enone approaches the Michael donor from the *re* side. All calculations been performed for the molecules in the gas phase. Preliminary calculations have shown that while the activation energies differ somewhat if the molecule is put into a dielectric continuum, the overall findings are not much changed.

### 2.1. Metal-free background reaction

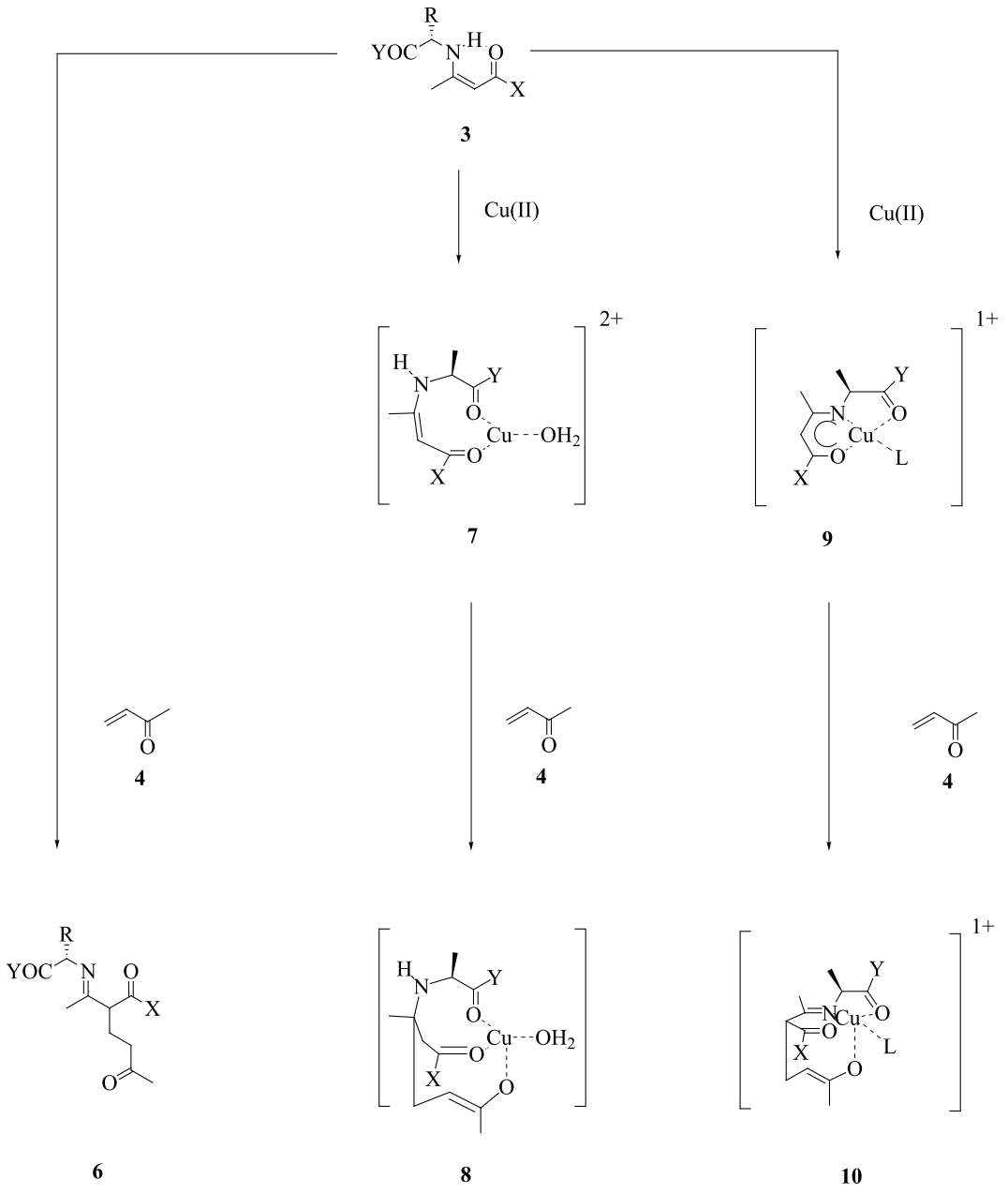
The experiments show that there is indeed a non-catalyzed background reaction which proceeds in the absence of any metal salt [10]. This reaction path is not only much slower than if catalyzed by the metal, but also shows lower enantioselectivity (typically, 57–70% ee for enamines derived from valine). According to our calculations, the direct addition of **3a** to **4** is a rather unfavourable step at least in the gas phase if one starts from the most stable conformation of **3** in which the hydrogen atom at the enamine nitrogen forms a hydrogen bond to the carbonyl O atom. The reason is, that the addition forms a highly polar, formally zwitterionic structure with a positive formal charge on the enamine nitrogen and a formal negative charge on the oxygen atom of the Michael acceptor. While there will be a relative stabilisation of a zwitterionic structure if one puts the system into a dielectric continuum that simulates the influence of an aprotic solvent, this is most likely not strong enough to make such a reaction attractive. Therefore, we looked for an alternate reaction path in which the N–H proton can be transferred to the oxygen atom of the acceptor upon C–C bond formation. The transition state for such a reaction path is shown in Fig. 1. In this figure (and the following ones), we marked the Michael acceptor with a shadow for the convenience of the beholder. Furthermore, a circle highlights the side chain of the amino acid (a methyl group in our calculations) which is the group that triggers the enantioselectivity of the reaction. Note that this group is much larger in actual applications with high enantioselectivities. The computed activation energy is 97 kJ/mol for the transition state **TS 3/6** (see Fig. 1) which leads to the addition product. This barrier height is consistent with the observation of a slow reaction at ambient temperature.

### 2.2. Nucleophilic attack through a coordinated enamine

Although the nucleophilicity of the enamine most likely *decreases* upon coordination to $Cu^{2+}$, this reaction path cannot be excluded from the outset since on the other hand activation of the Michael acceptor upon coordination to the Lewis acidic metal centre has to be expected. Our calculations show that the enamine **3** mainly binds through its carbonyl oxygen atoms to $Cu^{2+}$ while the enamine nitrogen binds, if at all, only loosely. There is also no tendency for the amide nitrogen at the C-terminus of the amino acid to coordinate. A neutral water molecule completes the coordination sphere of the copper ion in our model system **7**. Additional axial ligands have practically no tendency to bind. However, when this complex approaches the Michael acceptor **4**, its oxygen atom starts to orient itself towards the copper centre upon C–C bond formation. The reason is, that in the course of the reaction, this atom changes character from a carbonyl to an enolate oxygen which is much stronger donor ligand. The transition state **TS 7/8** of this step is shown in Fig. 2. The computed activation energy is 94 kJ/mol and thus of the same magnitude as for the background reaction. It seems unlikely that the copper catalyzed Michael reaction proceeds via this route since the experiments show that copper salts considerably accelerate the reaction.

### 2.3. Nucleophilic attack through a coordinated aza-enolate

In the case of the Fe(III) catalyzed Michael addition of β-diketones, the acidity of the latter is increased so much




Scheme 2.

upon coordination to $Fe^{3+}$ that it protonates the surrounding molecules and thus becomes a coordinated enolate. If the Cu(II) catalyzed reaction of the enamine derivative proceeds in an analogous way, this would require a deprotonation at the enamine nitrogen. Our calculations show that upon removal of this proton, the nitrogen atom forms a strong dative bond to the copper centre. As a consequence, the rigidity of the nearly square planar complex **9** is enhanced. We performed the calculations both with a water and with an acetic acid molecule (coordinated through its carbonyl oxygen, see below) occupying the fourth coordination site. These molecules were chosen to mimic any of the weak oxygen donors present in the reaction mixture. Originally it was assumed [10] that the enamine coordinates as a tridentate ligand to the face of an octahedral coordination geometry around the copper centre. According to our calculations, such an intermediate deserves no further consideration. It is not surprising that the deprotonation significantly increases the nucleophilicity of the complex. The activation energies for the C–C bond

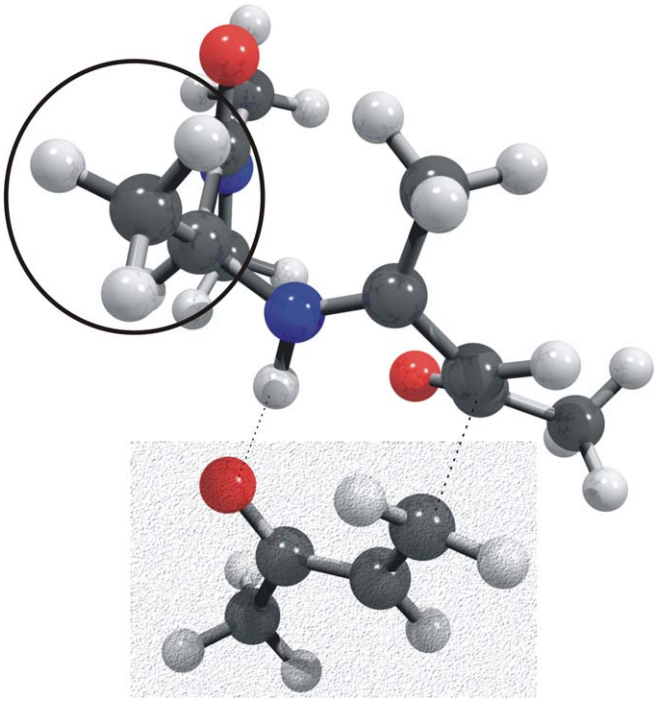


Fig. 1. Transition state **TS 3/6** for C–C bond formation in the metal-free background reaction. Note that proton transfer from N to O occurs simultaneously.

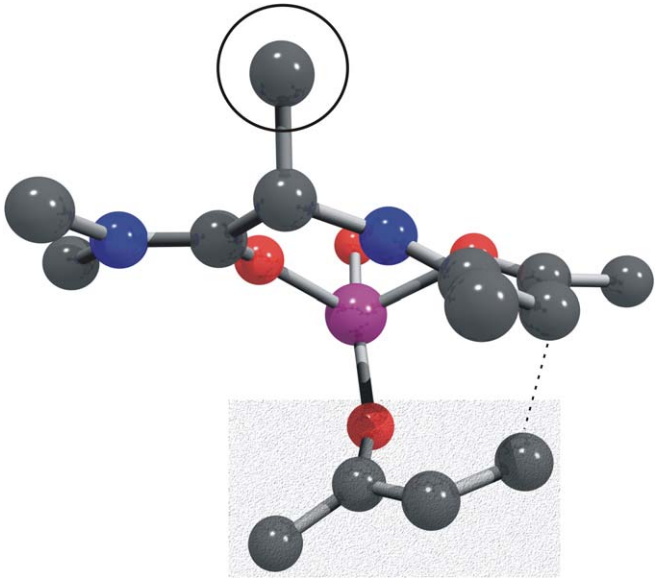


Fig. 2. Transition state **TS 7/8** for C–C bond formation between the coordinated neutral enamine and the Michael acceptor. A water molecule serves as co-ligand.

forming step of the reaction are greatly reduced, from 94 kJ/mol for the coordinated neutral enamine to 77 kJ/mol for a coordinated aza-enolate if water is used as a co-ligand (**9a**). If the water molecule is replaced by acetic acid (**9b**), the activation energy is further reduced a bit (to 70 kJ/mol) but stays in the same ball park. The transition state **TS 9b/10b** for this latter case is shown in Fig. 3. It can be seen that the amino acid side chain (a methyl group in our model system) adopts an angular position with respect to the coordination plane. Although we have not yet calculated the enantiomeric preference for this step, Fig. 3 suggests that an attack of the methyl vinyl ketone **4** from above will require a distortion of the coordination geometry that leads to a higher activation energy. We are currently investigating this for side chains of different size in our laboratory.

While it is not surprising that an aza-enolate is a much better nucleophile than an enamine, the question remains whether coordination to $Cu^{2+}$ increases the acidity of the enamine such that a coordinated aza-enolate exists in sufficient concentration in the reaction mixture. Gas phase calculations show a reduction of the proton affinity from 1538 kJ/mol for the free aza-enolate down to 606 kJ/mol for the square planar complex **9a** in case of a coordinated water molecule which is easily understood by electrostatic arguments. The proton affinity of the surrounding molecules is significantly higher (methyl vinyl ketone **4**: 858 kJ/mol; typical solvent molecules such as acetone: 844 kJ/mol). At first sight, these numbers suggest that a coordinated enamine is acidic enough to loose its proton to the reaction mixture. One should, however, be careful since the comparison of gas-phase proton affinities is not enough to calculate acid/base equilibria in solution. Furthermore, the acidity increase is smaller than in the case of the Fe(III) catalyzed Michael addition of enones, most likely due to the smaller charge of $Cu^{2+}$ compared to $Fe^{3+}$. We therefore also investigated a second possibility for the formation of a coordinated aza-enolate, namely the transfer of a proton to a basic co-ligand such as acetate (Scheme 3). This reaction is exothermic by 58 kJ/mol in the gas phase, and should remain so in solution, because the solvation energies of **11** and **9b** are probably similar. This implies that under these conditions, a coordinated aza-enolate most likely exists in sufficient concentration to become the key intermediate in the Michael reaction. Upon proton

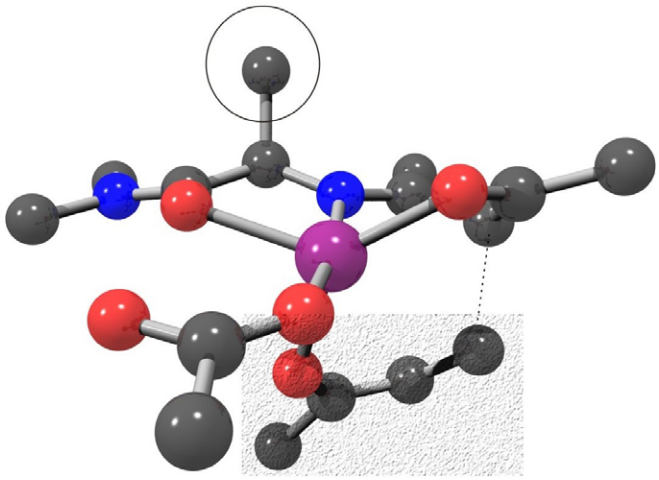
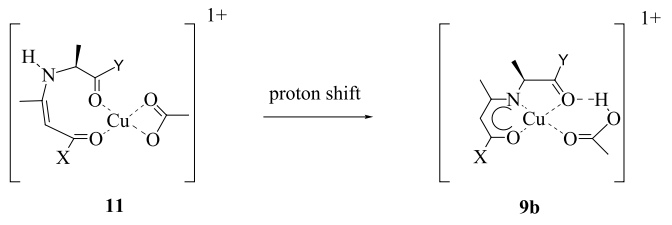


Fig. 3. Transition state **TS 9b/10b** for C–C bond formation between a coordinated aza-enolate and the Michael acceptor. An acetic acid molecule serves as co-ligand.




Scheme 3.

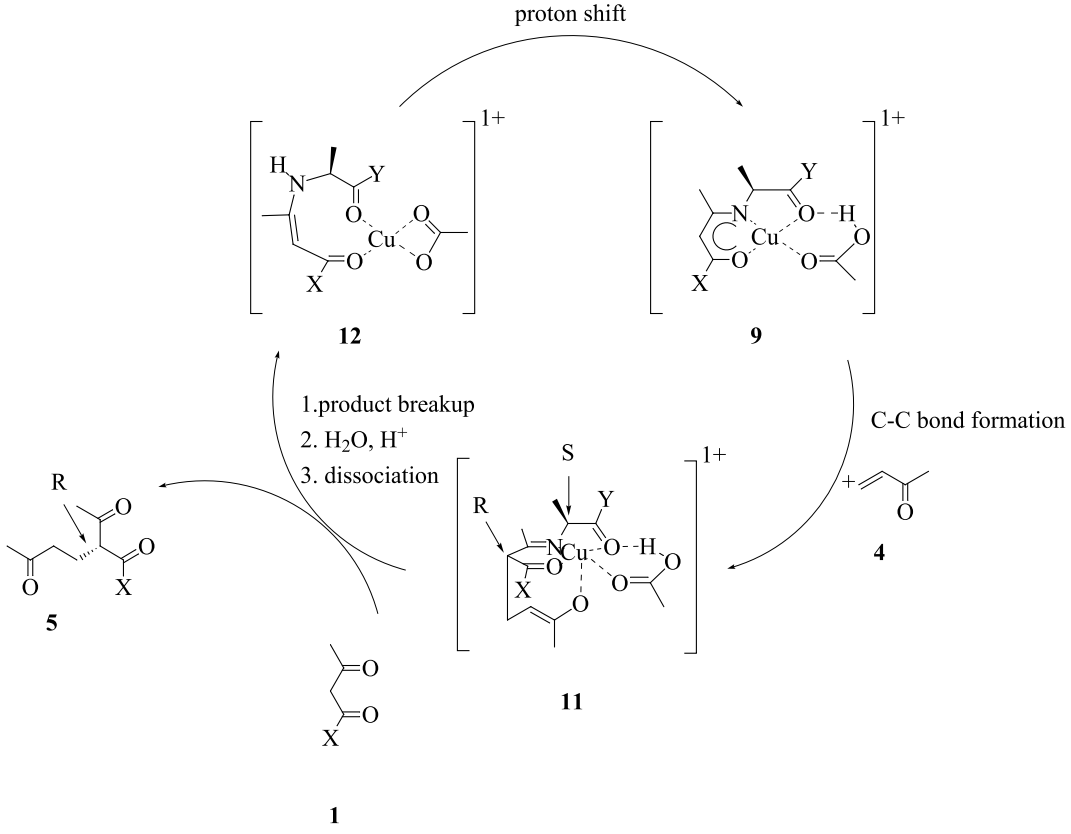
transfer, the bidentate acetate ligand is transformed to (monodentate) acetic acid, the enamine nitrogen taking over the coordination site thus released (Scheme 3). An analogous calculation with a triflate ligand instead of acetate shows a much reduced tendency to transfer a proton (in the gas phase this reaction is still exothermic by 28 kJ/mol). This reduction of course reflects the lower basicity of triflate compared to acetate.

## 3. Conclusion

The computational results strongly suggest that in the metal-free background reaction, the formation of a (formally) zwitterionic structure has to be avoided. While this is easily accomplished in protic solvents by releasing a proton at one side and quasi-simultaneously taking up another one at the other side, aprotic solvents pose a restriction on the accessible reaction channels to allow for a proton transfer concomitant with C–C bond formation. We found an intramolecular pathway to do so which in our view is the most likely scenario at least at low concentrations. Another result is that it is quite unlikely that C–C bond formation starts from a coordinated enamine in the presence of Cu(II). The computed reaction channel will hardly be much faster than the background reaction in marked contrast with experimental observations. Especially if $Cu(OAc)_2$ is used as a catalyst, a proton transfer from the enamine part to the acetate ligand will occur which then opens up a reaction channel with a barrier that is reduced by ~25 kJ/mol. This reaction channel not only supports a reasonably fast reaction at ambient temperature, but most likely also leads to the highest enantioselectivity because of the rigid transition state with the angular amino acid side chain. We therefore summarize our work by proposing the catalytic cycle given in Scheme 4.

## 4. Computational details

Density functional calculations were performed with the GAUSSIAN-03 [22] and TURBOMOLE [23,24] quantum chemical program packages. TZVP basis sets [25] have been used throughout. In all cases the B3LYP exchange correlation functional [26–29] has been used. For the reaction profiles, the minima and transition states were characterised by a harmonic vibrational analysis. The zero point vibrational energy has been added to the electronic energy to obtain reaction and activation enthalpies. The calculated proton




Scheme 4.

affinities have only been obtained as a difference of electronic energies since these are only used to get a rough estimate on relative acidities.

## References


[1] D. Evans, K. Scheidt, J. Johnston, J. Am. Chem. Soc. 123 (2001) 4480.
[2] Y. Hamashima, D. Hotta, M. Sodeoka, J. Am. Chem. Soc. 124 (2002) 11240.
[3] J. Christoffers, Eur. J. Org. Chem. 124 (1998) 1259.
[4] Y. Hamashima, D. Hotta, N. Umebayashi, et al., Adv. Synth. Catal. 347 (2005) 1576.
[5] V. Gallo, D. Giardina-Papa, P. Mastrorilli, et al., J. Organomet. Chem. 690 (2005) 3535.
[6] B. Kreidler, A. Baro, W. Frey, et al., Chem.-Eur. J. 9 (2005) 2660.
[7] B. Kreidler, A. Baro, J. Christoffers, Synlett 3 (2005) 465.
[8] J. Chataigner, C. Gennari, S. Ongeri, U. Piarulli, S. Ceccarelli, Chemistry 7 (2001) 2628.
[9] N. Krause, A. Hoffmann-Röder, Synthesis-Stuttgart 2 (2001) 171.
[10] J. Christoffers, A. Mann, Angew. Chem., Int. Ed. 39 (2000) 2752.
[11] J. Christoffers, A. Mann, Angew. Chem., Int. Ed. 40 (2001) 4591.
[12] J. Christoffers, A. Mann, Angew. Chem., Int. Ed. 112 (2000) 2871.
[13] J. Christoffers, U. Rössler, T. Werner, Eur. J. Org. Chem. (2000) 701.
[14] J. Christoffers, A. Mann, Chem. Eur. J. 7 (2001) 1014.
[15] J. Christoffers, H. Scharl, Eur. J. Org. Chem. (2002) 1505.
[16] J. Christoffers, T. Werner, S. Unger, W. Frey, Eur. J. Org. Chem. (2003) 425.
[17] J. Christoffers, B. Kreidler, H. Oertling, S. Unger, W. Frey, Synlett (2003) 493.
[18] J. Christoffers, B. Kreidler, S. Unger, W. Frey, Eur. J. Org. Chem. (2003) 2845.
[19] J. Comelles, M. Moreno-Manas, E. Perez, J. Org. Chem. 69 (2004) 6834.
[20] A. Alexakis, Pure Appl. Chem. 74 (2002) 37.
[21] S. Pelzer, T. Kauf, C. van Wüllen, J. Christoffers, J. Organomet. Chem. 684 (2003) 308.
[22] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, GAUSSIAN-03, Revision C.02, Gaussian, Inc., Wallingford, CT, 2004.
[23] TURBOMOLE (version 5.7) is a quantum chemical program package distributed by the university of Karlsruhe. The integration grids used in the density functional calculations are described in [24].
[24] R. Ahlrichs, O. Treutler, J. Chem. Phys. 102 (1995) 346.
[25] A. Schäfer, C. Huber, R. Ahlrichs, J. Chem. Phys. 100 (1994) 5829.
[26] A.D. Becke, Phys. Rev. A 38 (1988) 3098.
[27] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785.
[28] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.
[29] P.J. Stephens, F.J. Devlin, C.F. Chabalowski, M.J. Frisch, J. Phys. Chem. 98 (1994) 11623.