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Umpolung catalysis: assessment of catalyst and substrate reactivities in acyloin type reactions

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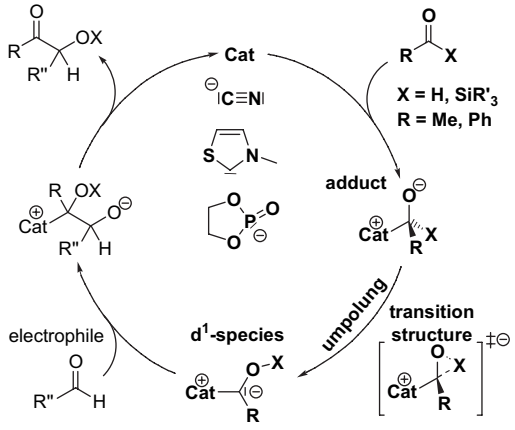
Abstract

The umpolung of aldehydes and acylsilanes in acyloin type reactions is computationally studied by a sequence of model reactions (CPCM-THF B3LYP/6-31G(d)//B3LYP/6-31G(d)) with three different types of catalysts. Cyanide, a nucleophilic carbene and a phosphite form adducts, transition structures for [1,2]-H-shifts or [1,2]-$SiMe_3$-Brook rearrangements and generate the umpoled d^1-species. Aliphatic and aromatic aldehydes and acylsilanes (i.e., acetaldehyde, benzaldehyde, acylsilane, and benzoylsilane) show that π-conjugation slightly favors the umpolung. For aldehydes, the nucleophilic carbene, *N*-methylthiazol-2-ylidene, is by far the most reactive catalyst, while cyanide is slightly superior to the glycole based phosphite. For all catalysts, a dramatic decrease of activation barriers is apparent with the acylsilanes due to [1,2]-$SiMe_3$-Brook rearrangements, thermodynamically formations of d^1-species with strong Si–O bonds become highly favored.

1. Introduction

The cyanide catalyzed benzoin reaction, i.e., the coupling of benzaldehyde to its diphenyl acyloin, was discovered by Wöhler and Liebig.[1] An α-hydroxyl carbanion is the key intermediate of the mechanism, which was first proposed by Lapworth (Scheme 1).[2] Such carbanionic intermediates, emerging from umpolung reactions, are now highly appreciated d^1-synthons from a synthetic point of view.[3] Thiazolium salts were found to catalyze the benzoin reaction as well,[4] and are now known as precursors for nucleophilic carbenes. The in vivo decarboxylation of pyruvic acid with such a thiazol-2-ylidene (vitamin B_1) is mechanistically similar to the benzoin coupling, with CO_2 rather than H^+ as migrating group (Scheme 1).[5] This carbene catalyzed 'Breslow mechanism' is analogous to Lapworth's cyanide mechanism,[5] and expands the scope of the reaction even to enantioselective acyloin type couplings with a much broader range of substrates.[6,7] It was recently found out that metallophosphites catalyze cross-acyloin type couplings of acylsilanes (X=SiR'_3, Scheme 1) with aldehydes.[8]



Scheme 1. Catalytic cycle of acyloin type reactions for the three types of umpolung catalysts and aldehyde (X=H) as well as acylsilane (X=SiR'_3) substrates.

Scheme 1 illustrates the common mechanistic scheme of all three types of umpolung catalysts, i.e., cyanide, carbenes, and phosphites. The cycle starts with the addition of the catalyst to the aldehyde (X=H) or the acylsilane (X=SiR'_3) to build an oxyanion. The migrating group (X) then leaves the carbon atom without binding electrons as an electrofuge and binds to the oxyanion, forming the crucial, carbanionic d^1-species.

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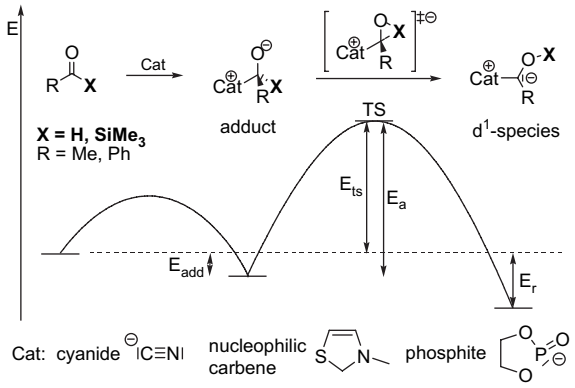
This umpolung is a [1,2]-H-shift with aldehydes (X=H) and a [1,2]-SiR′$_3$-Brook rearrangement[9] with acylsilanes (X=SiR′$_3$). Finally, the d^1-acyl anion equivalent adds to a carbonyl (or Michael) electrophile and the subsequent elimination of the catalyst leads to acyloin (or Stetter) products (Scheme 1).

Due to the high synthetic potential of these umpolung couplings, a better understanding of catalyst and substrate reactivities is necessary. Previous computational assessments[10] point to a large kinetic and thermodynamic preference for the umpolung step with carbenes compared to cyanide and phosphite catalysts.

How do the structures of substrates and catalysts affect the crucial umpolung step? We here describe kinetic and thermodynamic effects of catalyst variations as well as of substrate modifications (e.g., exchange of X=H vs SiMe$_3$) from catalyst additions to the crucial umpolung step during the formation of the central d^1-intermediate.

2. Results and discussion

Thermodynamic and kinetic effects during the formation of d^1-species[11] from carbonyl substrates in acyloin type reactions (Scheme 1) are computationally assessed by analyzing activation (E_a) and reaction energies (E_r, Scheme 2). *N*-methylthiazole-2-ylidene serves as an exemplary nucleophilic carbene catalyst. Cyanide and the glycole based phosphite catalysts are treated without counterions to estimate intrinsic effects only. Acetaldehyde, acylsilane, benzaldehyde, and benzoylsilane are chosen as aromatic and aliphatic substrates. Solvent polarity is modeled by THF-CPCM computations.



Scheme 2. Activation (E_a) and reaction energies (E_r) in acyloin type reactions (cf. Scheme 1).

Additions of cyanide and phosphite catalysts to acetaldehyde form destabilized adducts, relative to the isolated reactants (E_{add}=+3.7 and +7.0 kcal mol^{-1}), while the carbene adduct is stable (E_{add}=−1.3 kcal mol^{-1}, Table 1, Fig. 1). The activation barriers for the umpolung step of acetaldehyde are quite similar for cyanide and the phosphite (E_a=+51.6 and +53.4 kcal mol^{-1}), but E_a is significantly lower for the carbene (39.4 kcal mol^{-1}, Table 1, Figs. 1–4). The formation of the d^1-species is only exothermic for the carbene catalyst, yielding a neutral, electron rich alkene (E_r=−5.4 kcal mol^{-1}, Table 1, Fig. 1).

Table 1
Umpolung with different substrates and catalysts according to Scheme 2[a]

Substrate	Catalyst	E_{add}	E_a	E_{ts}	E_r
Acetaldehyde	Cyanide	3.7	51.6	55.3	25.4
	Carbene	−1.3	39.4	38.1	−5.4
	Phosphite	7.0	53.4	60.4	29.8
Acylsilane	Cyanide	4.9	2.8	7.7	−0.9
	Carbene	−0.4	1.7	1.3	−32.6
	Phosphite	10.1	6.1	16.2	3.4
Benzaldehyde	Cyanide	5.8	45.3	51.1	12.3
	Carbene	1.4 (−5.9)[b]	38.8	40.2	−5.0
	Phosphite	9.0	49.5	58.5	19.7
Benzoylsilane	Cyanide	3.0	1.3	4.3	−17.7
	Carbene	1.9	1.0	2.9	−35.4
	Phosphite	10.2	2.5	12.7	−8.2

[a] THF-CPCM-B3LYP/6-31G(d)//B3LYP/6-31G(d) with ZPE correction, scaled by 0.9806.
[b] Oxirane formation.

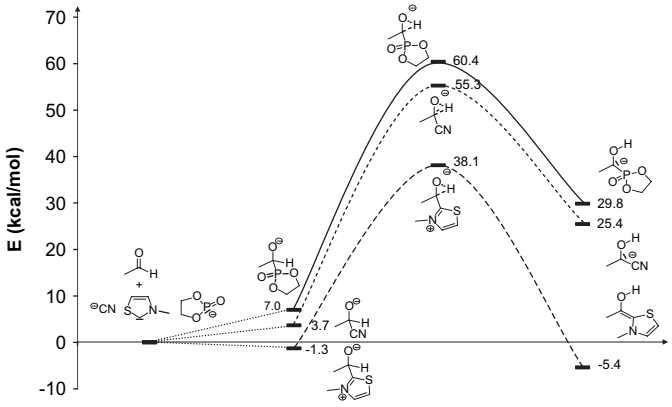


Figure 1. Umpolung of acetaldehyde with [1,2]-H-shift (THF solvent, CPCM-B3LYP/6-31G(d)//B3LYP/6-31G(d), relative electronic energies referring to isolated reactants).

Additions to the acylsilane substrate are less favored for all catalysts, relative to acetaldehyde, due to its lower carbonyl electrophilicity (Table 1, Fig. 5). However, the barriers for the umpolung step (i.e., the [1,2]-SiR′$_3$-Brook rearrangement) are extremely reduced for all catalysts with SiMe$_3$ as the migrating group (X) compared to acetaldehyde (X=H), due to the formation of strong Si–O bonds (Table 1, Fig. 5). These activation barriers (E_a) are as low as 2.8 and 1.7 kcal mol^{-1} for cyanide and the carbene, while it is slightly higher for the phosphite (E_a=6.1 kcal mol^{-1}, Table 1, Figs. 5–8).

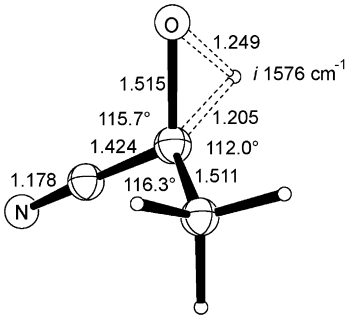


Figure 2. Transition structure of the cyanide-induced umpolung of acetaldehyde (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

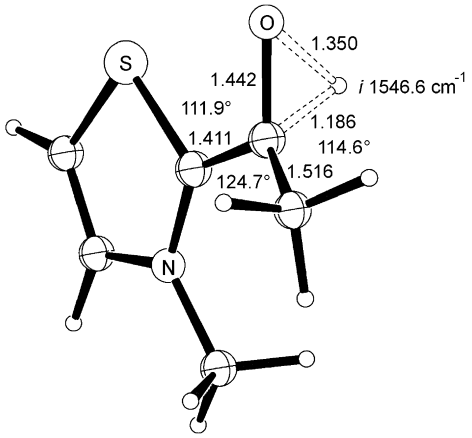


Figure 3. Transition structure of the carbene-induced umpolung of acetaldehyde (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

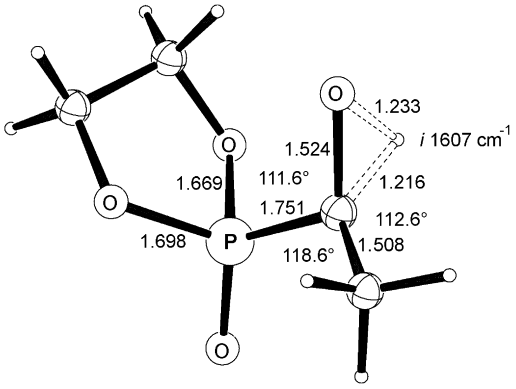


Figure 4. Transition structure of the phosphite-induced umpolung of acetaldehyde (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

Likewise, the silylated d^1-species are strongly favored versus the umpoled aldehyde, especially for the carbene (E_r=−32.6 kcal mol^{-1}), but also for cyanide and phosphite (E_r=−0.9 and +3.4 kcal mol^{-1}, Table 1, Fig. 5). The neutral silyloxy alkene makes the carbene umpolung strongly exothermic, while less stable d^1-carbanions are formed with cyanide and phosphite (Fig. 5).

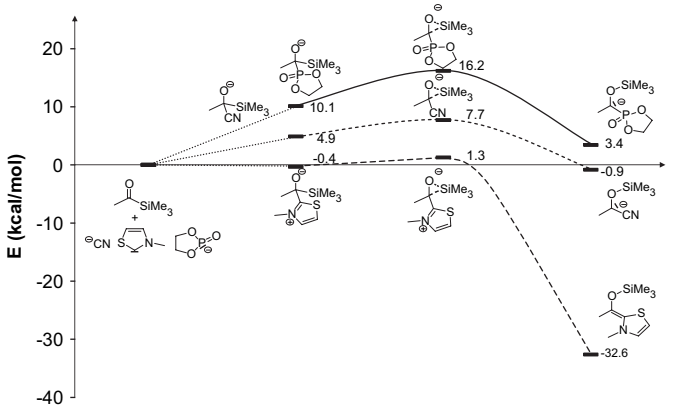


Figure 5. Umpolung of acylsilane with [1,2]-$SiMe_3$-Brook rearrangement (THF solvent, CPCM-B3LYP/6-31G(d)//B3LYP/6-31G(d), relative electronic energies referring to isolated reactants).

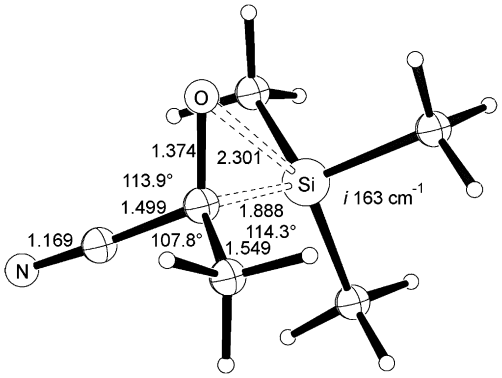


Figure 6. Transition structure of the cyanide-induced umpolung of acylsilane (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

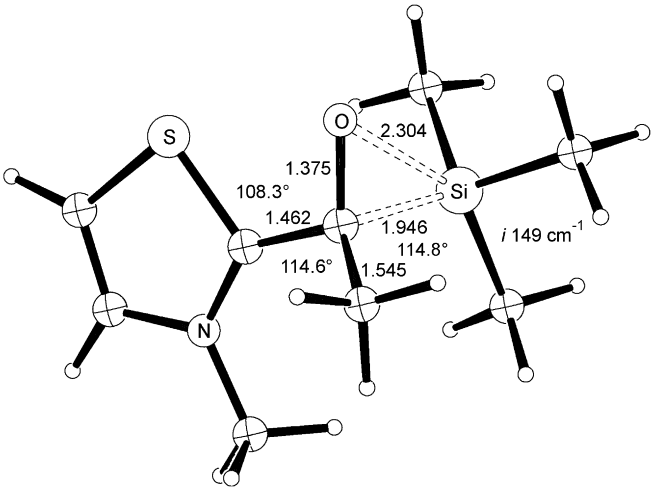


Figure 7. Transition structure of the carbene-induced umpolung of acylsilane (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

Similar to acetaldehyde, benzaldehyde as substrate gives unstable adducts (Table 1, Fig. 9). A more stable oxirane (−5.9 kcal mol^{-1}) can cyclize from the open carbene adduct (E_{add}=+1.4 kcal mol^{-1}). π-Conjugation stabilizes the transition structures of benzaldehyde with all catalysts relative to acetaldehyde, and therefore supports especially the weaker

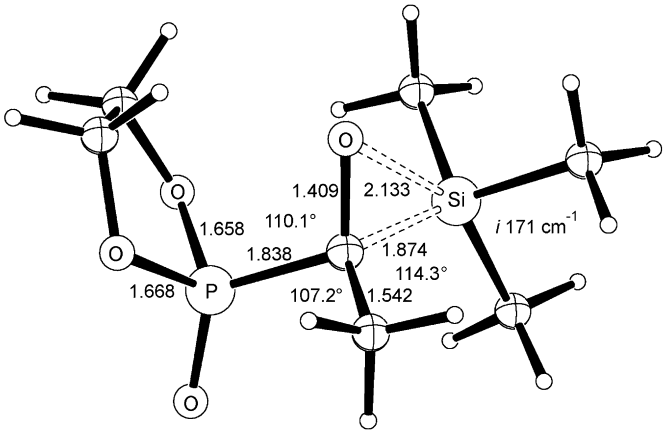


Figure 8. Transition structure of the phosphite-induced umpolung of acylsilane (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

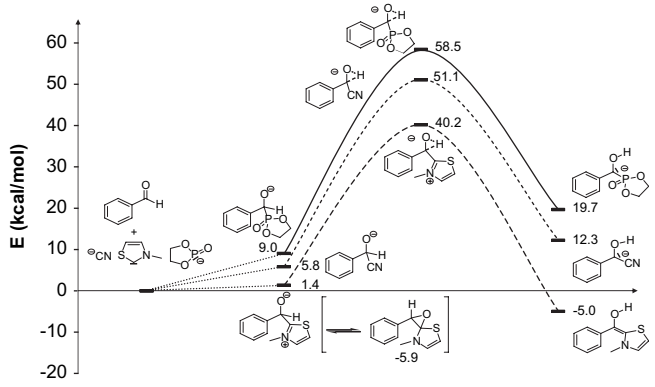


Figure 9. Umpolung of benzaldehyde with [1,2]-H-shift (THF solvent, CPCM-3LYP/6-31G(d)//B3LYP/6-31G(d), relative electronic energies referring to isolated reactants).

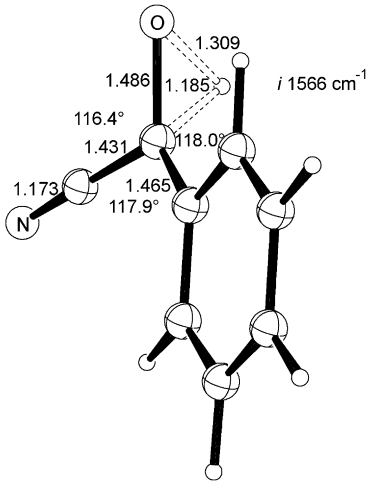


Figure 10. Transition structure of the cyanide-induced umpolung of benzaldehyde (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

cyanide- and phosphite-catalysis (E_a=+45.3[12] and +49.5 kcal mol^{-1}, Table 1, Figs. 9–12). This π-stabilization also leads to less destabilized d^1-species with cyanide ('benzoin-coupling')[1] and phosphite (E_r=+12.3 and

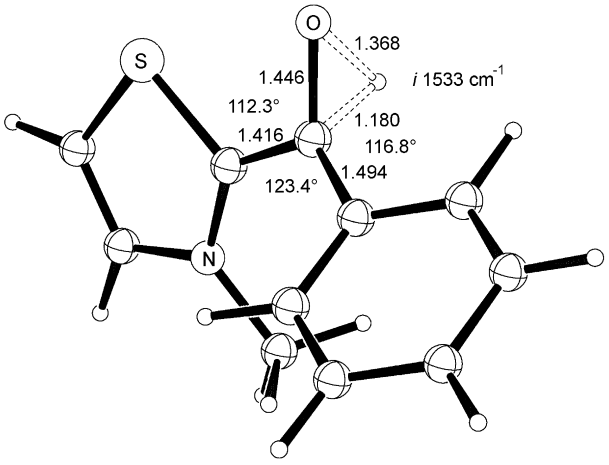


Figure 11. Transition structure of the carbene-induced umpolung of benzaldehyde (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

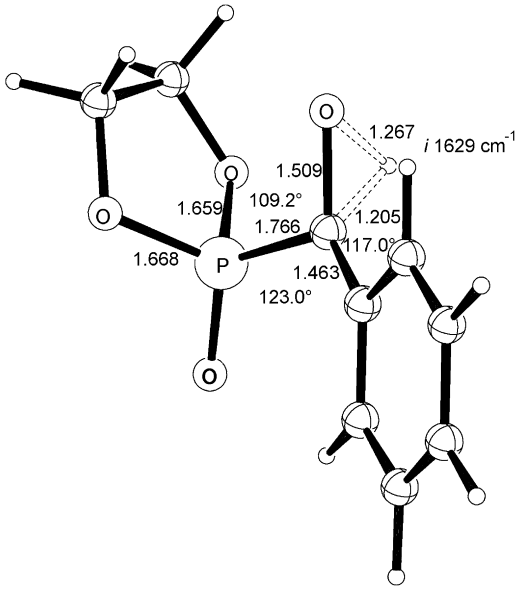


Figure 12. Transition structure of the phosphite-induced umpolung of benzaldehyde (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

+19.7 kcal mol^{-1}, Table 1, Fig. 9), while the difference to R=Me is only small for the carbene with R=Ph (E_r=−5.0 kcal mol^{-1}, Table 1, Fig. 9).

Benzoylsilane as substrate gives unstable adducts for all catalysts, again the carbene is most favored (E_{add}=+1.9 kcal mol^{-1}, Table 1, Fig. 13). Relative to benzaldehyde, a dramatic decrease of the barriers for the umpolung step, i.e., the [1,2]-SiR′$_3$-Brook rearrangement, is apparent for all catalysts (Table 1, Figs. 13–16), with the highest reactivity for cyanide. The strong Si–O bond also favors formation of the d^1-species (Table 1, Fig. 13).

The activation barriers (E_a) of the catalysts correlate for umpolung steps of aldehyde substrates well with the positions of the transition structures on the reaction coordinates (measured as C–X/O–X values, Fig. 17): the lower the activation barriers, the earlier are the transition structures on the reaction coordinate. With benzaldehyde, cyanide appears to be a very suitable catalyst for 'benzoin couplings',[1] following

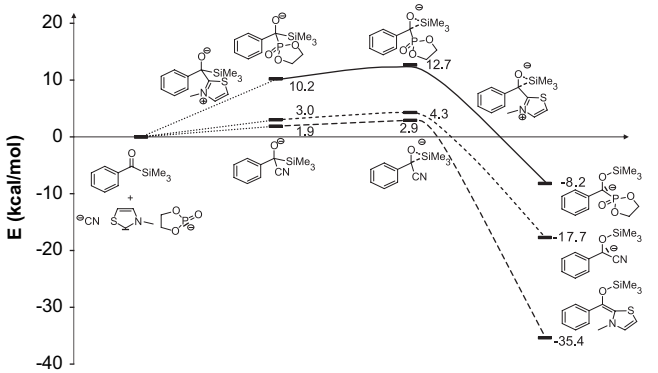


Figure 13. Umpolung of benzoylsilane with [1,2]-SiMe$_3$-Brook rearrangement (THF solvent, CPCM-B3LYP/6-31G(d)//B3LYP/6-31G(d), relative electronic energies referring to isolated reactants).

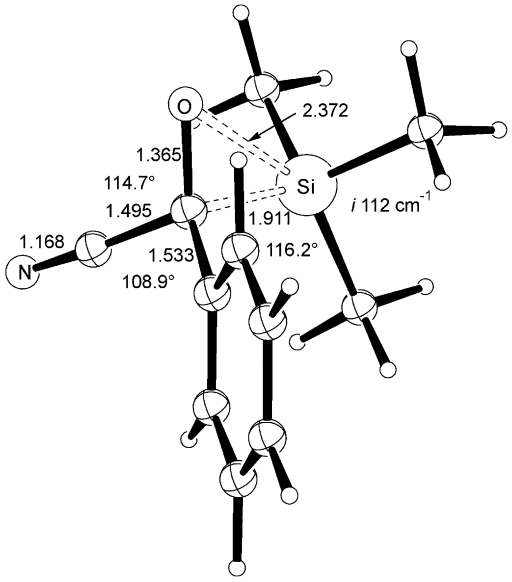


Figure 14. Transition structure of the cyanide-induced umpolung of benzoylsilane (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

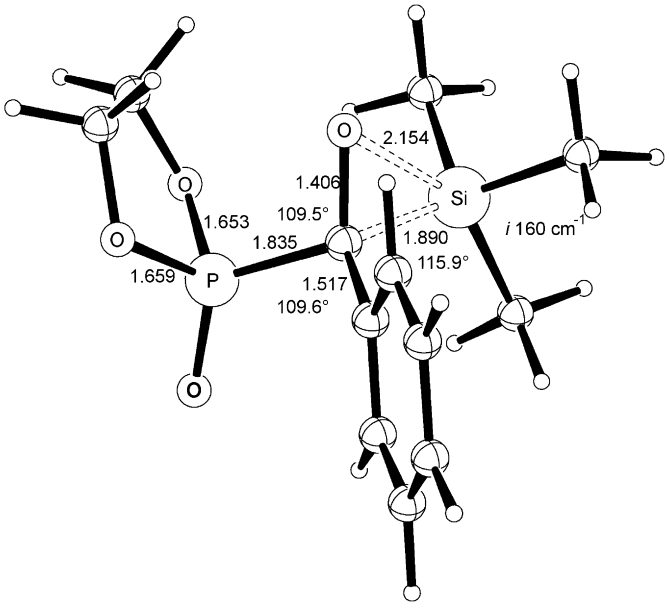


Figure 16. Transition structure of the phosphite-induced umpolung of benzoylsilane (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

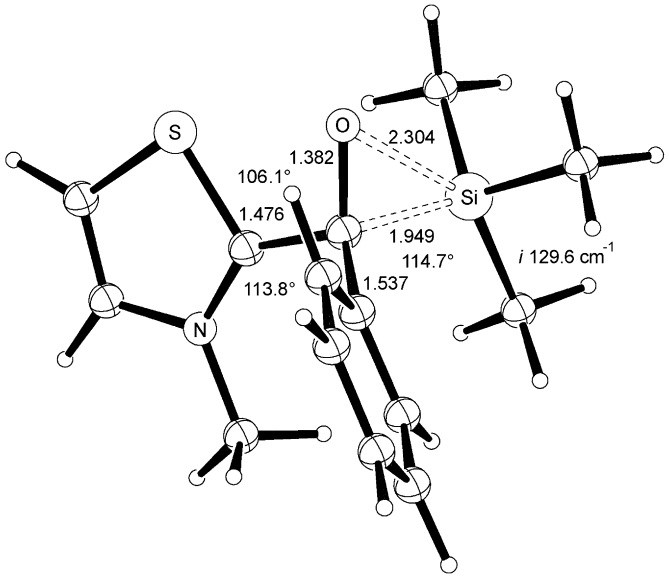


Figure 15. Transition structure of the carbene-induced umpolung of benzoylsilane (cf. Scheme 2, B3LYP/6-31G(d), bond distances in Å).

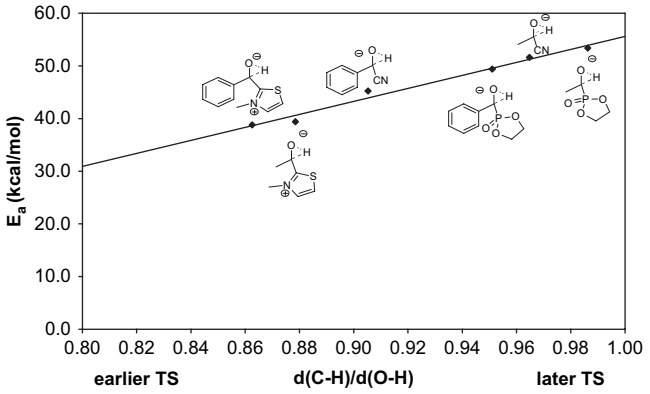


Figure 17. Activation energies vs positions of the transition structures on the reaction coordinates (quotient d(C−H)/d(O−H), y=123.4 x−67.8, cc=0.98) for aldehydes.

immediately the highly reactive carbene (Fig. 17). With acylsilanes only a rough correlation between E_a and the position on the reaction coordinate is apparent (Fig. 18), the strong reduction of activation barriers supported by Si−O formation is dominating for all types of catalysts.

3. Conclusion

Computational assessments of thermodynamic and kinetic characteristics for umpolung steps of aldehyde substrates show that the nucleophilic carbene is by far the strongest umpolungs' catalyst for the formation of the d^1-species, while cyanide is slightly superior to the phosphite.

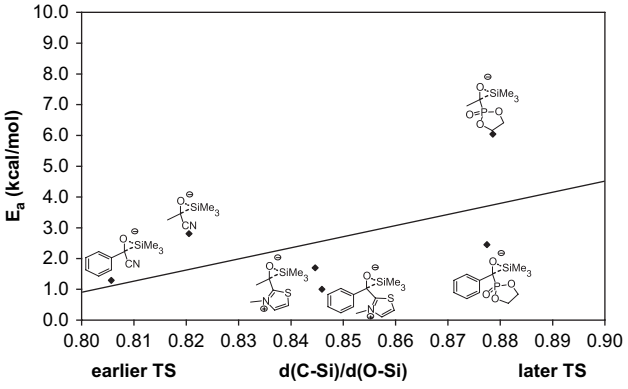


Figure 18. Activation energies vs positions of the transition structures on the reaction coordinates (quotient d(C−SiMe$_3$)/d(O−SiMe$_3$), y=36.1 x−28.0, cc=0.3) for acylsilanes.

The [1,2]-SiR′$_3$-Brook rearrangement in the umpolung of acylsilanes dramatically reduces activation barriers for all types of catalysts and also strongly favors thermodynamically the formation of d^1-species due to strong Si–O bonds. Hence, the intrinsically weak phosphite catalysts, which are, however, easily accessible and enantiopure from chiral diols, can become suitable catalysts for umpolung reactions of a wide range of acylsilane substrates. After umpolung, the next step in the catalytic cycle will be the addition of the d^1-intermediate to the electrophile. Subsequent studies will show if a higher nucleophilic reactivity of the phosphite d^1-species could overcompensate their lower umpolung reactivity relative to carbene catalysts in this C–C coupling.

4. Computational details

The computations were carried out with Gaussian03.[13] B3LYP/6-31G(d) optimizations were performed in the gas phase[11,14] and all stationary points were characterized by frequency calculation. Solvent effects (THF, ε=7.58) were considered by single point CPCM-SCRF calculations.[15] Zero point energies were scaled by 0.9806.[16]

Acknowledgements

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References and notes

1. (a) Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249; (b) Kluger, R. *Pure Appl. Chem.* **1997**, *69*, 1957.
2. Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.
3. (a) Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239; (b) *Umpoled Synthons*; Ager, D. J., Ed.; Wiley: New York, NY, 1987.
4. Ukai, T.; Tanaka, R.; Dokawa, T. A. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296; *Chem. Abstr.* **1951**, *45*, 5148.
5. (a) Dugas, H. *Bioorganic Chemistry*; Springer: Heidelberg, 1989; p 563; (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
6. Carbenes in acyloin type couplings: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534; (b) Burstein, C.; Glorius, F. *Angew. Chem.* **2004**, *116*, 6331; *Angew. Chem., Int. Ed.* **2004**, *43*, 6205; (c) Doudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 5770; (d) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem.* **2006**, *118*, 1491; (e) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: 2005; p 227; (f) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem.* **2006**, *118*, 3572; (g) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418; (h) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431; (i) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem.* **2007**, *119*, 3046; (j) Enders, D.; Balensiefer, T.; Niemeier, O. *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; p 331.
7. Carbenes in Stetter couplings: (a) Stetter, H.; Schreckenberg, M. *Angew. Chem.* **1973**, *85*, 89; *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81; (b) Stetter, H. *Angew. Chem.* **1976**, *88*, 695; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639; (c) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407; (d) Christmann, M. *Angew. Chem.* **2005**, *117*, 2688; *Angew. Chem., Int. Ed.* **2005**, *44*, 2632; (e) Enders, D.; Balensiefer, T.; Niemeier, O. *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; p 338.
8. Metallophosphites in acyloin type couplings: (a) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070; (b) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem.* **2005**, *117*, 2429; *Angew. Chem., Int. Ed.* **2005**, *44*, 2377; (c) Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751.
9. (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886; (b) Brook, A. G.; Warner, C. M.; McGriksin, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 981; (c) Brook, A. G.; Schwartz, N. V. *J. Am. Chem. Soc.* **1960**, *82*, 2435; (d) Brook, A. G.; Iachia, B. *J. Am. Chem. Soc.* **1961**, *83*, 827.
10. Goldfuss, B.; Schumacher, M. *J. Mol. Model* **2005**, *12*, 591.
11. (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724; (b) Rassolov, V. A.; Ratner, M. A.; Pople, J. A.; Redfern, P. C.; Curtiss, L. A. *J. Comput. Chem.* **2001**, *22*, 976.
12. Experimentally, the reaction is normally carried out under reflux conditions in 60% ethanol: Becker, H. G.; Berger, W.; Domschke, G.; Fanghänel, E.; Faust, J.; Fischer, M.; Gentz, F.; Gewald, K.; Gluch, R.; Mayer, R.; Müller, K.; Pavel, D.; Schmidt, H.; Schollberg, K.; Schwetlick, K.; Seiler, E.; Zeppenfeld, G. *Organikum*; Wiley-VCH: 1999; p 499.
13. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
14. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; Implementation: (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623; (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785; (d) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.
15. (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995; (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *6*, 669.
16. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.