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HSAB matching and mismatching in selective catalysis and synthesis

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Contents

1. Introduction

Pearson’s hard-soft acid–base (HSAB) principle, introduced in 1963,[1,2] has become one of the central constructs of modern chemistry. It has been so widely used because its bold Lewis acid/base statement that ‘soft likes soft; hard likes hard’ is easily understood, straightforwardly applied, and this idea rationalises a range of otherwise very disparate facts. The HSAB principle was first applied to selective organic synthesis in 1967[3] and progress in this area is the subject of five reviews. Ho summarised the application of HSAB ideas to organic chemistry in a book (1977)[4] and two reviews [1985 (*Tetrahedron Report* 177)[5] and 1975[6]]. Two German-language overviews discuss HSAB applications in homogeneous catalysis (1985),[7] but here the emphasis is on transition metal co-ordination chemistry. The aim of this review is to provide an up-to-date perspective of recent HSAB applications in organic synthesis concentrating on catalytic reactions (but also considering selective stoichiometric reactions when it is useful to do so). The material selected covers mainly the period 1985–2001 with an emphasis on reactions promoted by main group Lewis acids. Some earlier references have been included where no good summary articles exist. This review is intended to be an encyclopaedic and self-contained primary reference; hence some relatively basic material is included to keep all the key information ‘readily to hand’. Generally, the *soft* or *hard* functions in the catalytic/synthetic intermediates presented are easily identified, however, in some cases the symbols ⓢ ⓗ (introduced by Ho[4]) have been used to avoid ambiguity or to indicate the relative *hardness*/*softness* within transition states/intermediates.

Keywords: HSAB principle; stoichiometric reaction; enthalpy.

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Nomenclature

BDE	Mean Bond Dissociation Enthalpy ($\bar{D}$) [the enthalpy, under standard conditions (298 K, 1 atm), required to cause the homolytic cleavage of the average E–Y bond in EY_n. Calculated by $\bar{D}=\{\Delta H_f^o(E,g)+n\Delta H_f^o(L\cdot,g)-\Delta H_f^o(EY_n,g)\}/n$].
BEC	Bond Enthalpy Contribution ($\bar{E}$) [the enthalpy, under standard conditions (298 K, 1 atm), required to cause the homolytic cleavage of the average E–Y bond in EX_nY_m. Derived by apportioning the total atomisation enthalpy between all bonds present in EX_nY_m due to an agreed, but arbitrary set of distribution rules (see Ref. 9)].
$f(r)$	Fukui function. The first derivative of the electron density at r with respect to the number of electrons at constant temperature and external potential.[21,22,24,25]
PMH	Principal of Maximum Hardness. At constant external potential, the system with the maximum global hardness (η) is the most stable.[2c,25]
s	Local softness. The product of the global softness and the Fukui function. Intramolecular bonding interaction is favoured between sites of similar local softness.[22,24,25]
η and S	Global hardness (η). The second derivative of the system's electronic energy with respect to the number of electrons at constant temperature and external potential. It measures the resistance of the system towards charge transfer. Global softness $S=1/\eta$.[23–25]

2. Enthalpic approaches to the HSAB concept and its limitations

It is important to remember that, although the HSAB principle allows for *favourable moderation* of the enthalpy of interaction of a Lewis acid (LA) and ligand (L) when these constitute a matched hard–hard or soft–soft pair, it is not universally applicable. There exist many cases of strong bonds between mismatched LA–L pairs, of which H_2 (from H^+_{hard} and H^-_{soft}), is the archetypal example. Pearson has summarised the common misinterpretations of the HSAB principle.[2a] The very generality of the principle can, if one is not careful, lead to over interpretation: post-observational rationalisation rather than predictive power becomes the order of the day! In this review we concentrate on reactions of the hard/soft fragments shown in Table 1 from the basis of bond enthalpy values (Table 2 and Scheme 1). While the HSAB principle refers to heterolytic bond cleavages ($LA–L\rightarrow LA^++L^-$), homolytic bond cleavage energies (BDEs) can be used to make useful empirical comparisons.[2d] Tables of hard/soft character are widely available,[1–7] but thermochemical data are under-represented for catalytic/organometallic intermediates. Notwithstanding this, enthalpic approaches to HSAB matching can be very helpful in identifying viable, and novel, reactions. The bond enthalpy values ($\bar{D}$ and $\bar{E}$) in Table 2 have been taken from genuine Lewis acid reagents wherever possible. This is important as *nominal* average

Table 1. Selected hard and soft Lewis acid and base fragments used in selective synthesis. The Lewis acid and base centres are shown in bold italics

Lewis acids	Lewis bases
Hard Lewis acids	*Hard Lewis bases*
$\boldsymbol{H}^+$	$\boldsymbol{F}^-$, $\boldsymbol{O}^{2-}$, $RC\boldsymbol{O}_2^-$ $Tf\boldsymbol{O}^-$
$R\boldsymbol{C}O^+$, $R\boldsymbol{S}O_2^+$	$P\boldsymbol{O}_4^{2-}$, $S\boldsymbol{O}_4^{2-}$, $C\boldsymbol{O}_3^-$
$\boldsymbol{Li}^+$, $\boldsymbol{Na}^+$	$H\boldsymbol{O}^-$, $R\boldsymbol{O}^-$, $R_2\boldsymbol{N}^-$
$R\boldsymbol{Mg}X$, $R\boldsymbol{Mg}^+$, $X\boldsymbol{Mg}^+$ (X=Cl, Br)	$H_2\boldsymbol{O}$, $R_2\boldsymbol{O}$, $R(H)C{=}\boldsymbol{O}$, $R_2C{=}\boldsymbol{O}$
$\boldsymbol{La}^{3+}$, $\boldsymbol{Sc}^{3+}$, $\boldsymbol{Yb}^{3+}$	$\boldsymbol{N}H_3$, $H_2\boldsymbol{N}NH_2$, $R\boldsymbol{N}H_2$
$\boldsymbol{B}X_3$ (X=F, Cl), $\boldsymbol{B}(OR)_3$	
$\boldsymbol{Al}H_3$, $\boldsymbol{Al}R_3$, $\boldsymbol{Al}X_3$ (X=Cl, Br), $\boldsymbol{Al}(OR)_3$	
$R_3\boldsymbol{Si}^+$, $\boldsymbol{Si}Cl_4$	
$R_3\boldsymbol{Sn}^+$, $Cl_3\boldsymbol{Ti}^+$, $\boldsymbol{Ti}Cl_4$, $\boldsymbol{Ti}(OR)_4$	
Borderline Lewis acids	*Borderline Lewis bases*
$\boldsymbol{R}^+$ [softer $CH_3^+>RCH_2^+>R_2CH^+>R_3C^+>$vinyl$^+\sim$Ph$^+\sim RC{\equiv}C^+$ harder]	$\boldsymbol{Cl}^-$, $\boldsymbol{Br}^-$, $Al\boldsymbol{H}_4^-$
$\boldsymbol{Sc}X_3$, $\boldsymbol{Yb}X_3$ (X=Cl, OTf)[a]	$R_3\boldsymbol{N}$, $C_5H_5\boldsymbol{N}$
$R\boldsymbol{Zn}^+$, $X\boldsymbol{Zn}^+$	$R(H)C{=}\boldsymbol{N}R$, $R_2C{=}\boldsymbol{N}R$
$\boldsymbol{B}R_3$, $\boldsymbol{Ga}(OR)_3$	
$\boldsymbol{Sn}(OR)_4$,[a] $\boldsymbol{Sn}X_4$ (X=Cl, Br)[a]	
$L_n\boldsymbol{Rh}^{III}$, $L_n\boldsymbol{Ir}^{III}$	
$R(H)\boldsymbol{C}{=}O$[a] $R_2\boldsymbol{C}{=}O$[a]	
$R(H)\boldsymbol{C}{=}NR$[a] $R_2\boldsymbol{C}{=}NR$[a]	
Soft Lewis acids	*Soft Lewis bases*
$R\boldsymbol{M}^+$, $X\boldsymbol{M}^+$ (M=Cd, Hg), $\boldsymbol{M}^+$ (M=Cu, Ag, Hg)	$\boldsymbol{H}^-$, $\boldsymbol{I}^-$, $B\boldsymbol{H}_4^-$
$\boldsymbol{B}H_3$, $\boldsymbol{Ga}(SR)_3$, $\boldsymbol{Sn}(SR)_4$	$\boldsymbol{R}^-$ [softer $RC{\equiv}C^->$vinyl$^->(R_{sp^3})^-$ harder]
$(Ar_3P)_2\boldsymbol{Pd}^o$, $(Ar_3P)_2\boldsymbol{Pd}^{2+}$	$\boldsymbol{C}N^-$, $R\boldsymbol{S}^-$, $R\boldsymbol{Se}^-$
RO^+, RS^+	$R_2\boldsymbol{C}{=}\boldsymbol{C}R_2$, $R\boldsymbol{C}{\equiv}\boldsymbol{C}R$
	$\boldsymbol{C}O$, $RN\boldsymbol{C}$, $\boldsymbol{P}R_3$, $\boldsymbol{C}(NR_2)_2$ [carbene ligands]

For additional listings see Refs. 1–7.

[a] Some listings give these compounds as hard acceptors but their reactivity is more in line with borderline behaviour.

Table 2. Selected standard bond enthalpies (298 K, 1 atm) for organoelement species containing E–E, E–H, E–C, E–O, E–S and E–F bonds/kJ mol^{-1} (kcal mol^{-1})

Element (E)	E	H	C	O	S	F
Group 1						
Li	–	237 (**57**)[a]	Alkyl 267 (**64**)[b]	470 (**112**)[c*]	270 (**65**)[d*]	579 (**138**)[e]
Group 2						
Mg	–	209 (**50**)[f]	Alkyl 253 (**60**)[g], allyl 201 (**48**)[g], vinyl 287 (**69**)[g], aryl 289 (**69**)[g]	471 (**113**)[h*]	210 (**50**)[i*]	516 (**123**)[j]
Lanthanoids						
La	–	285 (**68**)[k]	272 (**65**)[l]	389 (**92**)[m]	254 (**61**)[n]	624 (**149**)[o]
Group 4						
Ti	–	232 (**56**)[p]	Alkyl 255 (**61**)[q]	447 (**107**)[r]	331 (**79**)[s]	585 (**140**)[t]
Group 12						
Zn	–	199 (**48**)[u]	Alkyl 285 (**68**)[v*]	381 (**91**)[w*]	190 (**38**)[x*]	408 (**97**)[y]
Cd	–	199 (**48**)[z]	Alkyl 251 (**60**)[v*]	140 (**33**)[aa*]	136 (**33**)[ab*]	339 (**81**)[ac]
Hg	–	150 (**36**)[ad]	Alkyl 255 (**61**)[v]	220 (**53**)[ae*]	213 (**51**)[af*]	257 (**61**)[ag]
Group 13						
B	373 (**89**)[ah*]	443 (**88**)[ai]	Alkyl 374 (**89**)[aj], aryl 468 (**112**)[ak]	519 (**124**)[al]	357 (**85**)[am]	644 (**154**)[an]
Al	–	282 (**63**)[ao]	Alkyl 283 (**68**)[ap]	418 (**101**)[aq*]	273 (**65**)[ar*]	592 (**142**)[as]
Ga	–	263 (**63**)[at]	Alkyl 264 (**63**)[au]	226 (**54**)[av*]	226 (**54**)[aw*]	452 (**108**)[ax]
In	–	234 (**56**)[ay]	Alkyl 205 (**49**)[az]	211 (**50**)[ba*]	222 (**53**)[bb*]	406 (**97**)[bc]
Group 14						
Si	337 (**81**)[bd]	378 (**90**)[be]	Alkyl 320 (**77**)[bf], aryl 352 (**84**)[bg]	419 (**100**)[bh]	213 (**51**)[bi*]	595 (**142**)[bj]
Sn	318 (**76**)[bk]	308 (**74**)[bl]	Allyl 224 (**54**)[bm], alkyl 262 (**63**)[bn], aryl 257 (**61**)[bo]	203 (**49**)[bp*]	200 (**48**)[bq*]	325 (**78**)[br*]

[a] $\bar{D}$(*Li–H*), Ref. 10.

[b] $\bar{D}$(*Li–Bu^n*), using data in Ref. 11 and ΔH_f^o (g, 298 K, ·Bu^n)= −25.1 kJ mol^{-1}.

[c] B3LYP/6-31G* calculated $\bar{D}$(*Li–OMe*), Ref. 12; heterolytic $\bar{D}$(*Li–OMe*) is considerably higher 769 (**184**), Ref. 13.

[d] Gaussian-2 calculated $\bar{D}$(*Li–SMe*), Ref. 14.

[e] $\bar{D}$(*Li–F*), Ref. 10.

[f] B3LYP/6-31G* calculated $\bar{D}$(H*Mg–H*), Ref. 12.

[g] $\bar{D}$(Br*Mg–R*) R=Me, CH=CH$_2$, CH$_2$CH=CH$_2$, Ph, Ref. 15.

[h] B3LYP/6-31G* calculated $\bar{D}$(MeO*Mg–OMe*), Ref. 12.

[i] B3LYP/6-31G* calculated $\bar{D}$(MeS*Mg–SMe*), Ref. 12.

[j] $\bar{D}$(F*Mg–F*), Ref. 10.

[k] HF-triple-ζ-STO calculated $\bar{E}$(Cp$_2$*La–H*), Ref. 16.

[l] HF-triple-ζ-STO calculated $\bar{E}$(Cp$_2$*La–Me*), Ref. 16.

[m] B3LYP/LANL2DZ calculated $\bar{D}$([MeO]$_2$*La–OMe*), Ref. 12.

[n] B3LYP/LANL2DZ calculated $\bar{D}$([MeS]$_2$*La–SMe*), Ref. 12.

[o] $\bar{D}$(F$_2$*La–F*), Ref. 17.

[p] B3LYP/SRLC calculated $\bar{D}$(H$_3$*Ti–H*), Ref. 12.

[q] $\bar{E}$(Cp$_2$Me*Ti–Me*), Ref. 11.

[r] $\bar{D}$([Pr^{i}O]$_3$*Ti–OPr^i*), Ref. 18.

[s] $\bar{E}$[Cp$_2$(SPr)*Ti–SPr*], Ref. 19.

[t] B3LYP/6-31G* calculated $\bar{D}$(F$_3$*Ti–F*), Ref. 20.

[u] B3LYP/SRLC calculated $\bar{D}$(H*Zn–H*), Ref. 12.

[v] $\bar{D}$(Me*E–Me*), Ref. 8a; $\bar{D}$ values significantly lower in Ref. 11; Zn: 186 (**44**), Cd: 149 (**36**), Hg: 130 (**31**). Additional $\bar{D}$ values: HgMe$_2$ 243 (**58**); Hg(CF$_3$)$_2$ 206 (**49**) $\bar{D}$ Ref. 21. Stepwise enthalpies for ZnR$_2$: R=Me, $\bar{D}_{\text{Zn–Me1}}$=267 (**63**) $\bar{D}_{\text{Zn–Me2}}$=103 (**25**); R=Et, $\bar{D}_{\text{Zn–Et1}}$=219 (**52**) $\bar{D}_{\text{Zn–Et2}}$=92 (**22**), Ref. 22.

[w] B3LYP/6-31G* calculated $\bar{D}$(MeO*Zn–OMe*), Ref. 12.

[x] B3LYP/SRLC calculated $\bar{D}$(MeS*Zn–SMe*), Ref. 12.

[y] ANO-MP2 calculated $\bar{D}$(F*Zn–F*), Ref. 23.

[z] HF-triple-ζ-STO calculated $\bar{D}$(*Cd–H*), Ref. 24.

[aa] B3LYP/SRSC calculated $\bar{D}$(MeO*Cd–OMe*), Ref. 12.

[ab] B3LYP/SRSC calculated $\bar{D}$(MeS*Cd–SMe*), Ref. 12.

[ac] ANO-MP2 calculated $\bar{D}$(F*Zn–F*), Ref. 23.

[ad] HF-MP(2–4) calculated $\bar{D}$(H*Hg–H*), Ref. 25.

[ae] Gas phase Hg–O Ref. 8a; B3LYP/LANL2DZ calculated $\bar{D}$(MeO*Hg–OMe*) unreliable, Ref. 12.

[af] General value given in Ref. 8b; B3LYPLANL2DZ calculated $\bar{D}$(MeS*Hg–SMe*) unreliable, Ref. 12.

[ag] $\bar{D}$(F*Hg–F*), Ref. 10.

[ah] B3LYP/6-31G* calculated $\bar{E}$([MeO]$_2$*B–B*[OMe]$_2$), Ref. 12.

[ai] $\bar{D}$(H$_2$*B–H*), calculated first DBE for H$_2$*B–H*, is significantly larger 444 (**106**) Ref. 26.

[aj] $\bar{D}$(Me$_2$*B–Me*), Ref. 10.

[ak] $\bar{D}$(Ph$_2$*B–Ph*), Ref. 11.

[al] $\bar{E}$([MeO]$_2$*B–OMe*), Ref. 27; lower in Ref. 18, $\bar{D}$([MeO]$_2$*B–OMe*)=495 (**118**).

[am] $\bar{D}$(MeS)$_2$*B–SMe*, Ref. 28; for higher thiolates RS, R=Et, Pr^n, Bu^n the mean BDE is 376 (**90**).

[an] $\bar{D}$(F$_2$*B–F*), Ref. 27; calculated first DBE for F$_2$*B–F*, is significantly larger 817 (**195**) Ref. 26.

[ao] HF-MP(2–4) calculated $\bar{D}$(H$_2$*Al–H*), Ref. 25.

[ap] $\bar{D}$(Me$_2$*Al–Me*), Ref. 10.

[aq] BDE calculation requires estimates based on studies of Al(acac) derivatives, Ref. 29. B3LYP/6-31G* calculated $\bar{D}$([MeO]$_2$*Al–OMe*) 410 (**98**), Ref. 12.

[ar] B3LYP/6-31G* calculated $\bar{D}$([MeS]$_2$*Al–SMe*), Ref. 12.

[as] $\bar{D}$(F$_2$*A–F*), Ref. 10.

[at] HF-MP(2–4) calculated $\bar{D}$(H$_2$*Ga–H*), Ref. 25.

[au] $\bar{D}$(Me$_2$*Ga–Me*), Ref. 8a.

[av] B3LYP/SRLC calculated $\bar{D}$([MeO]$_2$*Ga–OMe*), Ref. 12.

[aw] B3LYP/SRLC calculated $\bar{D}$([MeS]$_2$*Ga–SMe*), Ref. 12.

[ax] HF-MP(2–4) calculated $\bar{D}$(F$_2$*Ga–F*), Ref. 25.

[ay] HF-MP(2–4) calculated $\bar{D}$(H$_2$*In–H*), Ref. 25.

[az] $\bar{D}$(Me$_2$*In–Me*), Ref. 8a.

[ba] B3LYP/SRLC calculated $\bar{D}$([MeO]$_2$*In–OMe*), Ref. 12.

[bb] B3LYP/SRLC calculated $\bar{D}$([MeS]$_2$*In–SMe*), Ref. 12.

[bc] DFT calculated $\bar{D}$(F$_2$*In–F*), Ref. 25.

[bd] $\bar{D}$(Me$_3$*Si–Si*Me$_3$), Ref. 8a.

[be] Average $\bar{D}$(Me$_3$*Si–H*), Refs. 11, 8a, 30.

[bf] $\bar{D}$(Me$_3$*Si–Me*), Ref. 11.

[bg] $\bar{D}$(Ph$_3$*Si–Ph*), Ref. 11.

[bh] $\bar{D}$([EtO]$_3$*Si–OEt*), Ref. 8a.

[bi] B3LYP/SRLC calculated $\bar{D}$([MeS]$_3$*Si–SMe*), Ref. 12.

[bj] $\bar{D}$(F$_3$*Si–F*), Ref. 10.

[bk] $\bar{D}$(Me$_3$*Sn–Sn*Me$_3$), Ref. 8a.

[bl] $\bar{D}$(Me$_3$*Sn–H*), Ref. 8a.

[bm] $\bar{D}$(allyl$_3$*Sn–allyl*), using data in Refs. 11 and 8a and a value of ΔH_{vap}^o (Sn[allyl]$_4$)=52.0 kJ mol^{-1} given in Refs. 11, 31.

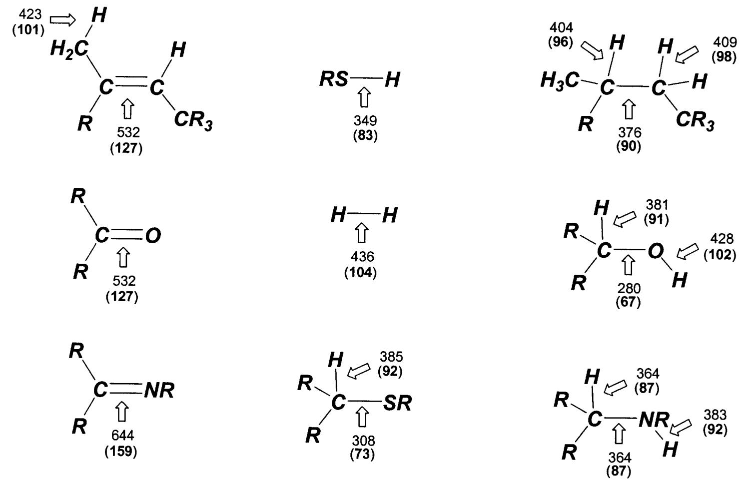
[bn] $\bar{D}$(Me$_3$*Sn–Me*), Ref. 8a.

[bo] $\bar{D}$(Ph$_3$*Sn–Ph*), Ref. 11.

[bp] B3LYP/SRLC calculated $\bar{D}$([MeO]$_3$*Sn–OMe*), Ref. 12.

[bq] B3LYP/SRLC calculated $\bar{D}$([MeS]$_3$*Sn–SMe*), Ref. 12.

[br] B3LYP/SRLC calculated $\bar{D}$(F$_3$*Sn–F*), Ref. 12.



Scheme 1. Useful bond enthalpy terms, in kJ mol^{-1} (kcal mol^{-1}), for substrates considered in this review (taken from Ref. 8).

values extrapolated from studies of gas-phase diatomics, the solid state (oxides, sulfides etc.), or ubiquitous $M(acac)_n$ complexes are often very dependent on the reference source selected.[8] As full thermochemical data for Table 2 are not available, some calculated values (shown underlined) are also given. In cases where there is a possibility of a significant error the footnote is shown with an asterisk (e.g. b*, c*, etc). It is also important to realise that average Bond Dissociation Enthalpy (BDE, $\bar{D}$) or average Bond Enthalpy Contribution (BEC, $\bar{E}$) values presented are generally significantly lower than the enthalpy change associated with the first LA–L bond dissociation in a species $LA(L)_n$. Nevertheless, even average values reveal useful HSAB trends. For example, the boron centre in BY_3 changes from a soft to hard centre across the series Y=H, alkyl, SMe (soft) to Y=OMe, F (hard). One very simple approach to defining the hardness of a given LA is to look at the bond energy difference between $\bar{D}$ (LA–OR) and $\bar{D}$ (LA–SR);[2] the larger this value the harder the Lewis acid centre. Such simple ideas are useful when discussing the relative softness of closely related species. For example, while the species $E(OMe)_3$ (E=B, Al, Ga) species clearly all contain hard centres, on the basis of the bond enthalpy data $Ga(OMe)_3$ is less hard than $B(OMe)_3$ [Table 2, $\Delta\bar{D}_{O,S}=162$ (39) B; 145 (36) Al; <20 (<5) Ga kJ mol^{-1} (kcal mol^{-1})]. Garmer and Gresh have studied such approaches in detail when considering the binding of M^{2+} (M=Zn, Mg, Ca, Cd) to a range of 'biological' ligands.[9]

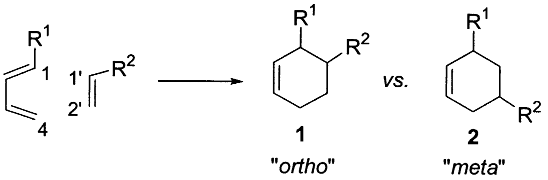
3. Theoretical treatments of the HSAB principle

Rigorous mathematical definitions of chemical hardness (softness) date to the introduction of the Fukui function $[f(r)]$[32,33] by Parr and its linking to the Principle of Maximum Hardness (PMH).[2c] The concepts of *global hardness* (η),[34] *global softness* (S)[34] and its local equivalent (s)[33] have also arisen out of quantum research in this area. Several useful synopses of this progress have appeared.[2b,35,36] The levels of theory in these approaches are currently outside the remit of most groups involved in synthetic organic chemistry. This situation is, however, changing rapidly. Already Density Function Theory (DFT) calculations, amongst others, have proved effective in rationalising the behaviour of real systems. For example, the chemoselectivity (E2 vs S_N2) in reactions of alkyl halides with nucleophiles, and the regiochemistries of enolate alkylation, 1,3-dipolar cycloadditions, and Diels–Alder reactions can be successfully predicted.[35] Specifically, the observed *ortho* selectivity (to **1** compared to **2**) in the reaction of 1-substituted dienes and a non-symmetrical dienophile was explained in terms of the summation of the local softness values (Scheme 2). In all cases, S_{ortho} is less than S_{meta} in line with the principle of maximum hardness. At present, few high level studies of the transition states of Lewis acid-promoted catalytic reactions have been reported and further work in this area would be most welcome.[37]

Simpler levels of theory are already within the scope of synthetic groups. For example, the majority of the LA–XMe (X=O, S) bond energy values in Table 2 were calculated using commercial packages in a straightforward manner (details of how these were attained are given in Ref. 12). The accuracy of such DFT calculations depends on the computational model and the orbital basis set

$$S_{ortho} = (s_1^- - s_{1'}^+) + (s_4^- - s_{2'}^+)$$

$$S_{meta} = (s_1^- - s_{2'}^+) + (s_4^- - s_{1'}^+)$$



1 "*ortho*"

2 "*meta*"

Scheme 2. Minimum global softness as an explanation for the *ortho* selectivity observed in Diels–Alder reaction. $R^1=NEt_2$, NMe_2, NH_2, OEt, OMe, Me, CO_2H; $R^2=CO_2H$, CO_2Me, COMe, CHO, NO_2. Nomenclature: (s_1^-) the local softness at site C(1), the function having a negative value.

selected. The widely available B3LYP for the former and 6-31G* for the latter were used for the elements Li to Ar in Table 2. These 'workhorse' functions can deliver average BDE values ($\bar{D}$) within a few kcal mol^{-1} of known experimental values.[38] Significant deviations are not uncommon, however, and their origins are often not easy to identify or predict. For this reason, such approaches have to be treated with caution and used for *qualitative* comparisons of, for example, thiophilicity via BDE comparison. Computational approaches have two advantages: firstly, the ability to attain enthalpy values for a *specific* bond cleavage process within a catalytic cycle and, secondly, to study experimentally inaccessible species. The inability of simple basis sets to deal with elements heavier than argon (e.g. lanthanides and 2nd and 3rd row elements) can be overcome by use of so called 'core potentials' (for specific examples from Table 2 see Ref. 12). The availability of such methods makes semi-quantitative comparisons of hard/soft character (and related studies) relatively easy in most systems.

4. HSAB binding of substrates

4.1. Structural outcomes of Lewis acid binding of acyclic carbonyls, thiocarbonyls and imines

Interrogation of the crystallographic database for the structures of exemplary Lewis acids that bind non-chelate aldehydes, ketones, enones, amides, thioamides and imines allows archetypal binding motifs to be identified [structures **A–C** (R_S, R_L are the small and large groups, respectively; D=O, S, NR), see also Table 3].[39] Motif **A** is the most common but this also shows the widest range of structural variation, encompassing linear ($\theta\sim180°$; ϕ variable)

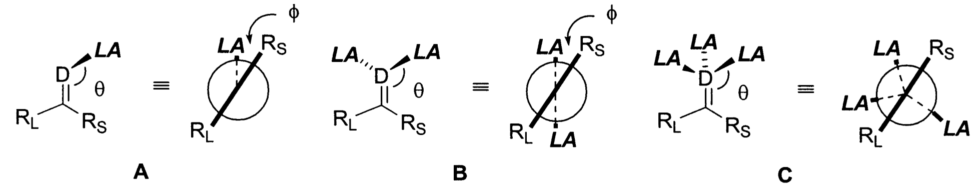


Table 3. Selected crystallographically observed co-ordination parameters for carbonyl [aldehydes and ketones (Y=H, R)], enones (Y=α-C=C), amides (Y=NR$_2$), thioamides (Y=NR$_2$) and imine (Y=H, R) complexes of the Lewis acids

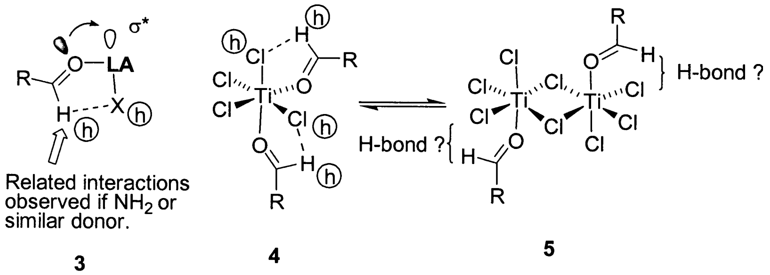
Lewis acid centre	No. of examples[a]	Lewis base(s)	Co-ordination modes	For d (Å)[b]	η^1-co-ordination θ (°)[b]	Mode (**A**) ϕ (°)[b]
Group 1						
$\mathrm{Li^{I}}$	13	O=CR(Y)[b]	**A**, **B**, **C**	1.88–1.98 (1.94)	125–151 (138)	0–47 (20)
Group 2						
$\mathrm{Mg^{II}}$	14	O=CR(Y)[b]	**A**	2.03–2.09 (2.06)	132–155 (143)	5–23 (14)
$\mathrm{Ca^{II}}$	11	O=CR(Y)[b]	**A**	2.26–2.34 (2.30)	135–165 (150)	10–75 (43)
Lanthanoids						
$\mathrm{La^{III}}$	13	O=CR(Y)[b]	**A**, **B**	2.41–2.54 (2.47)	133–157 (145)	26–76 (51)
Group 4						
$\mathrm{Ti^{IV}}$	15	O=CR(Y)[b]	**A**	1.95–2.13 (2.04)	140–159 (150)	3–34 (18)
Group 12						
$\mathrm{Zn^{II}}$	36	O=CR(Y)[b]	**A**	1.97–2.11 (2.04)	123–134 (128)	1–15 (8)
	6	S=CR(NR$_2$)[c]	**A**	2.34–2.35 (2.34)	104–109 (106)	4–28 (16)
$\mathrm{Cd^{II}}$	5	O=CR(Y)[b]	**A**	2.32–2.66 (2.49)	112–132 (122)	0–43 (17)
	7	S=CR(NR$_2$)[c]	**A**	2.56–2.68 (2.62)	105–114 (109)	10–27 (18)
$\mathrm{Hg^{II}}$	3	O=CR(Y)[b]	**A**, **B**	2.71–2.80 (2.76)	108–136 (122)	26–62 (45)
	10	S=CR(NR$_2$)[c]	**A**	2.43–2.57 (2.50)	100–109 (104)	1–7 (4)
Group 13						
$\mathrm{B^{III}}$	12	O=CR(Y)[b]	**A**	1.46–1.57 (1.52)	121–129 (125)	1–7 (4)
	2	YN=CR(Y)[b]	**A**	1.54, 1.60	130, 131	0, 5
$\mathrm{Al^{III}}$	6	O=CR(Y)[b]	**A**	1.88–1.95 (1.92)	132–149 (141)	7–16 (12)
	1	YN=CR(Y)[b]	**A**	3.87	147	7
$\mathrm{Ga^{III}}$	1	O=CR(Y)[b]	**A**	2.01	123	14
	1	YN=CR(Y)[b]	**A**	2.00	126	24
$\mathrm{In^{III}}$	7	O=CR(Y)[b]	**A**	2.24–2.33 (1.52)	122–131 (127)	1–20 (11)
Group 14						
$\mathrm{Si^{IV}}$	2	O=CR(Y)[b]	**A**	1.76, 1.93 (1.85)	130, 154 (142)	8, 31 (19)
$\mathrm{Sn^{IV}}$	31	O=CR(Y)[b]	**A**	2.21–2.42 (2.31)	124–136 (130)	2–22 (12)
	14	S=CR(NR$_2$)[c]	**A**, **B**[d]	2.50–2.73 (2.61)	102–107 (105)	43–76 (60)
	1	YN=CR(Y)[b]	**A**	2.27	117	10

[a] Molecules were selected on the criteria of coming from mono to trimetallic species. Data for separate co-ordinated substrates within one molecule were treated separately except for complexes with 3–8 near identical substrates. The latter were averaged before data entry (to avoid statistical over representation of such structures).

[b] A 1σ range is given for d, θ, and ϕ (average value in parentheses).

[c] Y=H, alkyl, enone, NR$_2$.

[d] One Sn(II) species (CIBMIJ) is known.



Scheme 3.

through to ‘π-like’ bonding (θ approaches 90°; ϕ approaches 90°).

Schreiber and Shambayati[40] have provided an excellent discussion on the binding of carbonyl compounds; these ideas are extended here concentrating on non-chelate systems. In very hard interactions (e.g. with Li^+, Mg^{2+}, Ca^{2+}, La^{3+}) the bonding is electrostatically dominated and co-ordination mode **A** with $\theta \sim 140–150°$ is observed. Such interactions are believed to be strongest when the metal ion is aligned with the dipole of the ligand (i.e. $\theta=180°$ for symmetrical ketones is expected) but the shallow energy minima in these species are easily distorted by steric factors. For softer Lewis acids co-ordination at the sp^2 oxygen lone pairs is observed. Extensive studies of boron and zinc non-chelate carbonyl complexes indicate that such Lewis acids bind carbonyls, in mode **A**, at their most sterically accessible, electron-rich lone pair; the zinc aldehyde complexes of Vahrenkamp[41] and BX_3–amide complexes of Corey[42] are typical. This may be attributed to a generalised anomeric effect involving the uncomplexed lone pair of the carbonyl oxygen and a suitable σ^* orbital on the Lewis acid (**3**, Scheme 3; small and large substituents given by R_S and R_L, respectively).[43] This regime accounts for the small range of binding angles (θ) and LA–O=C–R_S dihedral angle (ϕ) observed in these complexes. This situation is reinforced in aldehyde complexes of Lewis acids containing hydrogen bond acceptor substituents (normally halogens) resulting in an effectively cyclic coplanar structure. The HSAB-based hydrogen bonding in $TiCl_4(aldehyde)_2$ **4** is typical but here the picture is complicated by equilibration with a dimer **5** (Scheme 3).[44] The presence of aldehyde–H···Cl contacts in **5** is also likely but presently none is structurally characterised. One would predict that the harder the LA–O=CR_LR_S interaction becomes the less important frontier orbital control influences should be and, therefore, the more θ and ϕ should vary in the binding motif. This is born out to some degree—for example, carbonyl complexes of Li^+, Mg^{2+}, Ca^{2+}, and La^{3+} show the larger standard deviations on θ and ϕ compared to more covalent species (Zn, B, Al, etc. Table 3), but, in general, steric factors are more important. For strongly bound LA–O=CR_LR_S contacts (short *d* values) non-bonded interactions close to the bound carbonyl lead mainly to an increase in θ. This effect is clearly demonstrated in the structure of the cyclohexanone derivative YALMED[45] (Fig. 1a) but is also revealed in ^{13}C NMR studies of MCl_4-hindered enone complexes (M=Ti, Sn).[46] Unfortunately, features that lead to increases in *d* also lead to dramatic variations in θ and ϕ regardless of the nature of the hard/hard, hard/soft or soft/soft interaction, e.g. as seen in the base adducts of fourth and fifth period Lewis acids due principally to the increased contact distance d and associated with both weakened bonding and the *absence* of intramolecular contacts. On the basis of HSAB theory one might also predict that *mismatched* systems will demonstrate lengthened bonds. In practice, however, this effect is also normally small as shown in the *bis*-trimethylaluminium adduct of ketoimine DUJBUF[47] (Fig. 1b).

The generalised anomeric effect (**3**) disfavours double (or higher) co-ordination of Lewis acids to carbonyl groups as electron density is removed from the remaining lone pair. Such multiple bonding motifs (**B**, **C**) have only been observed, thus far, in Li^+, lanthanides, and Hg(II) structures. The former two Lewis acids overcome the anomeric problem through very hard–hard ionic-like interactions that negate the requirement for the bonding to be

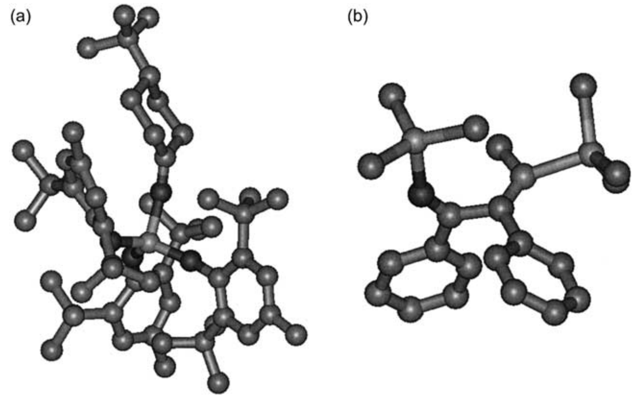
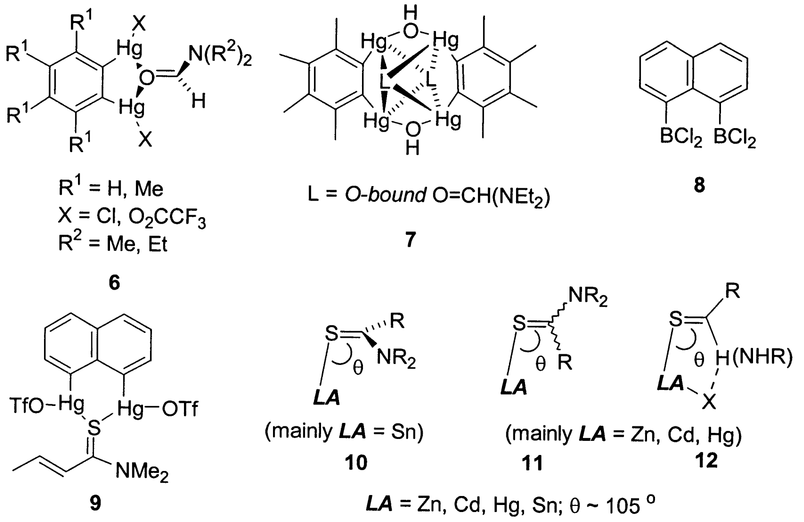


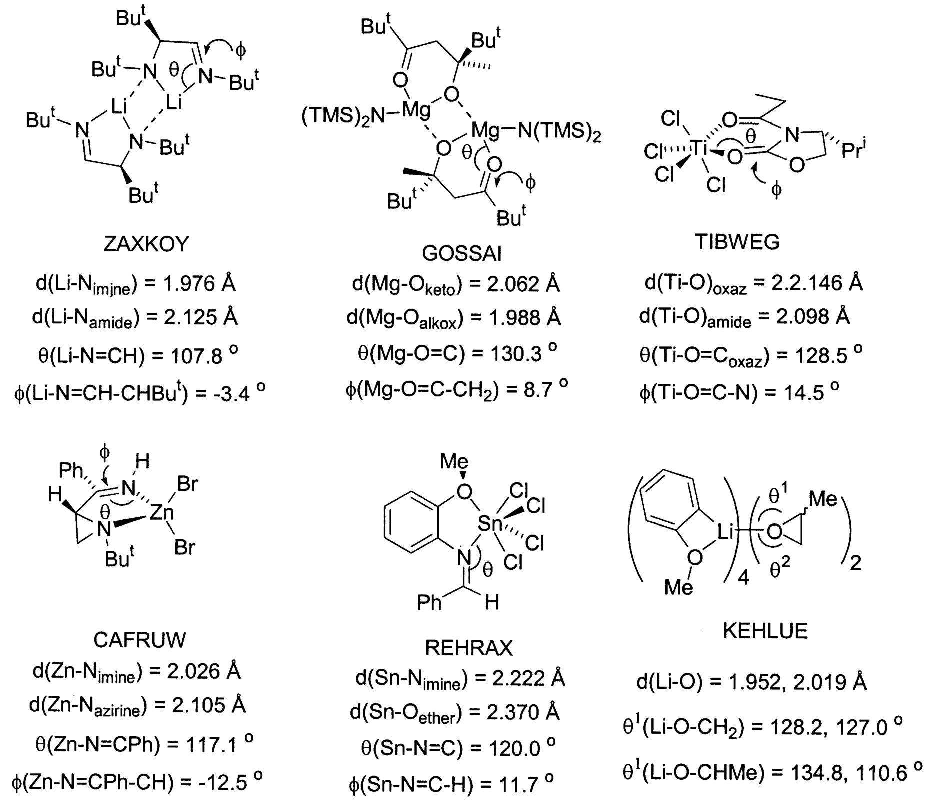
Figure 1. Selected bond distances (Å) and angles (deg.); for YALMED[44]: $d(Al–O_{ketone})$ 1.840, θ(Al–O=C) 165.8, ϕ(Al–O=C–CH_2) 4.1, −176.1; for DUJBUF[46]: $d(Al–O_{ketone})$ 1.983, $d(Al–N_{imine})$ 2.089, θ(Al–O=C) 142.0, θ(Al–N=C) 146.5, ϕ(Al–O=C–Ph_{ipso}) −167.3, ϕ(Al–N=C–Ph_{ipso}) −7.0.



Scheme 4.

directional. In the latter case, mismatching of basic amide donors (hard) with organomercury Lewis acids (soft) may create rather weakly bound complexes that seize the chance to be stabilised somewhat by secondary interactions resulting in double (or even quadruple!) co-ordination (**6**, **7**, Scheme 4).[48] Removing the co-ordinated counter anions gives a harder mercury cation and allows the normal bonding mode (**A**) to be re-established. Consistent with the above ideas attempts to use potentially doubly co-ordinating moderately hard Lewis acids (e.g. diboranes **8**,[49] Scheme 4) have not been very successful: two type-**A** interactions in 2:1 complexes are always formed. Such interactions are, however, apparently possible either with soft donor/acceptor pairs as in the spectroscopic detection of **9**[49] or by use of *bis*-aluminium complexes (proposed to account for the high activity of such species in catalytic Tishchenko reactions).[49c]

The identity of the triad, Zn(II), Cd(II) and Hg(II), together with Sn(IV) as soft metals is indicated by the CSD database. Within the selection of Table 3, these are the only species that lead to crystallographically-characterised thioamide



Scheme 5.

complexes. These compounds all display greatly reduced θ values. In a number of cases the co-ordination mode of such species can be thought of as approaching (but not yet attaining) a π-like mode (**10**, Scheme 4). For the Group 12 metals, the dihedral angles ϕ are normally close to 180 or 0° (**11**, **12**), especially the latter if enforced by hydrogen bonding, as in **12**. A single tin(II) structure containing a bridging thioamide ligand has been reported (CIBMIJ).[50] Some HSAB listings give Sn(IV) species as hard Lewis acids, but, X-ray data clearly indicate their behaviour as soft centres especially when X (in $\mathrm{SnX_4}$) is already a soft donor (the so called symbiosis effect[4,5]).

4.2. Structural effects in Lewis acid complexes of chelates, aziridines and epoxides

The *softer* nature of the imine donor disfavours their co-ordination to hard Lewis acid centres and this is borne

Table 4. Selected energies of interaction [in kJ mol^{-1} (kcal mol^{-1})] for the binding affinity of Lewis acids (LA) to neutral ligands (L)

Phase[a]	Lewis acid (LA)	Ligand (L)	Total no. (L)	Binding affinity[b] (kJ mol^{-1} (kcal mol^{-1})) per ligand L	Reference
A. Protic solvents/reagents					
Gas	$\mathrm{Li^+}$	$\mathrm{H_2O}$	1	135 (**32**)[c]	57
Gas	$\mathrm{Na^+}$	$\mathrm{H_2O}$	1	92 (**22**)	59
Gas	$\mathrm{Na^+}$	$\mathrm{H_2S}$	1	58 (**14**)	59
Gas	$\mathrm{Na^+}$	$\mathrm{NH_3}$	1	107 (**26**)	59
Gas	$\mathrm{Li^+}$	MeOH	1	154 (**37**)[c]	57
Gas	$\mathrm{Na^+}$	MeOH	1	102 (**24**)	59
Gas	$\mathrm{Na^+}$	$\mathrm{MeNH_2}$	1	111 (**27**)	59
Gas	$\mathrm{Na^+}$	MeSH	1	73 (**18**)	59
B. Aprotic solvents					
Gas	$\mathrm{Li^+}$	$\mathrm{Me_2O}$	1	165 (**39**)[c]	57
Gas	$\mathrm{Na^+}$	$\mathrm{Me_2O}$	1	92 (**22**)[c]	57
Gas	$\mathrm{K^+}$	$\mathrm{Me_2O}$	1	73 (**17**)[c]	57
Gas	$\mathrm{Li^+}$	$\mathrm{MeOCH_2CH_2OMe}$	1	241 (**58**)[c]	57
Gas	$\mathrm{Na^+}$	$\mathrm{MeOCH_2CH_2OMe}$	1	158 (**38**)[c]	57
Sol.	$\mathrm{BF_3}$	THF	1	90 (**22**)	62
Sol.	$\mathrm{TiCl_4}$	THF	2	148 (**35**)	63
Sol.	$\mathrm{TiCl_4}$	THT[d]	2	119 (**28**)	63
Sol.	$\mathrm{BF_3}$	$\mathrm{NEt_3}$	1	136 (**33**)	62
Sol.	$\mathrm{ZnCl_2}$	Pyridine	2	156 (**37**)	58
Sol.	$\mathrm{BF_3}$	Pyridine	1	128 (**31**)	62
Sol.	$\mathrm{SiCl_4}$	Pyridine	2	117 (**28**)	64
C. Aldehydes, ketones and enones					
Gas	$\mathrm{Na^+}$	$\mathrm{O{=}CH_2}$	1	98 (**24**)	59
Gas	$\mathrm{Na^+}$	$\mathrm{O{=}CH(Me)}$	1	115 (**28**)	59
Sol.	$\mathrm{BF_3}$	$\mathrm{O{=}CH(Me)}$	1	59 (**14**)	60
Gas	$\mathrm{Na^+}$	$\mathrm{O{=}CMe_2}$	1	129 (**31**)	59
Sol.	$\mathrm{BF_3}$	$\mathrm{O{=}CH(Ph)}$	1	70 (**17**)	62
Sol.	$\mathrm{BF_3}$	$\mathrm{O{=}CMe_2}$	1	76 (**18**)	62
Sol.	$\mathrm{BF_3}$	$\mathrm{O{=}CMe(Ph)}$	1	75 (**18**)	62
Sol.	$\mathrm{AlMe(BHT)_2}$[e]	$\mathrm{O{=}CPh_2}$	1	67 (**16**)[f]	65
Sol.	$\mathrm{TiCl_4}$	$\mathrm{O{=}CMe(Ph)}$	2	121 (**29**)	63
Sol.	$\mathrm{TiCl_4}$	$\mathrm{O{=}CMe(CH{=}CMe)_2}$	1[g]	75 (**18**)	60
Sol.	$\mathrm{BCl_3}$	$\mathrm{O{=}CMe(CH{=}CMe)_2}$	1	106 (**25**)	60
sol.	$\mathrm{SnCl_4}$	$\mathrm{O{=}CMe(CH{=}CMe)_2}$	1[g]	51 (**12**)	60
D. Amides					
Gas	$\mathrm{Na^+}$	$\mathrm{O{=}CH(NMe_2)}$	1	155 (**37**)	59
Sol.	$\mathrm{BF_3}$	$\mathrm{O{=}CH(NMe_2)}$	1	111 (**26**)	62
Sol.	$\mathrm{SnCl_4}$	$\mathrm{O{=}CH(NMe_2)}$	2	119 (**57**)	66
Sol.	$\mathrm{ZnCl_2}$	$\mathrm{O{=}CMe(NMe_2)}$	2	147 (**35**)	58
Sol.	$\mathrm{Ca^{2+}}$	$\mathrm{O{=}C(NMe_2)_2}$	6	295 (**71**)	67
Sol.	$\mathrm{ZnCl_2}$	$\mathrm{O{=}C(NMe_2)_2}$	2	142 (**34**)	68
Sol.	$\mathrm{CdCl_2}$	$\mathrm{O{=}C(NMe_2)_2}$	2	226 (**54**)	68
Sol.	$\mathrm{HgCl_2}$	$\mathrm{O{=}C(NMe_2)_2}$	2	119 (**28**)	68
Sol.	$\mathrm{BF_3}$	$\mathrm{O{=}C(NMe_2)_2}$	1	109 (**26**)	62
Sol.	$\mathrm{SnCl_4}$	$\mathrm{O{=}C(NMe_2)_2}$	2	130 (**31**)	66
Sol.	$\mathrm{SnCl_4}$	$\mathrm{S{=}C(NMe_2)_2}$	2	129 (**31**)	66
Sol.	$\mathrm{SnBr_4}$	$\mathrm{O{=}C(NMe_2)_2}$	2	125 (**30**)	66
Sol.	$\mathrm{SnBr_4}$	$\mathrm{S{=}C(NMe_2)_2}$	2	112 (**27**)	66

[a] Conditions under which data were collected.

[b] Per ligand at 298 K unless stated otherwise.

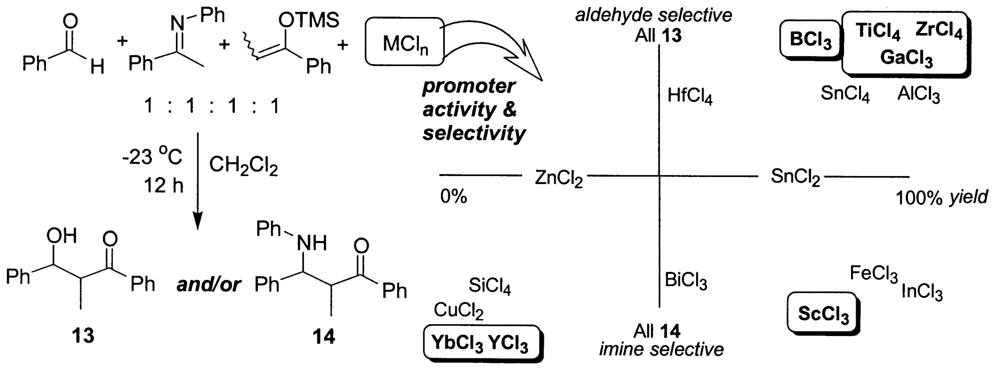
[c] At 0 K.

[d] THT is tetrahydrothiophene.

[e] BHT is deprotonated 2,6-di-*tert*-butyl-4-methoxyphenol (butylated hydroxytoluene).

[f] Enthalpy of reaction.

[g] Formation of $\mathrm{MCl_4(L)_2}$ avoided by use of excess $\mathrm{MCl_4}$ (M=Ti, Sn).

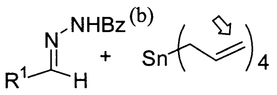
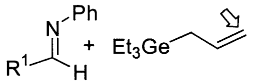
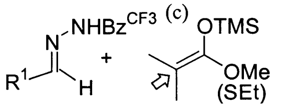
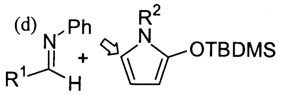
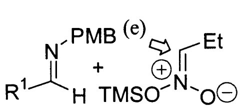
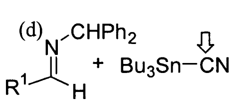
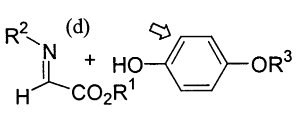
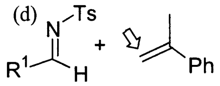


Scheme 6.

out by the relatively few examples of genuine simple η^1-imine complexes present in Table 3. Chelation strategies offer an approach to overcoming this mismatching problem as shown by the structure ZAXKOY[51] (Scheme 5). The imposition of a chelate ring in these structures enforces low dihedral angles. This favours access to a range of ring conformers in such species. The magnesium species GOSSAI,[52] for example, crystallises in a mixture of half chair and twist boat conformations while the titanium compound TIBWEG[44] adopts an envelope conformation with the Ti centre just below the plane of the two carbonyls.

The softer nature of Zn(II) and Sn(IV) Lewis acids means that they are more easily able to co-ordinate nitrogen-based substrates. In this case the chelate simply acts to restrict the conformation as in structures CAFRUW[53] and REHRAX.[54] Aside from imines and carbonyl compounds epoxides are popular targets for activation by Lewis acids. Crystallographically-characterised main-group epoxide complexes are, however, extremely rare: a single lithium compound is known (KEHLUE).[55] Disorder prevents the *syn*/*anti* bonding mode being clearly identified in this case. Only five other epoxide complexes (bound to Cd^{II}, Ag^{I}, Mn^{III}

Table 5. Selected uses of catalytic $M(OTf)_3$ (M=Sc, Yb) in reactions of aldimines[a]

Reaction	R^1, R^2, R^3	M	Mol%	Conditions	Reference
	R^1=alkyl, aryl, vinyl	Sc	5	H_2O/THF (1:9), 30°C, 24 h	72
	R^1=aryl, Bu^t, Cy	Sc	10	MeCN, rt, 0.25–2 h $MeNO_2$, rt	73 74
	R^1=alkyl, Ph, vinyl	Sc	5	MeCN, −78°C to rt, 4 h, depending on substrate	75
	R^1=alkyl, aryl, R^2=alkyl	Yb	5	EtCN, −45°C, 0.5 h	76
	R^1=alkyl, aryl	Sc	4	MeCN, 0°C, 2 h	77
	R^1=alkyl, aryl	Sc	10	H_2O, rt, 20 h	78
	R^1=alkyl, R^2=2,4-$Cl_2C_6H_3$, R^3=alkyl	Sc	20	CH_2Cl_2, 4 Å-sieves, $MgSO_4$/TMSCl, rt, 16 h	79
	R^1=Me, Pr^i, Ph	Yb	50	CH_2Cl_2/THF, TMSOTf, rt, 1 h	80

[a] In all cases the reactions give synthetically useful yields, typically 70–90%. The arrow indicates the site of alkylation. [b] Bz=benzoyl. [c] Bz^{CF3}=4-$CF_3C_6H_4C(=O)$. [d] Imine formed in situ. [e] PMB=4-$MeOC_6H_4CH_2$.

and Ru^{II}) have been reported so far.[56] Based on this data, the preferred metal co-ordination mode is binding of the lone pair *anti* to any substituent on the epoxide ring with a Metal–O–$C_{epoxide}$ angle of ~130° (equivalent to an angle of 140±12° between the M–O bond and the centre of the C_2O plane), regardless of HSAB metal type.

4.3. Thermochemical data for binding of acyclic carbonyls, thiocarbonyls and related species

Experimental data on the binding of organic substrates (carbonyl and related neutral donors) to Lewis acids used in organic synthesis are sparse (and are non-existent for the lanthanoids). Additionally, there are a number of problems in making comparisons between these data sets. Mass spectrometry studies, for example, lead to the binding affinity at 0 K (as opposed to values at 298 K).[57] Many older thermochemical experiments exclude solvation and sublimation effects and equate the enthalpy of reaction directly with the 'bond energy' via application of various approximations.[58] Finally, theoretical simulations in this area are prone to significant errors.[59] These facts aside, selected data are presented in Table 4. In principle this should be a ripe area for the application of HSAB theory. In practice, however, HSAB effects are often masked by other factors (electronic, steric and solvent) affecting the intrinsic bond strength, electrostatic effects dominating the binding of Group 1 Lewis acids. While all have hard character the bond strength for Me_2O binding halves over the series Li^+, Na^+, K^+. Similarly, the binding affinity of Li^+ for a water molecule falls from 135 kJ mol^{-1} (32 kcal mol^{-1}) for $[Li(OH_2)]^+$ to 70 kJ mol^{-1} (17 kcal mol^{-1}) for $[Li(OH_2)_4]^+$.[57] Comparison of the binding of tetramethylurea complexes (Table 4) confirms the expected features in that this ligand binds most effectively to Ca^{2+} (hard) while the weakest interaction is with $HgCl_2$ (soft). Even in this series, however, hard/soft discrimination expected for SnX_4 (X=Cl, Br) complexation of the urea vs. the thiourea is absent. The conclusion is that, as the majority of the binding affinities cover a relatively small range, predictions as to which Lewis acid will be suitable for a given reaction are problematic. An alternative procedure, selection based on the binding of the final carbonyl (or imine etc) derived product (e.g. alkoxide etc.), can prove more useful as HSAB effects are displayed more readily in the binding of anionic donors (see Table 2). Based on ^1H NMR binding studies of crotonaldehyde, Childs proposed that the relative binding affinity of Lewis acids to carbonyl O-donors was: $BBr_3>BCl_3>SbCl_5\sim AlCl_3>BF_3\sim EtAlCl_2>TiCl_4>Et_2AlCl>SnCl_4>AlEt_3$.[60] This series broadly reflects the hardness of the Lewis acids involved and is reminiscent of the reactivity order proposed by House: $BCl_3>AlCl_3>TiCl_4>BF_3>SnCl_4>ZnCl_2$ (based on alkene acylation studies).[61]

Finally, it is important to realise that co-ordination of carbonyls, and related donors, to Lewis acids can result in modification of the reactivity of the Lewis acid itself, for example, theoretical studies (G2/CBS-4) on BH_3 indicate that $O{=}CH_2$ binding dramatically weakens the B–H bond (by ~50%) even though the carbonyl is only weakly bound. The origin of this effect is the strength of the B–$O_{alkoxide}$ bond in reaction co-ordinates developing from the bound carbonyl intermediate.[69]

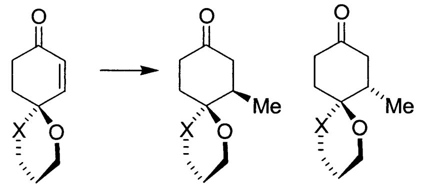
4.4. Azaphilic Lewis acids: aldehyde vs aldimine binding and reactivity

A number of Lewis acids show a distinct preference for binding and activating substrates with sp^2 hybridised nitrogen. Such behaviour can be described as borderline hard/soft. The most significant contributions in this area are due to Kobayashi who has conducted competition reactions of benzaldehyde (leading to **13**) and *N*-benzylideneaniline (giving **14**) with a silyl enol ether.[70] A selection of results is shown in the chart within Scheme 6 with the most useful promoters boxed. As lanthanoids are normally regarded a hard donors the behaviour of $ScCl_3$, YCl_3 and $YbCl_3$ is unexpected and, indeed, these species can (and do very effectively) activate O-donor substrates.[71] At present, there is no theoretical description of this dichotomous behaviour in the lanthanoid group but clearly solvation and ionisation effects will be very important for these species. From a practical point of view, these Lewis acids should be regarded as particularly iminophilic in much the same way as copper(II) and other transition metals can act. The aldimine selectivity shown by MX_3 (M=Sc, Y, Yb) is strongly dependent on the ligand X^-. With weakly basic counter anions (X^-=OTf^-, ClO_4^-) the aldimine selectivity and activity increases and with strongly basic donors (X^-=OAc^-, ^-OPh), it is suppressed. These effects are of high synthetic utility and $M(OTf)_3$ (M=Sc, Yb) are useful catalysts in imine-based reactions (Table 5).

5. Directing groups based on HSAB principles

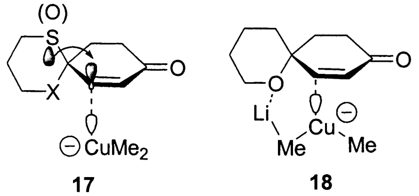
5.1. Substrate-based: chemo- and stereoselection

It is not the purpose of this section to provide a comprehensive listing of substrate-directed reactions (a number are



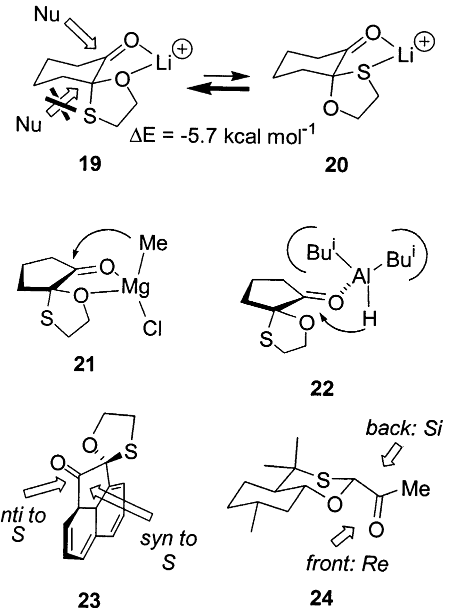
15 **16a** **16b**

X	*conditions..*	*Addn. outcome..*	**16a** : **16b**
S	MeMgBr, cat. Cu^I	*anti* to S	93:7
CH_2	$LiCuMe_2$, TMSCl	*anti* to O	0:100
CH_2	$LiCuMe_2$	*syn* to O	92:8



17 **18**

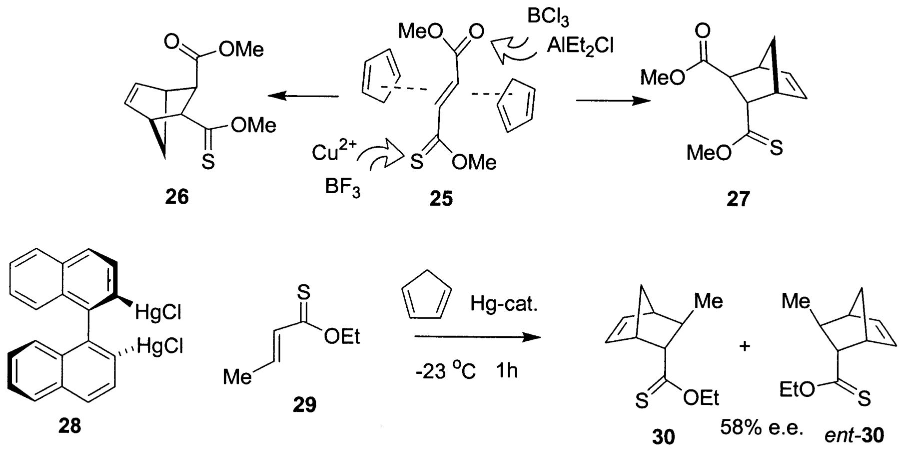
Scheme 7.



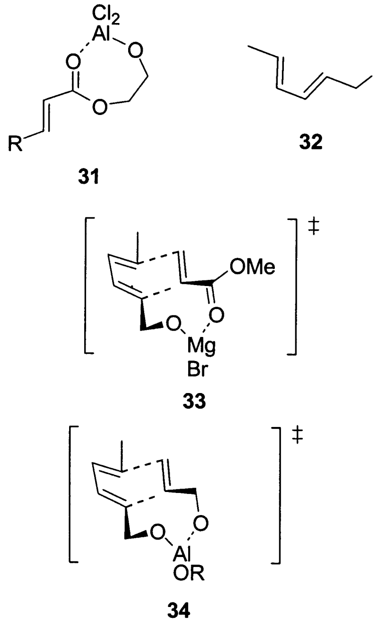
Scheme 8.

already available[81]) but to note recent reactions where HSAB effects are an important factor in the observed reactivity. The areas sampled will be oxathiane, thiocarbonyl, alkoxide, alkyne, and metal donor groups. Starting with the former class, complex behaviour is shown by spiro oxathioacetal species. Reaction of **15** (X=S) with MeMgBr in the presence of a CuBr·SMe$_2$ catalyst results in conjugate addition *anti* to the thiofunction (leading to **16a** as opposed to **16b**). Similar *anti* addition results on treatment of **15** (X=CH$_2$) with LiCuMe$_2$ addition in the presence of TMSCl (Scheme 7).[82] In the absence of TMSCl an otherwise identical run with **15** (X=CH$_2$) results in methyl addition *syn* to oxygen. The former *anti* additions can be rationalised as being due to stabilisation of the developing C$_{\text{enone}}$–Cu bond by n→σ* donation by a sulfur (efficient) or oxygen (less efficient) lone pair. One representation of this stereoelectronic effect is **17**.[83] The formation of **16a** (X=CH$_2$) is less easily accounted for but the presence of a hard/hard Li···O$_{\text{acetal}}$ contact, as in **18**, may help such an intermediate compete against the dominant stereoelectronics. A clearer-cut case of HSAB effects is presented by **19** (Scheme 8). Computational (B3LYP/6-31G*) studies indicate Li–O co-ordination in **19** to be 23.7 kJ mol^{-1} (5.7 kcal mol^{-1}) more favoured than Li–S interaction (**20**).[84] Clearly, the top face of **19** is the most accessible and addition *anti* to sulfur results with MeLi (91:9 diastereoselectivity) and other nucleophiles.[85] Similar Mg–O vs Mg–S stability is calculated for **21** again predisposing the Grignard reagent to fashion the *anti* to sulfur product in accord with experimental observation. Hindered Bu$^i_2$AlH is the only reagent to give nucleophilic addition *syn* to sulfur. Modelling of this reaction suggests that a chelate is not formed due to the bulk of the Lewis acid and that the least-cluttered arrangement predisposes the small Al–H to sit on the bottom face prior to *syn* addition **22**. In these oxathiane systems, there is apparently strong competition between steric, chelation and stereoelectronic factors. The high *anti* to sulfur selectivity in reaction of **23** with MeLi (98:2), for example, suggests a stereoelectonic effect (sulfur lone-pair/CO$_{\pi^*}$) but NaBH$_4$, LiAlH$_4$, and other reducing agents give a majority of *syn* products (~70:30) (Scheme 8).[86] The origin of this difference is not clear. Similar observations apply to the simplest of Eliel's substrates **24**. Reaction with PhMgBr gives the *Re* product in some selectivity (78:22) while PhLi reacts stereorandomly. It has been suggested that Li$^+$ is softer than MgBr$^+$ and competing *O,S*-chelation (vs *O,O*) with **24** is possible.[87] This is unattractive given the high selectivity shown in the O,O vs *O,S* equilibrium between **19** and **20**, but is in accord with the thermodynamic data of Table 2. One alternative might be to point out that, while Li$^+$ is hard, its intrinsic binding affinity for many substrates is high (Table 4) and this can lead to a lack of discrimination in binding or the observation of multiple binding modes (Table 3).

Differential ester vs. thioester binding has been exploited in Diels–Alder chemistry, the nicest case being due to Brown (Scheme 9).[88] Use of the oxophilic hard Lewis acids AlEt$_2$Cl or BCl$_3$ promoters in the reaction of **25** with excess cyclopentadiene has been suggested to proceed from the *s-trans*, *s-trans* conformer via HSAB selective binding at the ester carbonyl. Useful selectivities to **26** are realised (AlEt$_2$Cl: 58% de; BCl$_3$: 92% de). Conversely, use of soft Cu(OTf)$_2$ affords **27** in 78% diastereomeric excess. Surprisingly, in this case BF$_3$·OEt$_2$ acts as a soft donor and this is the most selective reagent for the formation of **27**. While the



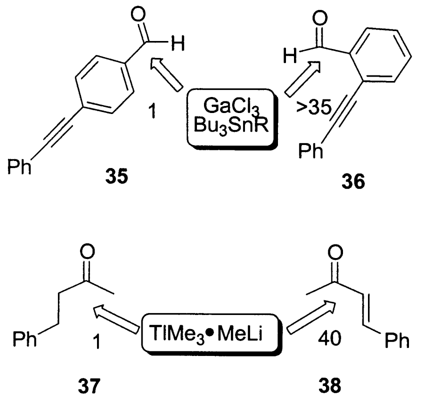
Scheme 9.



Scheme 10.

O-binding of BCl_3 to **25** can be clearly identified by the ^{13}C NMR shift of the carbonyl carbon, no such shift is observed for the thiocarbonyl carbon in the presence of $BF_3{\cdot}OEt_2$ indicating only a weak interaction. Thioester coordination is also thought to be important in mercury Lewis acid-catalysed Diels–Alder reactions of **29**,[89,90] and an asymmetric version has been reported: use of **28** (10 mol%) leads to **30** in 58% ee[90]

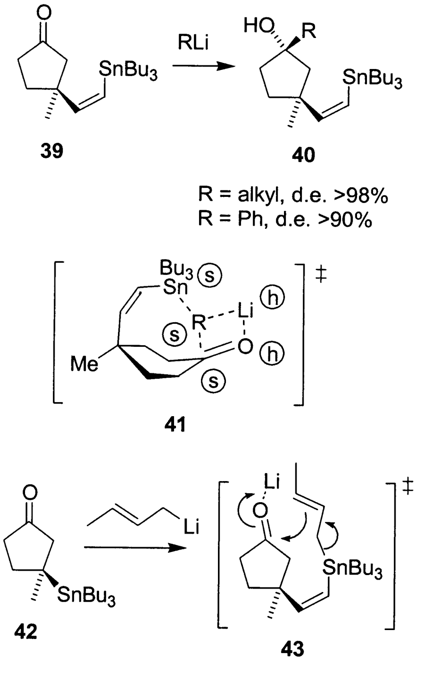
Hard–hard interactions using alkoxides can also be used to great effect in Diels–Alder reactions. Shipman[91] has proposed that reaction of $EtAlCl_2$ with 2-hydroxyethyl esters allows the formation of the chelate **31** which permits higher reactivity at the chelate over other potentially competing co-ordination sites (Scheme 10). Sorbic alcohol (2,4-hexadienol) **32** is also an excellent substrate to which hard Lewis acid activation may be applied. Reaction with methyl acrylate results in the formation of only a single *syn* diastereomer through transition state **33**.[92] Such is the organisation in the transition state of these reactions that even electron rich allylic alcohols can be persuaded to react as dienophiles (albeit at 160°C!). The modest *syn* diastereoselectivity (up to 4:1) observed here is thought to be associated with transition state **34**.[93]



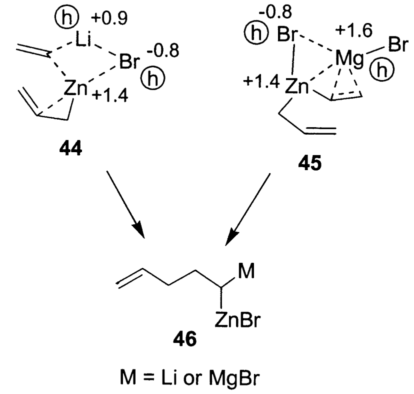
Scheme 11.

While alkenes and alkynes are archetypal soft donors in transition metal chemistry they are seldom used as directing functions with main group reagents. Recently, it has been suggested that the combination $GaCl_3/Bu_3SnR$ (R=H, allyl) fashions a reagent that selectively complexes alkynes γ to the carbonyl function; the competition reactions of **35** and **36** for the reagent are typical (Scheme 11).[94] If the alkyne is truly co-ordinated, then a significant ^{13}C NMR shift for the alkyne carbons is expected, but no spectroscopic data are presently available on this system. Related reactivity has been demonstrated in competition reactions (**37** vs **38**) of enones with thalium 'ate' reagents, but here soft–soft metal–alkene interactions were discounted in favour of a SET mechanism.[95]

Finally in this section metals themselves are considered as directing groups–these can show some extremely powerful HSAB effects. Reaction of **39** with RLi (R=Me, Bu, Ph) leads to highly selective formation of the *syn* addition products **40** (Scheme 12).[96] The most credible rationale for this reactivity is via transition state **41** whereby the stannane acts as an anchoring point for the organolithium in accord with HSAB principles. The limitations of these directing-group effects are demonstrated by **42**. Reaction with MeLi proceeds stereorandomly to the derived *tert*-alcohol as the directing group is too distant. Addition of 2-butenyllithium, however, proceeds with complete allyl inversion and *syn* selectivity in accord with transition state **43**. Aside from these soft–soft interactions hard–hard effects have been detected computationally in the reaction of metalloalkenes with allylzinc bromide, the reaction of vinyllithium (or vinyl magnesium bromide) with $CH_2{=}CHCH_2ZnBr$ leading to the organised intermediates **44** and **45** (Scheme 13).[97] The highly ionic hard interactions between the metal cations and the bromide anion appear to



Scheme 12.



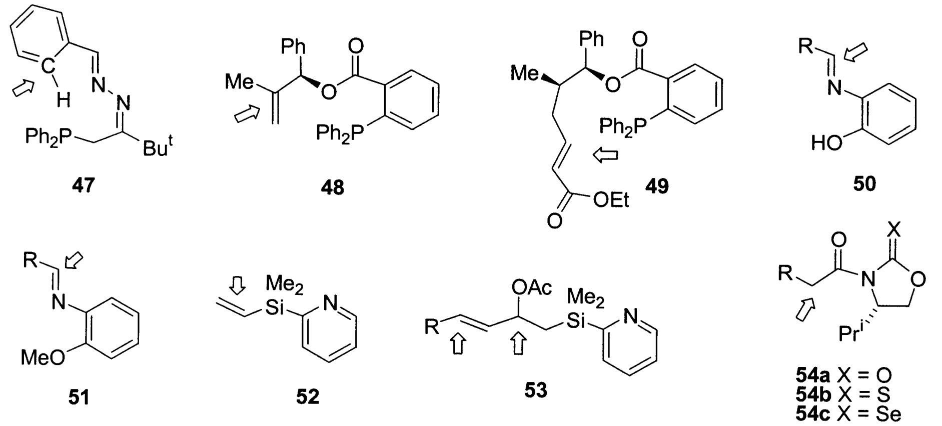
Scheme 13. Reagent pre-organisation in carbometallation of metallo-alkenes. Selected calculated partial charges are shown.

be responsible for the facile nature of these carbometallations (leading to **46**) compared to the equivalent reaction of ethylene, which was found to be endothermic at an equivalent point on the reaction co-ordinate. It is clear that in these reactions the metal function on the metalloalkene plays a similar role to heteroatom directing-groups in 'normal' carbometallations.[98]

5.2. 'Reagent-directing groups': chemo- and stereo-selection

The concept of a 'reagent-directing group' (RDG)—an auxiliary brought into the molecule to activate a specific functionality—was apparently first used by Shaw,[99] but has been popularised recently by Breit.[100] Selected HSAB-based examples (**47**–**54**) are shown in Scheme 14 while details of their applications are given in Table 6. Should the RDG be able to deliver stereochemical induction then its effect is identical to a chiral auxiliary—the ubiquitous Evans species **54a**–**c** are obvious examples in this area.

Despite the slight differences between them, the reactivity of **50** and **51** can be very appreciable and this is due to the ability of the former compounds to make alkoxide bonds. Use of **50** in asymmetric Strecker reactions using Bu_3SnCN as a terminal cyanide source, however, gives an essentially pure product (92% yield, 91% ee) while **51** is inferior (45% yield, 5% ee). For chelation of the harder Lewis acid Li^+ substrate **51** (R=Ph) suffices. Collapse of **55** leads directly to the [2+2] addition product **56** which adds a second equivalent of **51** (R=Ph) to fashion **57** as a single diastereomer (Scheme 15).[104] Yoshida's use of **53** demonstrates just how powerful the RDG approach can be. Catalytic



Scheme 14. Selected substrates with 'reagent directing groups' attached. The arrow shows the sites of C–C (C–M in the first case) bond formation.

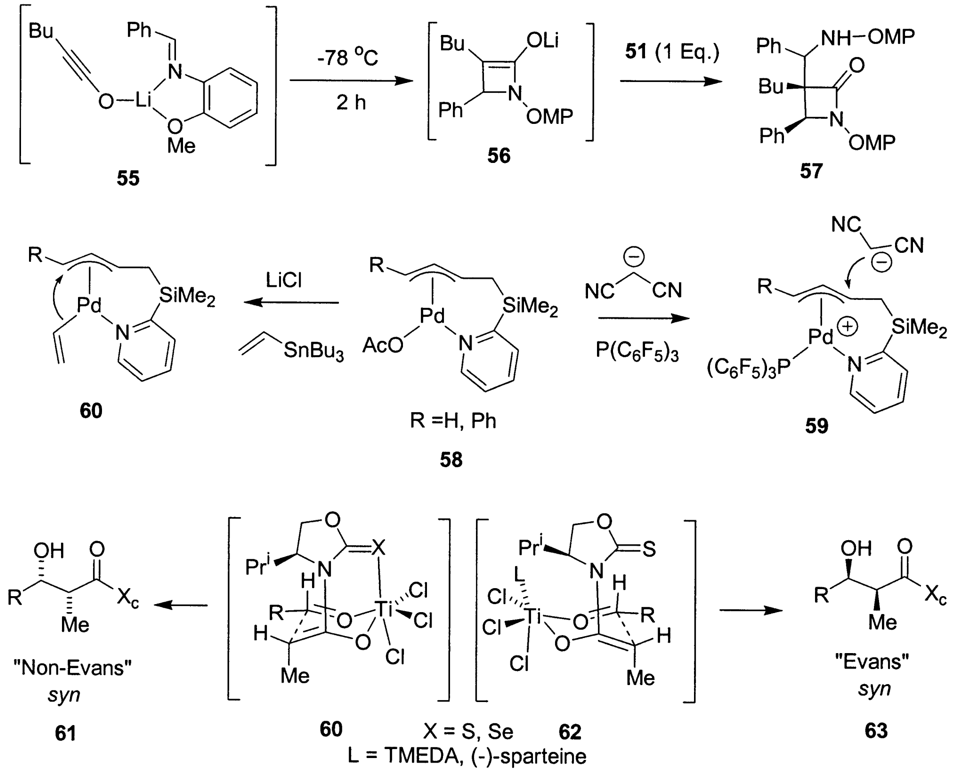
Table 6. Selected uses for 'reagent-directing groups'

RDG[a]	Reaction	Co-ordinated reagent/catalyst	Contact	Comments	Reference
47	C–H cleavage	$IrCl(CO)_2L_n$	Ir···P	Stoichiometric	99
48	Hydroformylation	$RhH(CO)L_n$	Rh···P	Catalytic	100
49	Conjugate addition	$[CuMe_2]^-$	Cu···P	Stoichiometric	100
50	Imino aldol[b]	Zr^{IV}-Br_2BINOL[c] or VAPOL catalyst	Zr···O,N	Nucleophile is Me_2C–COMe(OTMS)	71b,101
50	Imine allylation	Zr^{IV}-Br_2BINOL[c] or Cl_2BINOL[c] catalyst	Zr···O,N	Nucleophile is H_2C–$C(CH_2OH)CH_2SnBu_3$	102
50	Asymmetric Strecker synthesis	Zr^{IV}-Br_2BINOL[c]	Zr···O,N	Nucleophile is Bu_3SnCN	103
51	Cycloaddition	LiOC≡CR	Li···O,N	[2+2] Addition of lithium ynolate leads to β-lactam	104
52	Carbomagnesation	RMgCl	Mg···N		105
53	Allylic alkylation	PdL (L=Cl, PPh_3)	Pd···N	See Scheme 15	106
54b-c	Asymmetric aldol	$TiCl_x(amine)_y$	Ti···O	See Scheme 15	107

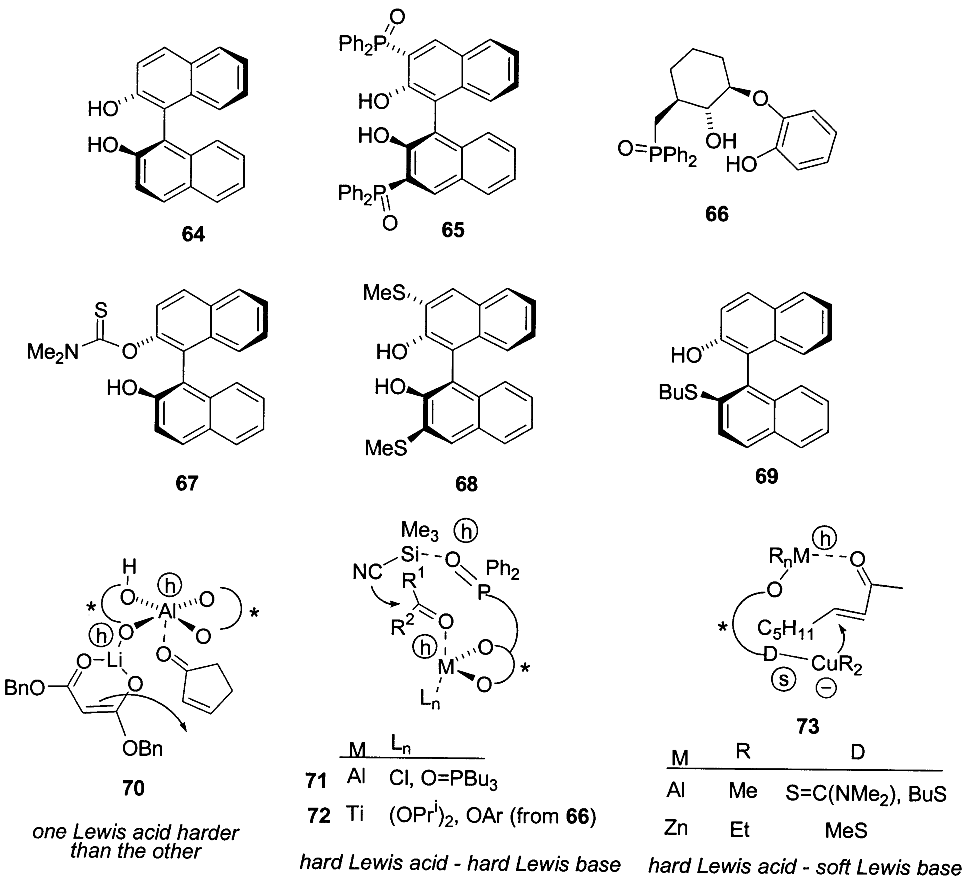
[a] 'Reagent directing group' used from Scheme 14.

[b] Also referred to as asymmetric Mannich chemistry.

[c] 6,6′- or 3,3′-dihaloBINOL.



Scheme 15.



one Lewis acid harder than the other

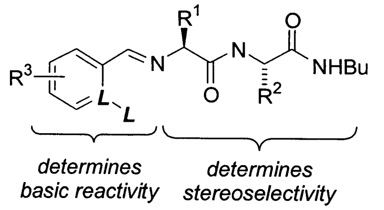
	M	L_n
71	Al	Cl, O=PBu$_3$
72	Ti	(OPr^i)$_2$, OAr (from **66**)

hard Lewis acid - hard Lewis base

M	R	D
Al	Me	S=C(NMe$_2$), BuS
Zn	Et	MeS

hard Lewis acid - soft Lewis base

Scheme 16.

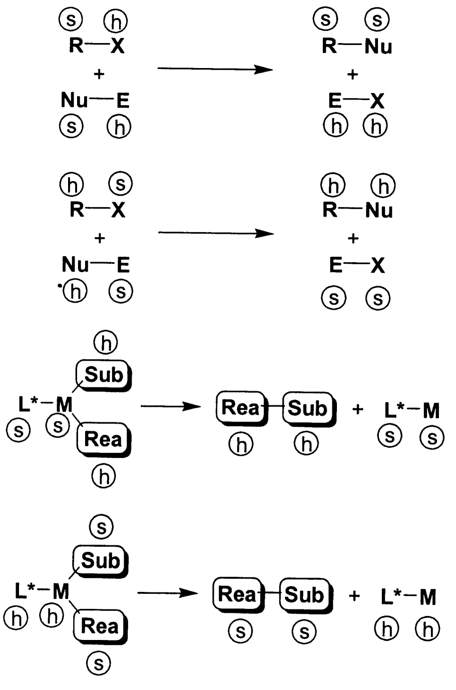


Catalyst for...	L-L	R^3
[Cu-catalysts]		
S_N2' addition to allylic phosphates	N	6-OPr^i
1,4-addition to enones	C-PPh$_2$	
[Ti-catalysts]		
CN addition to epoxides	C-OH	2-Np[a]
CN addition to imines	C-OH	3,5-Br$_2$
[Zr-catalysts]		
ZnEt$_2$ addition to imines	C-OH	

[a] Np = anchor is 2-naphthol based

Scheme 17. Modular ligands containing variable directing groups. R^1, R^2 are optimised substituents discovered by high throughput screening.

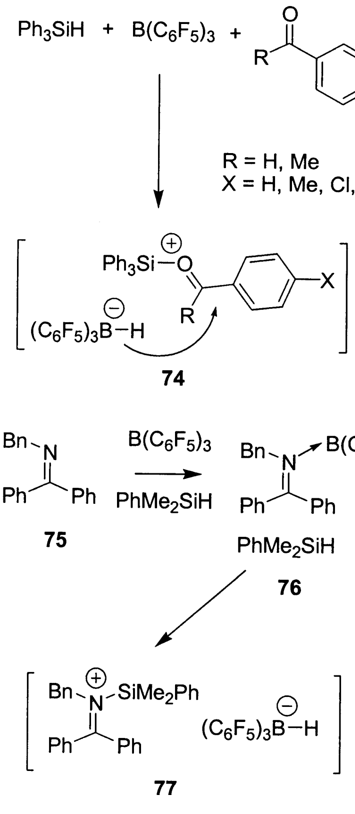
allylation of **53** with $Pd_2(dba)_3$ proceeds through **58** where, in the presence of $P(C_6F_5)_3$, key intermediate **59** is accessed allowing for nucleophilic attack *trans* to phosphorus. If instead LiCl is used as an additive then the derived chloride can be metathesised with organostannanes which reductively eliminate at the other allyl terminus. Both regioisomers can therefore be accessed by simple modification of the reaction conditions (Scheme 15).[106] Interesting HSAB factors are observed in the reaction of the Evans auxiliary analogues **54b**,**c**. Reaction of **54b** with $TiCl_4$ and one equivalent of $NEtPr^i_2$ and an aldehyde RCHO is proposed to lead to the chelate transition state **60** (X=S) containing a weak Ti···S=C contact.[107] This accounts for the formation of **61** (non-Evans, as it is the opposite enantiomer to that realised by **54a**/Bu_2BOTf under standard Evans conditions[108]). Similar non-Evans selectivity is realised using **54c** presumably also via **60** (X=Se). The mismatched titanium–sulfur contact in **60** can be cleaved by addition of a second equivalent of harder amine. Under these conditions the transition state reverts to the more normal dipole–dipole controlled form **62** and **63** is fashioned selectively (Scheme 15).



Scheme 18. Useful applications of Savile's rules in selective synthesis. Definitions: RX (a generalised alkyl halide), Nu (nucleophile), E (electrophile), L* (chiral ligand), M (catalytic metal centre), Sub (a generalised substrate), Rea (a generalised reagent).

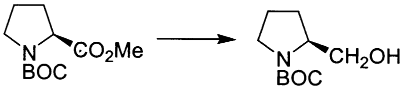
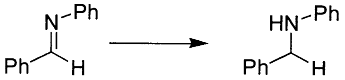
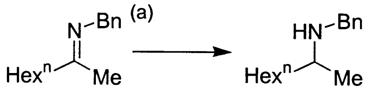
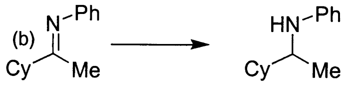
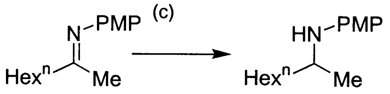
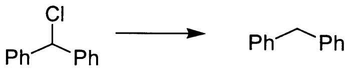
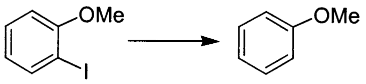
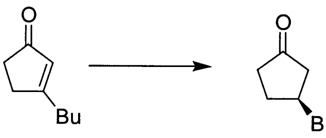
5.3. HSAB-based directing groups in catalysts

One of the nicest ways to exploit the HSAB principle in asymmetric catalysis is to build into the ligand architecture a function that can act as a weak anchoring point for an approaching achiral reagent. This strategy is clearly related to that in Section 5.2 except that a 'catalyst-directing group' (CDG) can carry out its task many times, as opposed to just once, making this approach inherently more efficient. Selected examples of asymmetric catalysts using this approach are given in Scheme 16. The lead in this area has been given by Shibasaki and co-workers.[109] In an early example they prepared Li[Al(BINOL)$_2$] from **64**, a species which is able to carry out Michael additions of malonates to cyclopentenone with unprecedented levels of asymmetric induction. ^{27}Al NMR studies revealed that the malonate binds exclusively to lithium, suggesting that transition state **70** is responsible for the observed enantioselectivity. It might be speculated that a difference in hardness between the two competing Lewis acids could account



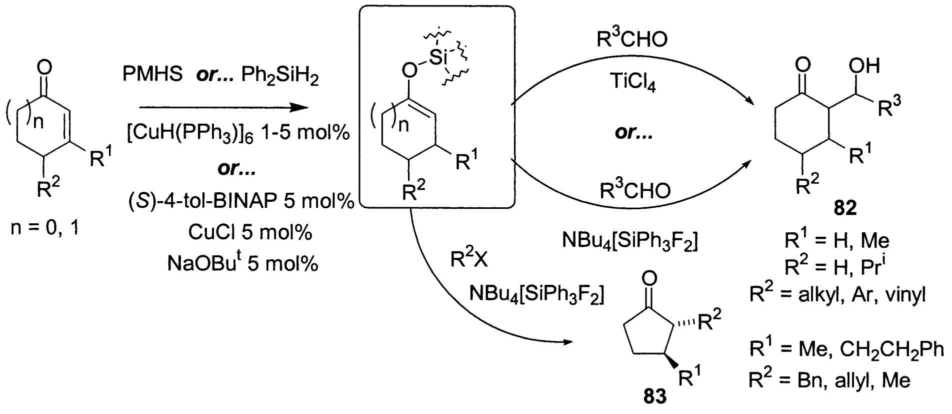
Scheme 19.

Table 7. Selected recent catalytic systems using PMHX **78** as a terminal hydride source

Transformation	Catalyst (mol%)	Yield (%)	Reference
A. Ester reduction			
$PhCO_2Me \rightarrow PhCH_2OH$	**79**/2EtMgCl (2)	93	119
	**79**/2EtMgCl (2)	70	119
B. Imine reduction			
	**80** (10)	82	120
	**80** (10)	81	120
	**81** (2)	63 (99% e.e.)	121
	**81** (2)	70 (88% e.e.)	121
C. Halogen reduction			
	Bu_3SnCl (20)	45	122
	Bu_3SnCl (10)	96	122
D. Conjugate reduction			
	CuCl/NaOBu^t/4-tol-BINAP	84 (98% e.e.)	123

[a] Bn=benzyl. [b] Cy=*cyclo*-C_6H_{11}. [c] PMP=4-MeOC_6H_4.

for the observed chemoselective complexation. More interesting examples come from species having both a Lewis acid and base within the same chiral catalyst. Shibasaki first attained catalysts of this type (**71**, **72**) either by reaction of **65** with Et_2AlCl[110] or by combination of **66** and Ti(OPr^i)$_4$.[111] The former catalyst promotes highly stereoselective TMSCN addition to aldehydes, the latter to ketones. This superlative reactivity is attained through HSAB ordering in **71**/**72** via aluminium (or titanium) co-ordination of the carbonyl and hypervalent expansion at silicon. Clearly, in catalysts relying on transition states of type **71**/**72** the parent ligand must be carefully designed



Scheme 20. Tandem conjugate Si–H addition/aldol or alkylation chemistry.

so that it does not inhibit itself through intra- or intermolecular self co-ordination. An alternative approach to avoiding such inactivation is to arrange for HSAB mismatching of the Lewis acid/base donors. This is the 'trick' utilised in ligands **67–69** which are thought to lead to transition states of type **73** when catalysing the addition of $AlMe_3$ or $ZnEt_2$ to aliphatic enones.[112] In a beautiful series of papers, Hoveyda has taken the concept of a CDG to its logical extreme,[113] and the basic reactivity of his modular peptide catalysts are modified by an appropriate anchor in the terminal position. Such modular ligand approaches combined with rapid parallel screening can lead quickly to identification of catalysts of superlative performance for a range of transformations (Scheme 17). It is apparent that, in some of these complex structures, positive identification of distinct parts of the ligand as specific directing groups is not always clear.

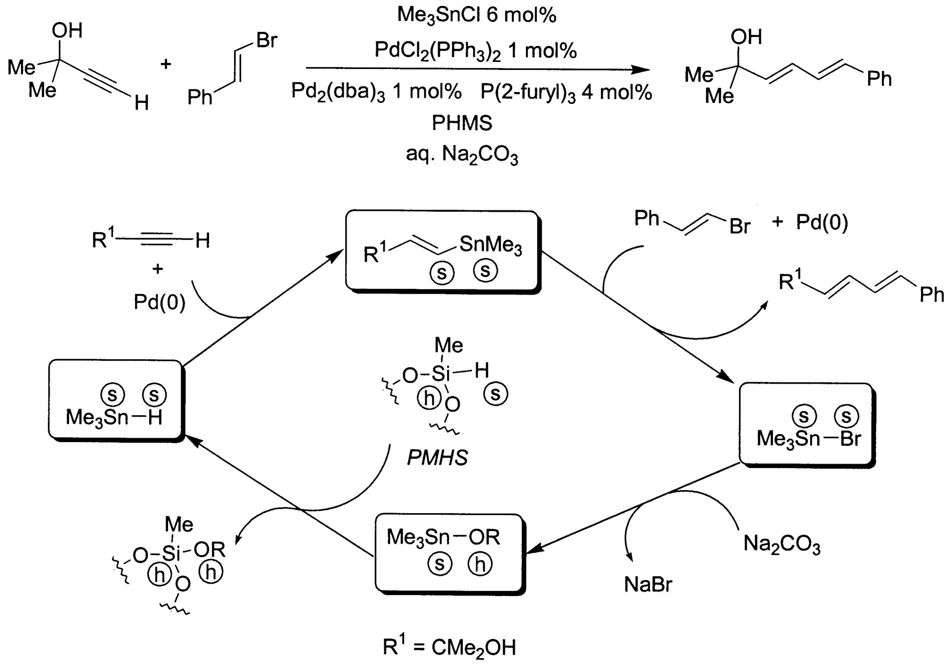
6. Saville's rules: HSAB matching and mismatching as reaction drivers

Saville's rules are a useful tool in HSAB-based chemistry to predict the sense in which an equilibrium will evolve based on the hard/soft nature of the reactants.[4,114] One form of the rules states that reaction of an alkylating agent R–X with a nucleophile (Nu) electrophile (E) pair is maximised when HSAB mismatching in the reagents is maximised (or conversely that in the products R–Nu and E–X is minimised) (Scheme 18). In the area of chiral catalysis a useful alternative statement of these ideas is also given in Scheme 18 where M represents the catalytic metal, L^* the chiral ligand, Sub a generalised substrate and Rea a generalised reagent. There are distinct advantages to keep only soft elements (metal and ligands) in the catalyst and only hard elements in the substrate/reagent pair. If a mismatched catalytic intermediate can be prepared, the system should evolve towards product formation. An additional advantage of this scenario is that it engenders strong co-ordination of the chiral ligand at the catalytic metal centre. These arguments also apply of course to situations where the soft elements are in the substrate/reagent pair and the metal/ligand pair are hard. In general, the most successful applications of these ideas have been to systems where a weak HSAB mismatched bond (e.g. B–H, Si–H, Si–S, etc.) is added across a polarised unsaturated π-system (normally carbonyls or enones). In some cases, however, HSAB matched systems [e.g. B–B, Si–Si bonds and O-atom abstraction by $Ti(OR)_4$ reagents] can be of use. Examples of HSAB mismatching/matching approaches are given in Sections 6.1–6.4.

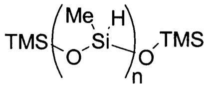
6.1. Reagents containing Si–H and B–H bonds

The high oxophilicity of boron and silicon makes their hydridic reagents ideal reducing sources for carbonyl compounds and for space reasons, this section concentrates on recent catalytic reactions. In most of these reactions the function of the terminal borane or silane reagent is to 'scrub' the product molecule from the catalytic centre, setting the stage for another turnover of the catalytic cycle.

The addition of Ph_3SiH to carbonyl compounds is promoted by 1–4 mol% $B(C_6F_5)_3$ (Scheme 19).[115] Binding studies indicate that the best substrates are those which bind least to the $B(C_6F_5)_3$ Lewis acid [e.g. k_{rel}(acetophenone)=$2.4k_{rel}$(benzaldehyde)]. The borane is believed to abstract the soft silyl hydride via a transient bridged hydride $[Ph_3Si–H–B(C_6F_5)_3]$ releasing harder Ph_3Si^+ which intercepts the carbonyl compound fashioning **74**. Collapse of the ion pair leads directly to the observed product. While **74** cannot be detected directly its presence can be inferred from model reactions of $Ph_3Si^+[B(C_6F_5)_4]^-$ with acetophenone which generates the cation in **74** but with a stable $[B(C_6F_5)_4]^-$ anion. Supportive evidence for this



Scheme 21. HSAB effects in one-pot hydrostannylation/Stille coupling. The OR group respresents a generalised hydroxide, alkoxide, or carbonate ligand.



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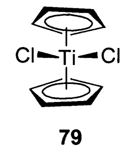

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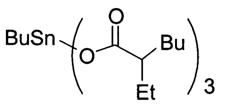

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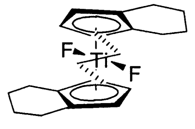


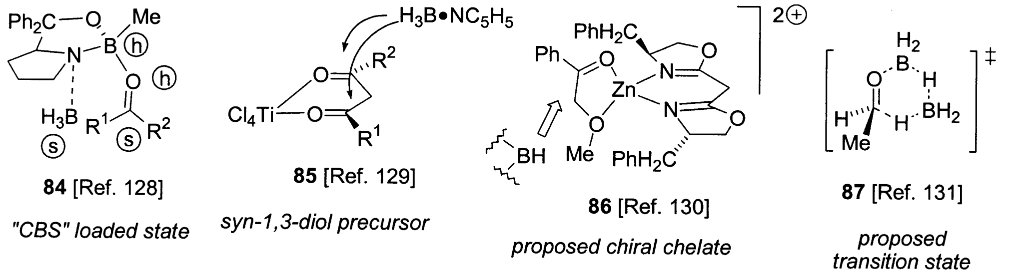
81

reaction mechanism is given by the equivalent reduction of ketimine **75** (Scheme 19),[116] which, with equimolar amounts of $PhMe_2SiH$ and $B(C_6F_5)_3$, leads to initial reaction of the borane with the imine yielding **76**. Over time, the formation of **77** can be detected by multinuclear NMR spectroscopy. It is not presently known however, if **77** is reduced by the borate or by a second molecule of $PhMe_2SiH$. Related $PhSiH_3$ reductions of aldimines and ketimines, formed in situ from the carbonyl compound and aniline, proceed under Bu_2SnCl_2 catalysis but the mechanism of this reaction is not known.[117]

Air stable polymethylhydrosiloxane (PMHS) **78** is an effective terminal hydride source to use in HSAB-based catalytic carbonyl reductions. The strength of the Si–O bond allows effective alkoxide exchange at the catalytic centre while the nucleophilicity of the PMHS can itself be promoted by use of hard anionic species, such as F^-, by formation of hypervalent 'ate' species. Similar arguments can be made for the reduction of imines and C–halogen bonds. The use of PMHS is the subject of a recent review[118] and only selected recent applications (using **78**–**81**) are given in Table 7. As conjugate addition of silanes to enones leads directly to silyl enol ethers there exists the possibility to use these directly in aldol or alkylation reactions. Lipshutz has demonstrated the former idea adding PMHS, amongst others, to cyclohexenones.[124] Subsequent reaction with aldehydes, under either $TiCl_4$ or fluoride promotion, leads directly to **82**. As an alternative Buchwald has utilised his (*S*)-4-tol-BINAP/CuCl system to provide key enol ethers in high enantiomeric purity from cyclopentenones.[125] These also undergo fluoride-promoted alkylation to provide **83** as essentially single stereoisomers (Scheme 20). In apparently closely related chemistry Morken and co-workers have carried out $[MCl(cod)]_2$ (M=Rh, Ir) catalysed reductive aldol reactions of acrylates in the presence of aldehydes and Et_2MeSiH,[126] but the mechanisms of these reactions have not yet been delineated.

Maleczka has demonstrated a one-pot hydrostannylation/Stille coupling sequence (Scheme 21) that is a nice example of exploiting HSAB mismatching effects in a catalytic cycle.[127] The redundant Me_3SnBr, generated by the first pass of Stille catalysis, is transformed into a mismatched Sn–OR species (OR most likely an alkoxide or carbonate-like species) via exposure to aqueous Na_2CO_3. This species is then susceptible to reduction by PMSH affording HSAB matched Me_3SnH. The latter participates in a palladium-catalysed hydrostannylation, the regiochemistry being controlled by the bulk of the R^1 substituent, to afford the matched vinyltin for the next Stille coupling.

The discussion of carbonyl reduction by boranes in this review is selective: details of reductions by oxazaborolidine 'CBS' catalysts are excluded as these are the subject of a recent review[128] but one HSAB approximation of the key transition state is given in structure **84** (Scheme 22).[128–131] Co-ordination of the hard carbonyl oxygen by hard Lewis acids is a key feature of most borane reductions, some selected recent examples of which are given in Scheme 22 (**85**, **86**). It is of note, that for BH_3, although the transition state **87** has been suggested, attempts to locate such a transition state computationally were not successful, questioning its validity. Few catalytic systems using boranes have been specifically designed to exploit the HSAB principle. DiMare and co-workers serendipitously discovered that alkoxides activate catecholborane towards carbonyl reduction via **88**—a mechanism that is essentially HSAB controlled



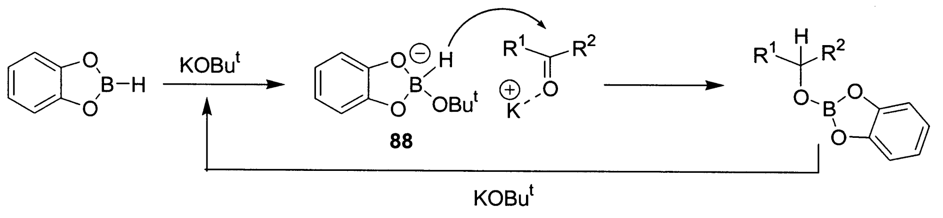
84 [Ref. 128]
"CBS" loaded state

85 [Ref. 129]
syn-1,3-diol precursor

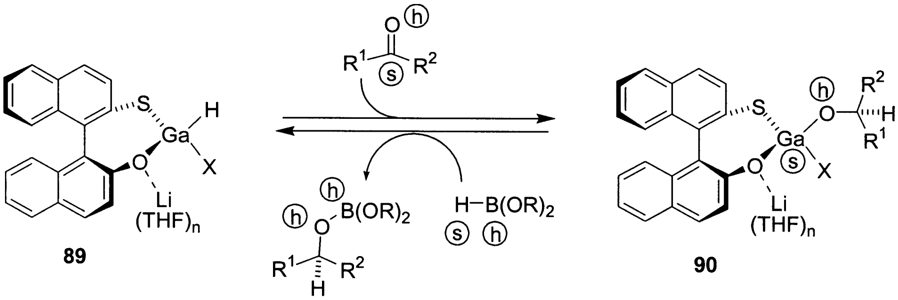
86 [Ref. 130]
proposed chiral chelate

87 [Ref. 131]
proposed transition state

Scheme 22.



Scheme 23.



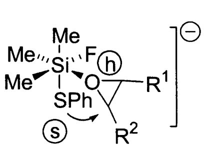
Scheme 24.

(Scheme 23).[132] In a more explicit approach, the gallium complex **89** has been proposed to reduce prochiral ketones by the mechanism of Scheme 24.[133] The role of the catecholborane is to liberate the product alkoxide from the gallium while the chiral ligand is retained. This proposal is clearly in line with Saville's rules, as outlined in Scheme 18, where species **90** constitutes the mismatched catalyst state. Consistent with these ideas the combination of the softer gallium catalytic centre and the softer thiolate ligand is crucial to the success of the reaction. This system is not perfect, however, since trace quantities of **88** provide competing catalysis and the system fails to duplicate the behaviour of the stoichiometric BINAL-H reagent from which it was developed. Additionally, the proposed hydride **89** could not be detected and so alternative mechanistic properties cannot be discounted.

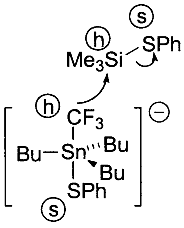
6.2. Reagents containing Si–S, Si–Se, B–S and Al–S bonds

Use of the reagents R_3SiSR was initially popularised by Evans, Mukaiyama, and others. The hard–soft mismatched interaction in these compounds is reflected in the low Si–S bond energy (213 kJ mol^{-1}, 51 kcal mol^{-1}; Table 2). These species add to carbonyl groups, imines, epoxides, Michael acceptors (and related electrophiles) but additionally can also activate other nucleophilic reagents by HSAB-favoured transmetallations. In all cases stronger matched bonding pairs are formed (Table 8). Mechanistic studies available on R_3SiSR species indicate reaction at silicon with strong σ-donors and at sulfur for Lewis/Brønsted acids; the former activation is considered first. Formation of *O*-silylhemithioacetals and dithioacetals constitute early examples of $Me_3Si–SR$ (R=Ph, Et, Me) use in the presence of Lewis bases.[134] The phenyl and ethylthio reagents can be activated by initiation with K(18-crown-6)X (X=CN, F) and the reaction is mediated by the presence of small amounts of RS^- (liberated by Me_3SiX formation) such that *O*-silylhemithioacetals result (Scheme 25). Typically *only* reactive substrates, e.g. aldehydes, participate under these conditions.

Such Lewis base-promoted reactions have some generality and can be applied to the preparation of Me_3SiCF_3 and thioesters, the regioselective opening of epoxides and promotion of conjugate addition of thiolates to Michael acceptors (Table 8). Fluoride-initiated reactions have also been used for the preparation of 4-thiazolidinones, via additions to imines, but they are not as stereoselective as Lewis acid-promoted reactions (see later). These Lewis base-promoted processes are proposed to proceed via hypervalent silicon or tin intermediates, structures **91** and **92** being typical. The mismatching in these species leads to rapid turnover.



91



92

An interesting tandem approach is Michael addition of PhSLi to acrylates followed by trapping of the resulting enolate with aldehydes.[152] Closure of the catalytic cycle is effected by subsequent reaction with Me_3SiSPh (Scheme 26). The high *anti* C(2)–C(3) selectivity could be rationalised by approach of the aldehyde to the more open enolate face of **93**. For hindered aldehydes, control of all three stereocentres can be achieved via transition state **94**; all of the C–C, C–S and O–Si bonds are formed under HSAB-matching conditions.

Lewis acids are potent activators of $R_3Si–SR$ reagents in the presence of carbonyl compounds. Both aldehydes and ketones react under these conditions to yield dithioacetals (ketals) and $Me_3Si–O–SiMe_3$ (Table 8).[134] If the Lewis acidity of the catalyst is attenuated (for example by the addition of imidazole), however, the *O*-silylhemithioacetals (ketals) can also be prepared by this route.[134] An alternative general approach to preparing such species is by combination of HSAB-matched Me_3SiOR^2 with mismatched Me_3SiSPh in the presence of a carbonyl compound.[135] Pivaldehyde, acetone, $Me_3Si–C{\equiv}C–CHO$ and aldehydes having hetero substituents β to the carbonyl group give poorer yields due to steric, electronic and Lewis acid co-ordination factors, respectively. Because of the lability of acetal and ketal product moieties to attack by Lewis acids these can be additionally used as attractive precursors for closely related chemistry in their own right (Table 8). In these systems formation of HSAB-matched $Me_3Si–OR$ is the driving force. Consistent with this idea, 5-ring cyclic acetals (ketals) do not react, presumably due to reversible closure of the $R^1C(SR)(CH_2CH_2OSiMe_3)R^2$ intermediate. A very nice example of a well-matched HSAB catalytic process is the synthesis of $R^1CH(SEt)R^2$ from a carbonyl compound, $Me_3Si–SEt$ and Et_3SiH.[138] Only a combination

Table 8. Catalytic reactions of HSAB mismatched Si–S, Si–Se, B–S and Al–S bonded reagents and accelerants

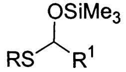
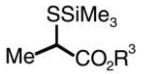
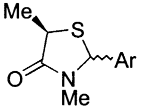
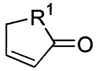
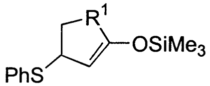
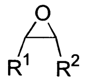
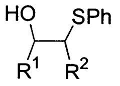
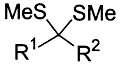
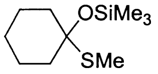
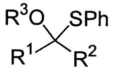
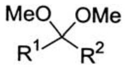
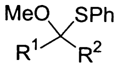
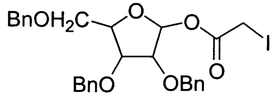
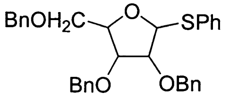
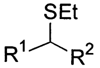
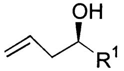
Substrate	R^1	R^2	Reagent(s)[a]	Catalyst/comments	Product	Yield (%)	References
A. Lewis base catalysed							
R^1CHO	Ph, $Me(CH_2)_4$	–	Me_3SiSEt	K(18-crown-6)CN (0.05 mol%)		82–95	134
$R^1CH{=}NMe$	Ph, 3-Py	–		Bu_4NF (2 mol%), poor *cis*/*trans* selectivity		36–67	135
	CH_2, $(CH_2)_2$	–	Me_3SiSPh	K(18-crown-6)CN (0.05 mol%)		88–100	134
	$Me(CH_2)_5$	H	Me_3SiSPh	Bu_4NF (2 mol%) followed by desilylation		63–88	136
	Ph	H					
	Me	CO_2Me					
Bu_3SnCF_3	–	–	Me_3SiSPh	Bu_4NF[b]	Me_3SiCF_3	85	137
R^1COCl	$Me(CH_2)_6$, Pr^iCH_2, $MeCH{=}CH$, Ph		Me_3SiSEt	K(dicycloheyyl-18-crown-6)F (6 mol%)	R^1COSEt	85–98	138
B. Lewis acid catalysed							
$R^1C({=}O)R^2$	$Me(CH_2)_5$	H	Me_3SiSMe	ZnI_2 (0.3 mol%)		85–93	134
	Pr^i	H					
	$-(CH_2)_4-$	–					
$R^1C({=}O)R^2$	$-(CH_2)_5-$	–	Me_3SiSMe	ZnI_2 (0.3 mol%) plus imidazole (1.5 mol%)		88	134
$R^1C({=}O)R^2$	Me, Et, Pr^i	H	Me_3SiSPh	Me_3SiOTf (4–10 mol%), lowest yield with ketone		40–81	139
	Ar	H	Me_3SiOR^3; $R^3{=}CH_2CH{=}CHR$ or CH_2Ar				
	Me	Me					
	$Me(CH_2)_7$	H	Me_3SiSPh	Me_3SiOTf (30 mol%)		98	140
			Me_3SiSPh	$SnCl_2$ (20 mol%)		46	141
$R^1C({=}O)R^2$	$Ph(CH_2)_2$	H	Me_3SiSEt	$InCl_3$ (20 mol%) plus Me_3SiCl (50 mol%)		81–98	142
	$Me(CH_2)_7$	H	Et_3SiH				
	Ph	Me					
	$-(CH_2)_5-$	–					
R^1CHO	$Ph(CH_2)_2$	–	Me_3SiSPr^i	(*R*)-(BINOL)-Ti^{IV} catalyst **102** (5 mol%), followed by desilylation		60–83 (83–95% ee)	143

Table 8. (*continued*)

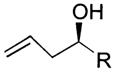
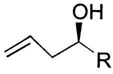
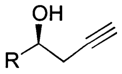
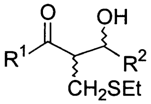
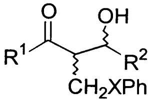
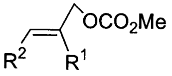
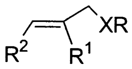
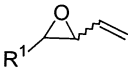
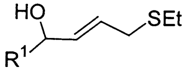
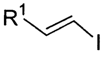
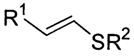
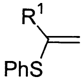
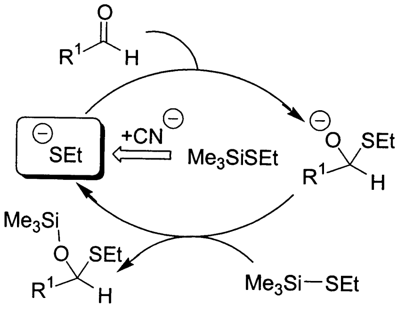
Substrate	R^1	R^2	Reagent(s)[a]	Catalyst/comments	Product	Yield (%)	References
	Hex^n	–	$Bu_3SnCH_2CH{=}CH_2$				
	Cy	–					
	Ph	–					
R^1CHO	$Ph(CH_2)_2$	–	Et_2BSPr^i	(*R*)-(BINOL)-Ti^{IV} catalyst **102** (5 mol%), followed by desilylation		67–89 (88–95% ee)	144
	Hex^n	–	$Bu_3SnCH_2CH{=}CH_2$				
	Cy	–					
	Ph	–					
R^1CHO	$Ph(CH_2)_2$	–	Et_2AlSPr^i	(*R*)-(BINOL)-Ti^{IV} catalyst **102** (5 mol%), followed by desilylation		45–91 (57–85% ee)	144
	Hex^n	–	$Bu_3SnCH_2CH{=}CH_2$				
	Cy	–					
	Ph	–					
R^1CHO	$Ph(CH_2)_2$	–	Et_2BSPr^i	(*R*)-(BINOL)-Ti^{IV} catalyst **102** (5 mol%), followed by desilylation		52–86 (91–95% ee)	145
	Hex^n	–	$Bu_3SnC(H){=}C{=}CH_2$				
	Cy	–					
	Ph	–					
	Pr^iCH_2	–					
$R^1COCH{=}CH_2$	Me	Ph	Me_3SiSEt	EtSSnOTf (10 mol%) followed by desilylation		48–76	146,147
	Me	$Ph(CH_2)_2$	R^2CHO	*syn*/*anti* ~90:10			
	Ph	$Ph(CH_2)_2$					
$R^1COCH{=}CH_2$	Me, Et	Me, Et, Pr^i, Bu, Ph	Me_3SiXPh (X=S, Se), R^2CHO	Chiral (acyloxy)borane **106** (20 mol%) followed by desilylation, *syn*/*anti* ~95:5		55–88 (50–96% ee)	148
$R^1CO_2SiMe_3$	Me	–	Me_3SiSAr (Ar=Ph, 4-$MeOC_6H_4$)	$TiCl_4$ (10 mol%) and AgOTf (30 mol%)	R^1COSAr	88–95	149
	Bu^t	–	$(4\text{-}F_3CC_6H_4CO)_2O$				
C. Palladium catalysed							
	CH=CHMe	Me	Me_3SiXR (XR=SEt, SPh)	$Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and $P(OPr^i)_3$ (30 mol%)		68–95	150
	Me	Prenyl					
	$Ph(CH_2)_2$	–	Me_3SiSEt	$Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and $P(OPr^i)_3$ (30 mol%)		81	150
4-$R^1C_6H_4I$	H	Ph, Bu^s	9-BBN-SR^2	$PdCl_2(dppf)$ (3 mol%)	4-$R^1C_6H_4SR^2$	87–91	151
	Me	Bu^t	K_3PO_4				
	NMe_2						
	CO_2Me						
	CN						
	$Me(CH_2)_3$	4-MePh	9-BBN-SR^2	$PdCl_2(dppf)$ (3 mol%)		91–99	151
	Ph	Bu^s	K_3PO_4				

Table 8. (*continued*)

Substrate	R^1	R^2	Reagent(s)[a]	Catalyst/comments	Product	Yield (%)	References
$R^1C{\equiv}CH$	Bu^t C_8H_{17} $Cl(CH_2)_3$ $NC(CH_2)_3$ $Ac(CH_2)_4$	Ph	9-BBN-SPh	$Pd(PPh_3)_4$·(3 mol%)		69–81	151

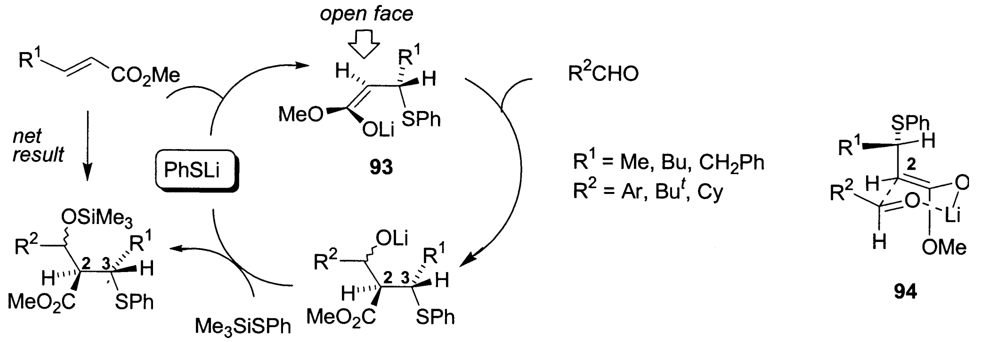
[a] HSAB miss-matched reagents.

[b] Precise catalytic loading not given, estimated at ~3 mol%.

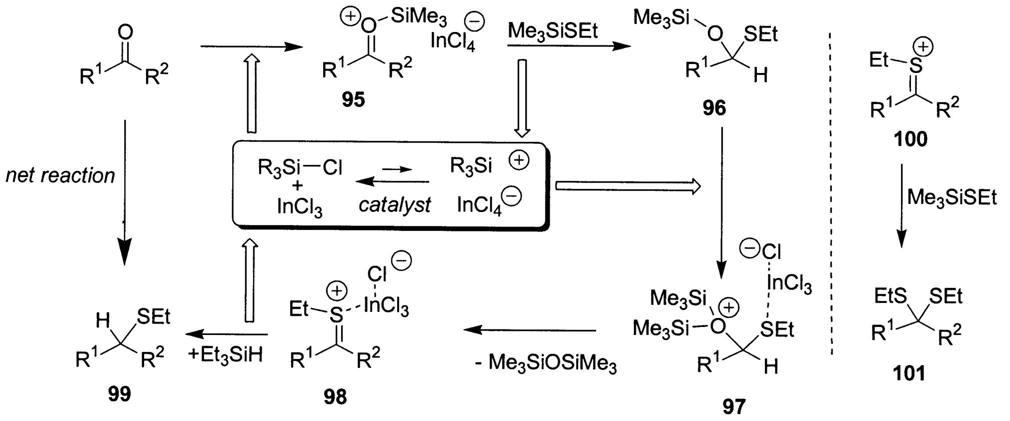


Scheme 25.

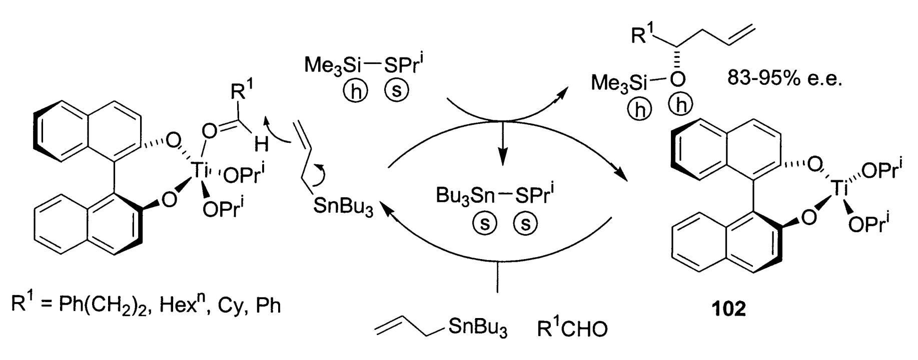
of Me_3SiCl and $InCl_3$ is highly efficient in catalysis of this reaction. One interpretation of this result is shown in Scheme 27. Activation of the carbonyl oxygen of the starting material is achieved in **95** using the hard–hard interaction provided by '$Me_3Si^+[InCl_4]^-$'. This allows soft–soft C–S bond formation at the carbonyl carbon fashioning **96** and returns the catalyst. The nature of the intermediates leading to the sulfide $R^1CH(SEt)R^2$ can only be speculated ont, but the observed chemoselectivity is likely to result through hard–hard activation of the trimethylsiloxy group in an intermediate of type **97** which collapses to **98**. A soft–soft substrate–$InCl_3$ association might explain the formation of *only* **99** through subsequent



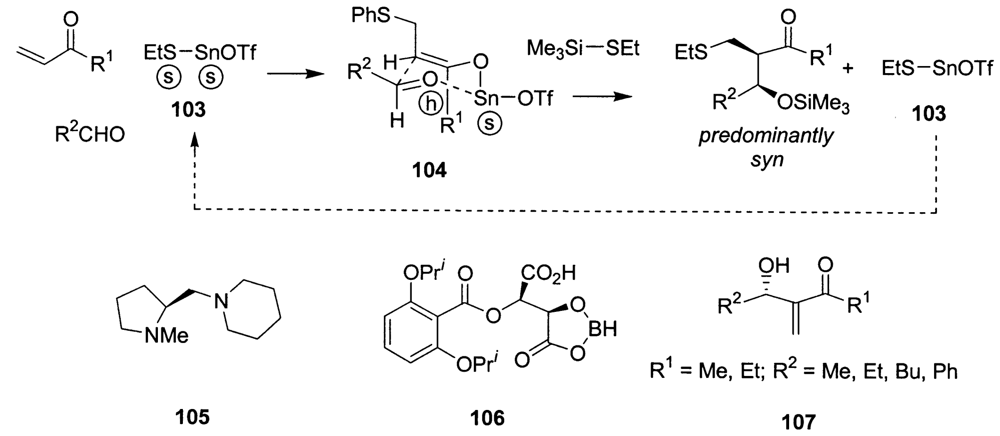
Scheme 26.



Scheme 27. Mukaiyama synthesis of sulfides. R=Me (first cycle), Et (subsequent cycles); R^1=Ph, $Ph(CH_2)_2$, $Me(CH_2)_2$; R^2=H, Me (not all combinations of R^1/R^2 used).



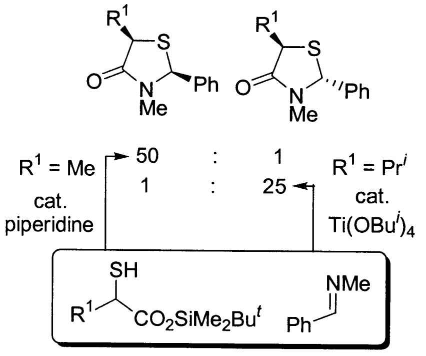
Scheme 28.



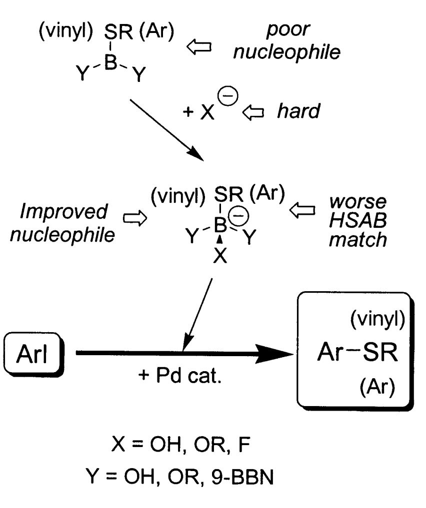
Scheme 29.

attack of Et_3SiH with generation of a new catalyst carrying an Et_3SiCl component. Such a soft–soft interaction in **98** can be postulated, based on the observation that harder Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$, Me_3SiOTf, Me_3SiI) catalyse only the disproportionation of **96** to dithioacetals (ketals) **101** via the formally identical thionium species **100**. Alternatively, Mukaiyama has argued that the chemistry is driven by the strength of the Si–O interaction in **97** alone, with *no* interaction with indium species.

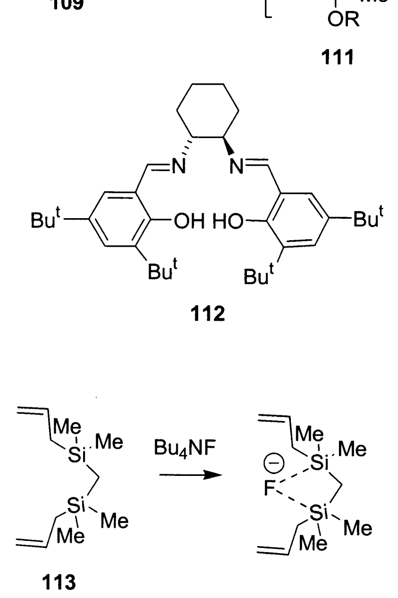
Yu has beautifully applied the HSAB-matching approach in catalytic asymmetric syntheses of homoallylic alcohols (Scheme 28).[143,145] The high enantioselection in these reactions is realised by reaction of allyltributyltin with BINOL-Ti^{IV} co-ordinated aldehydes. After the carbonyl addition, however, product dissociation is disfavoured by the presence of relatively strong Ti(catalyst)···O–alkoxide (hard–hard) interactions as Sn–O product bond develops. By adding Me_3SiSPr^i (1.2 equiv.) to efficiently sequester the reaction product, catalyst **102** is freed for the next cycle. The strong rate acceleration realised by this approach allows these reactions to reach completion in a few hours at −20°C using 5 mol% Ti^{IV}. Even at 1 mol% catalyst loading,



Scheme 30.



Scheme 31.



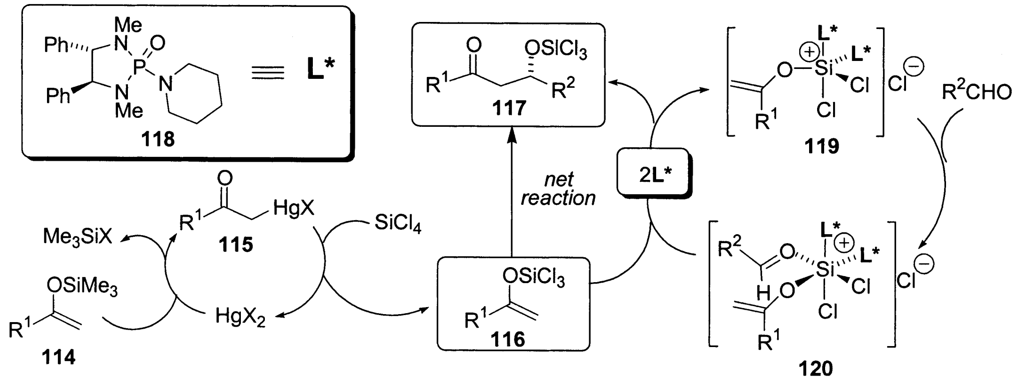
Scheme 32.

useful levels of enantioselectivity are realised (61–91% ee).[143] This approach is quite powerful and Yu has extended it to other mismatched promoters: Et_2BSPr^i and Et_2AlSPr^i. The former promoter allows efficient asymmetric aldehyde prop-2-ynylation (Table 8).

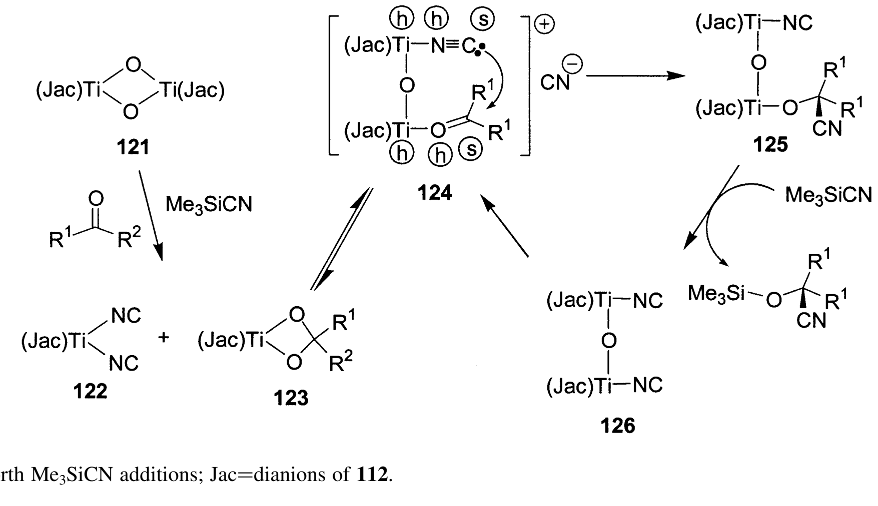
In a series of seminal papers, Mukaiyama introduced tin triflate-derived Lewis acid catalysts for the conjugate addition of Me_3SiSEt to enones and trapping of the resultant tin enolates with aldehydes (Scheme 29, Table 8). The preparation of the matched intermediate **103** is still overcome by the inherent weakness of the Si–S bond in the accelerant. In its original format this reaction is not suitable for asymmetric synthesis as the Lewis acidity of the tin centre is so reduced by the addition of amine **105** that a chiral analogue of transition state **104** cannot be realised and only simple conjugate addition products (as opposed to tandem ones) are obtained. This problem has been overcome by Barrett, who has introduced the use of $Me_3SiSePh$ in the presence of catalyst **106**. Treatment of the intial *syn*/*anti* mix with H_2O_2 leads to spontaneous elimination of the derived selenoxides fashioning a succinct route to the Baylis–Hillman products **107** (50–96% ee).

Because of the delocalisation associated with carboxylate anions the oxygen is softer than that of a simple alkoxide and, coupled to an apparently weakened $C_{carbonyl}–OSiR_3$ bond strength compared to normal esters, this allows for facile ester (or amide) formation under appropriate conditions. A simple example is the diastereoselective formation of 4-thiazolidinones under piperidine or $Ti(OBu^i)_4$ catalysis (Scheme 30).[135] By using electronic control in related reactions it is possible to carry out thioesterifications using Me_3SiSPh and $(4\text{-}F_3CC_6H_4CO)_2O$. The hardening of the carbonyl substituent in the electron-deficient anhydride leads to selective ester formation. In general, < 0.5% of $4\text{-}F_3CC_6H_4COSAr$ is formed (Table 1).[149] Stoichiometric reactions[153] based on similar ideas have also appeared, together with a useful preparation of vinyl sulfides from silyl enol ethers.[154]

The use of late transition metal Lewis acids in R_3SiSR activation has been rather limited. This is not overly surprising as most of the platinum metals show rather strong M–SR bonds due, in part, to the well-matched soft–soft interactions. In a few instances, this problem has been overcome in palladium-catalysed chemistry. Trost has used carbonates and epoxides as superlative leaving groups in the synthesis of allyl sulfides using Me_3SiSR to overcome any unfavourable energetics (Table 8).[150] Activation of B–S and Si–S bonds by $PdCl_2(dppf)$ has been used for thiolation of vinyl and aryl iodides (Table 8), the 'trick' to making the rather stable well HSAB-matched catalytic intermediates turnover in these cycles being the use of K_3PO_4 as the promoting base. The formation of strong hard–hard matched B–O bonds in the nucleophilic coupling partner



Scheme 33. Denmark's Lewis base catalysed asymmetric aldol technology. R^1=alkyl, R^2=aryl, vinyl, or Bu^t for most effective reactions.



Scheme 34. Belokon'-North Me_3SiCN additions; Jac=dianions of **112**.

Table 9. Selected additions of reagents containing Zn–C, Sn–C bonds to O=CR^1(R^2)

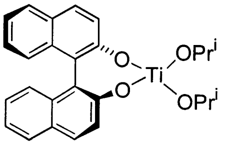
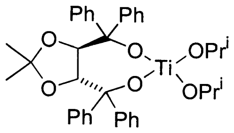
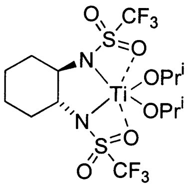
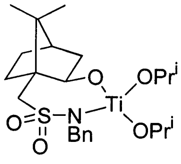
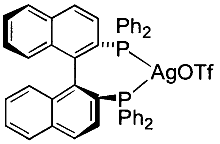
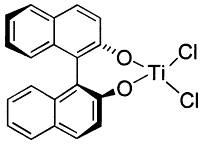
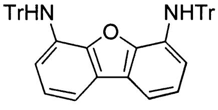
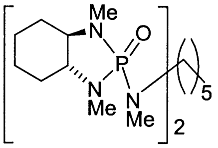
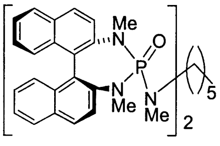
R^1	R^2	Reagent	Catalyst	Additive	Comments	Reference
A. ZnR$_2$/Ti(OPr^i)$_4$ systems						
Aryl, alkyl, CH=CHR, CCSiR$_3$	H	ZnR$_2$, R=Me, Et, Bu, Pent^n	 **102** 10–20 mol%	Ti(OPr^i)$_4$ 1.2–1.4 equiv.	High yield, typically ~85–99% ee for Ph, 4- or 3-substituted Ph; ee suffers (60–70%) if 2-substituted Ph or ZnMe$_2$ used	167, 168
Aryl, alkyl, CH=CHR, CCMe	H	ZnR$_2$, R=Et, alkyl, vinyl	 **127** 5–20 mol%	Ti(OPr^i)$_4$ 1–2 equiv.	High yield, typically >95% ee	169
Aryl, alkyl, CH=CHR	H	ZnR$_2$, R=Me, Et, Bu, Pent^n, (FG–R)[a]	 **128** 4–8 mol%	Ti(OPr^i)$_4$ 1.2–2.2 equiv.	High yield, typically ~90–99% ee	170,171
3-py, 4-py, (CH$_2$)$_2$PPh$_2$	H	ZnR$_2$, R=Et, Bu, Pent, (CH$_2$)$_4$OPiv[a]	**128**, 8 mol%	Ti(OPr^i)$_4$ 1–2 equiv.; BR$_3$ (1 equiv., R=Et, H)	High yield, typically ~85–95% ee BEt$_3$ for pyridyl substrates; BH$_3$ for phosphines	172
Hex^n, Cy, CH$_2$CH$_2$Ph	H	ZnEt$_2$	 **129**	Ti(OPr^i)$_4$ 1.3 equiv.	73–93% ee, ArCHO give negligible selectivity	173
Ph	Me, Et, Bu^n	ZnR$_2$, R=Me, Et	**129**, 20 mol%	Ti(OPr^i)$_4$ 1.3 equiv.	Yield ~55–95%, 72–89% ee. Slow reaction; PhCOBu^t and α-tetralone do not participate	174
B. Organotin reagents						
2-MeOPh, 4-MeOPh	H	Bu$_3$Sn(allyl)[b]	B(C$_6$F$_5$)$_3$ 20–100 mol%	–	Allyl abstraction mechanism	175
Aryl, CH=CHR, (CH$_2$)$_2$Ph	H	Bu$_3$SnR, R=CH$_2$CMe=CH$_2$, CH$_2$CH=CHMe	 **130**	–	Yield ~60–95, ee ~90–97%; for crotyltin *anti/syn* ~5.7:1. Alkyl substrate poor (low yield, 70% ee)	176
Aryl	Me	Sn(allyl)$_4$[b]	 **131** 10–20 mol%[c]	–	Yield ~70–90%, ee 55–81%	177

Table 9. (*continued*)

R^1	R^2	Reagent	Catalyst	Additive	Comments	Reference
Ph, 2-$C_{10}H_7$	Me	Sn(allyl)$_4$[b]	**102** 60 mol%[b]	 30 mol%	Yield 95–98%, ee 90–92%	178
Ph	H	$Cl_3Si(allyl)$[b]	 **132** 10 mol%	–	Yield 49, 80% ee	180
Ph, 2-$C_{10}H_7$, CH=CHPh		$Bu_3Sn(prop)$[d]	 **133** 5 mol%	$SiCl_4$	Excellent yield, 87–93% ee	181

[a] Piv=COBu^t.

[b] Allyl=CH_2CH=CH_2.

[c] Catalyst obtained from a mixture of $TiCl_2(OPr^i)_2$ and BINOL **64** structure **131** is the assumed product.

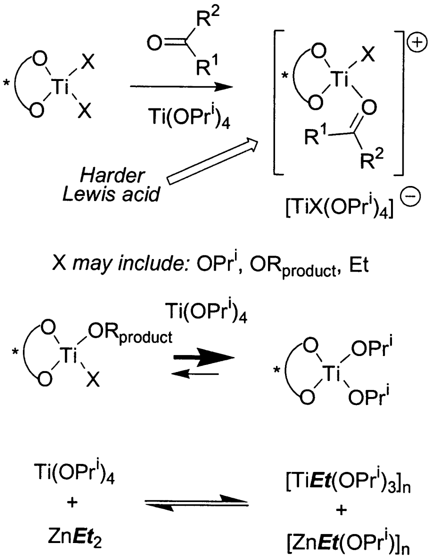
[d] Prop=CH_2=C=CH_2.

and inorganic by-products drives the reaction to completion (Scheme 31).[151] These effects are analogous to those observed in Suzuki-based couplings of boronic acids and related species where addition of strong σ-donors to the boron harden this centre. The resulting mismatch in the B–S (or B–C) bond together with anionic charge dramatically improves the reagent's nucleophilicity.[155] Care must be taken not to over exploit the HSAB principle as in these complex palladium systems the full bond energetics are not normally known.[156]

6.3. Reagents containing Si–C, Si–OCR(=CR$_2$) and Al–C bonds

If it is accepted that Me_3SiCF_3 and Me_3SiCN act as incipient sources of the soft stabilised carbanions F_3C^- and CN^-, then the HSAB descriptions **108** and **109** are appropriate (Scheme 32). The mismatching in these reagents renders them energetically predisposed for addition across polar π-bonds (Scheme 1, Table 1). Progress in the use of Me_3SiCF_3 is the subject of a recent review[157] and only mechanistic features are considered here. Hard Lewis bases, especially F^- and alkoxides, lead to the formation of hypervalent **110**. While CsF is an effective promoter, the HSAB principle favours decomposition to Me_3SiF and CsF, the best choice for these reactions being $[NBu_4][Ph_3SiF_2]$ (TBAT); tetrabutylammonium fluoride is ineffective as its hygroscopic nature causes hydrolysis of **108**. The TBAT 'trick' is particularly effective for additions of **108** to imines.[158] Langlois has offered an alternative strategy based on mixtures of HCF_3 and $N(SiMe_3)_3$ in reactions with ketones, the final product distribution being consistent with Saville's rules (Scheme 18).[159] Similar HSAB-controlled Lewis base activation of **109** is favoured. Of particular note are the contributions of Kagan who has employed lithium monoanions of BINOL **64** or Jacobsen's ligand **112** to fashion chiral versions of **111** which alkylate benzaldehyde in 56–86% ee[160] While fluoride and alkoxide promotion of Me_3SiCF_3 and Me_3SiCN are highly effective, the transfer of other organofunctions is problematic. Effective allylation can, however, be achieved by use of *bis*(allyl)silanes, such as **113**, which can be activated by Bu_4NF and used in PhCHO allylation. The chelate nature of **113** is crucial in attaining HSAB activation, since Me_3SiCH_2CH=CH_2 is ineffective as an allyl source in the presence of fluoride (Scheme 32).[161] The superlative enantioselectivity shown by Shibasaki's catalyst **65** (in the presence of Et_2AlCl, Scheme 16) has already been discussed and recent mechanistic studies support the presence of both hypervalent silicon and aluminium in transition states **71** and **72**.[162]

Denmark has used a related approach in designing novel aldol processes (Scheme 33), and a rich vein of HSAB reactivity runs through this chemistry.[163] The trichlorosilyl enolates **116** are converted to **117** in the presence of chiral Lewis base **118** in high enantiomeric excess. The starting material **116** for this catalytic reaction is prepared by mercury(II)-catalysed *trans*-silylation of TMS enol ethers **114** via **115.** Every step of these cycles represents an HSAB-matched encounter. In the asymmetric aldol reaction **116** captures 2 equiv. of ligand **118** which causes ionisation of one Si–Cl bond leading to **119**. This cation is a much more effective (and harder) Lewis acid than **116** and this efficiently captures the aldehyde R^2CHO generating **120**. Collapse of the latter species gives the final product of the



Scheme 35. Activation of **L**Ti(OR)$_2$ and related species. The ligand L (**102**, **127–129**) is shown by a strap.

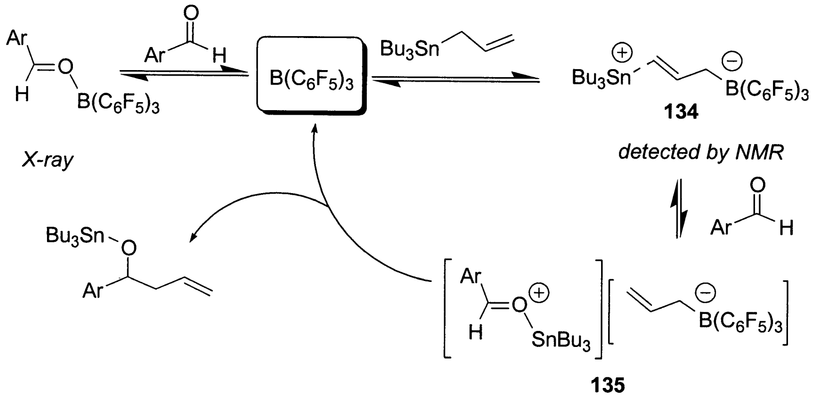
reaction, regenerating **118** for use in the next cycle. In order to attain the highest enantioselectivities it is important that the effective concentration of **118** remains high. If this is depleted, the competition from mono ligated cations results and these species show lower selectivity. Base **118** has also been used for aldehyde allylation and propargylation and for the opening of epoxides. The former reactions are considered in Section 6.4 while the latter is currently an area of controversy.[164] From an HSAB perspective, the opening of epoxides by AlEt$_3$ demonstrated by Schneider is a lot more interesting. These reactions are strongly promoted by catalytic amounts of EPh$_3$ (E=P, As, Sb; 5 mol%), but amines are totally ineffective. It is likely that the hard–soft Et$_3$Al·EPh$_3$ reagents which are formed suffer weakening of the Al–Et bonds, facilitating alkylation, but that the mismatching promotes catalyst dissociation, leading to promotion of the next cycle.[165] Similar chemistry may be promoted using soft Arduengo-type carbenes.

Activation of Me$_3$SiCN by Lewis acids is also possible. Within the context of this review the most interesting system is that of Belokon', North and co-workers (using **121** as a catalyst precursor).[166] This uses a catalyst based on the Jacobsen ligand **112** (Scheme 34; Jac=dianion of **112**). Under the reaction conditions the crystalline precatalyst is transformed into catalytically inactive **122**/**123**. Kinetic data reveal that these species are in equilibrium with a key dimeric species, proposed to be **124**. Consistent with the HSAB characteristics the cyanide is N-bound and predisposed to cyanate the bound carbonyl compound. The reaction kinetics show zero order dependence on carbonyl concentration, indicating that carbonyl co-ordination in **124** is facile. Salt **124** then collapses to **125** and the catalytic cycle is completed by Me$_3$SiCN-promoted stripping of the product from the titanium centre leading to **126**. It is important to note that, although **124** is a completely matched HSAB system, the substrate binding is very weak and thus the favourable bond energetics in the product force its evolution.

6.4. Reagents containing Zn–C and Sn–C bonds

A myriad of organometallic and related reagents add to carbonyl compounds, imines and related acceptors in reactions which can all, to a greater or lesser extent, be described as HSAB controlled. In this section, only recent zinc and tin reactions which demonstrate instructive hard–hard, soft–soft interactions are presented. Selected examples (using species **102** and **127–133**) are given in Table 9. It should be further noted that the work of Yu (Scheme 28) has already been described.

The alkylation of aldehydes, and occasionally ketones, by ZnR$_2$ reagents in the presence of chiral chelate ligands and Ti(OPr^i)$_4$ is particularly instructive. From an HSAB perspective, all of these reactions are identical (Scheme 35). The Ti(OPr^i)$_4$ is thought to play two roles: firstly, the abstraction of alkoxides from the precatalyst or rest state;[169] and secondly it is implicated in the formation of the active alkylating agent. Both of these transformations are HSAB/bond energy controlled but, in the latter case, NMR studies reveal that the speciation is complicated by aggregation effects.[170a] Knochel has used the HSAB concept to good effect in the alkylation of aldehydes containing either pyridyl or phosphine substituents—classes of compounds which perform very poorly under normal titanium-catalysed conditions. By picking appropriate Lewis acid additives (BEt$_3$ for –C$_6$H$_4$N; BH$_3$ for –PPh$_2$) competitive

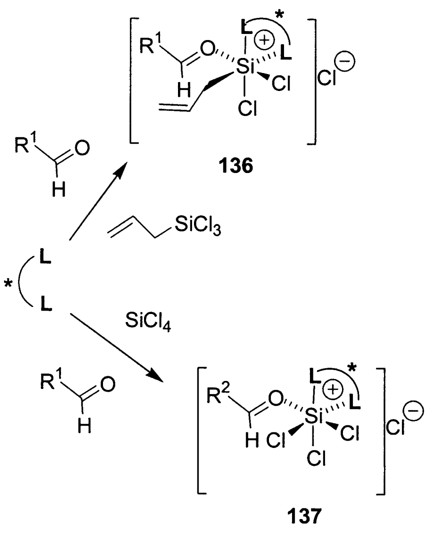


Scheme 36.

co-ordination of these groups is suppressed, allowing the reaction to proceed with enantioselectivity.[172]

Very recently Piers has demonstrated that abstraction processes are also important in $B(C_6F_5)_3$-catalysed allylation reactions.[175] While $B(C_6F_5)_3$ binds aldehydes as expected, the catalytic reaction shows substrate inhibition, indicating that this is not important to the reaction cycle. Multinuclear NMR studies (at −60°C) revealed clean formation of the borate **134**, presumably driven by the disparate Sn–C/B–C bond energies (Scheme 36) (Table 1). This smoothly adds aldehydes, yielding the ion-pair **135**, which can also be detected by ^{19}F NMR spectroscopy. Interestingly, formation of **135** is fastest with *O*-anisaldehyde, presumably as the hard Bu_3Sn^+ cation is favoured by chelation in this substrate. On warming to room temperature **135** expels the addition product, regenerating $B(C_6F_5)_3$.

HSAB factors can work both in favour of, or against, catalytic cycles. Compare the first three allylation reactions of section B, Table 9. Aldehyde methallylation or crotylation promoted by **130** has in place the factors that allow it to exploit Saville's rules (Scheme 18). The catalyst integrity is helped by the very soft–soft nature of the metal–ligand interaction while the developing Sn–O bond of the kinetic alkoxide product is sufficiently harder to promote facile reaction. In the titanium-based systems (**102** and **131**) the situation is reversed, and it is the hard elements that are present in the catalyst metal and ligand. These are, however, now quite similar in HSAB characteristics to the substrate/reagent manifold and this can cause problems. In particular, **131** suffers from competing background reactions at lower catalyst loadings. The origin of this effect was first discovered by Young.[179] As the reaction progresses, the transfer of allyl groups results in increased concentrations of $[Sn(OR_{product})_n(allyl)_{4-n}]$, with $n=2,3$. This hardens the tin centre (the so called symbiosis effect[4]), leading to greater mismatch in the Sn–C bond and thus greater background reactivity. Finally, Denmark's Lewis base-promoted aldehyde allylations (and propargylations) also rely on HSAB hardening to achieve efficient catalysis. For the allylations selected, this is achieved by ionisation of the allylchlorosilane to generate an intermediate **136** akin to that in their aldol process (Scheme 37).[180] In a recent development, $SiCl_4$ has been transformed from a weak Lewis acid to a strong hard **137** which is able to co-ordinate aldehydes and thus activate them for attack of organotin reagents.[181]



Scheme 37. Chiral ligands **132–133** as shown as a representative strap.

7. Conclusions and outlook

Given the generality of the HSAB principle, no review in this area can aim to be comprehensive. Within the space available, little can be done but to update the reader on current thoughts on HSAB theory and to pick what appear to be the most appropriate results from recent literature examples. Even the most casual scan of this report will note glaring omissions—there is, for example, no coverage of the HSAB reactivity of B–B, Si–Si and related HSAB-matched (but weak!) bonds.[182] Given the present ease with which specific transformations are easily uncovered by the Beilstein[183] and Scifinder[184] databases, I have tried here to concentrate on basic underlying physical properties and mechanisms which, in my experience, are far harder to gather electronically.

Despite the best part of 40 years of research effort, the HSAB principle is still left with just two qualitative tags: hard and soft. Clearly, in multicomponent reactions, such as catalytic reactions this is less than satisfactory. For accurate prediction of regio- and stereochemical issues accurate data regarding both the energetics and orbital HSAB matching at the proposed point(s) of reaction are required. By traditional methods, this data has proved impossible to attain but the recent theoretical activities in this area are likely to become a strong adjunct to synthetic chemists within the next decade. An ability to differentiate between the relative softness (or hardness) of two similar, but non-identical, sites will dramatically improve the utility of the concept for chemists carrying out Lewis acid- or base-catalysed reactions.

Acknowledgements

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