Novel N-heterocyclic activations mediated by magnesium reagents having sterically hindered ligands

By

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This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

To my mum and dad, just a small thank you.

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Abstract

Building on recent advances on the synthesis of homometallic Mg compounds bearing highly sterically demanding ligands, but going significantly beyond the state-of-the-art, this thesis report focuses on the synthesis of new sodium magnesiates and magnesium reagents supported by bulky *N*-chelating ligands $\{Ph_2Si(NAr^*)_2\}^{2-}$ and $\{Ar^*N{=}C(Me)CH(Me)NAr^*\}^-$ (nacnac) as well as their exploitation within the areas of deprotonative metallation, heterocyclic activation and catalytic application in hydroamination reactions of organic heterocumulenes.

Firstly, a series of novel sodium magnesiates bearing the sterically demanding bis(amido)silyl ligand $\{Ph_2Si(NAr^*)_2\}^{2-}$ (Ar*= 2,6-*i*-Pr_2-C_6H_3) has been prepared. Thus alkyl derivatives $[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(R)(THF)\}^-]$ (R= Bu, **2**; CH_2SiMe_3, **5**) have been synthesised and isolated as crystalline solids by reacting bis(amine)silyl $[Ph_2Si(NHAr^*)_2]$ **1** with the relevant sodium magnesiate $NaMg(Bu)R_2$ (prepared *in situ* by co-complexation of BuNa with the relevant magnesium alkyl MgR_2). In addition, compound **5** has been used as a precursor for the synthesis of a new series of amido sodium magnesiates $[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(NR_2)(THF)_x\}^-]$ (NR_2 = HMDS, x=1, **6**; NR_2= NPh_2, x=1, **7**; NR_2 = N^iPr_2, x=1, **8**; NR_2 = DMP, x=1, **9**; NR_2 = TMP, x=0, **10**). The reactions of NH_2Ar^* and pyrrole with complex **5** led to the formation of mixed-metal complexes $[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)(NHAr^*))Mg(NHAr^*)_2(THF)\}^-]$ **11** and $[\{(Ph_2Si(NAr^*)(NHAr^*))Mg(NC_4H_4)_2(THF)Na(THF)_2\}]$ **12** respectively.

Reactivity studies disclosed that TMP derivative **10** was able to carry out the α-magnesiation of thiophene to yield $[\{Na(THF)_6\}^+\{Ph_2Si(NAr^*)_2)Mg(C_4H_3S)(THF)\}^-]$ **13**. In moving to reactivity studies with 1,3 benzoazoles complex **2** promotes the chemeoselective magnesiation of methylbenzimidazole (MeBIm) to yield $[\{Na(THF)_5\}_2^+\{(Ph_2Si(NAr^*)_2)Mg(MeBIm^*)\}_2^-]$ **14** (MeBIm* = methylbenzimidazolyl), analysis of bond parameters, NMR data and DFT studies suggest that N-methylbenzimidazolyl ligand displays a metal carbene character. The

reaction of **2** with benzothiazole (Btz) promotes a unique activation process of this heterocycle initiating an unprecedented cascade of reactions, where the initial magnesiation of Btz is followed by an intricate sequence of C-C coupling, ring opening, benzothiazolyl insertion into a C=N bond and intramolecular deprotonation leading to the ring opening and functionalisation of three Btz molecules resulting in novel sodium magnesiate [$L_2Mg_2Na_2(THF)_5$] **15**. Extending these studies to the diazine molecule quinoxaline allows the synergic entrapment of radical anion ($Qox^{\bullet}$) in the form of dimer [$\{Na(THF)_6\}_2^+\{(Ph_2Si(NAr^*)_2)Mg(Qox^{\bullet})\}_2^-$] **20** resulting from the homoleptic cleavage of Mg-C bond in the alkyl precursor **2**. EPR studies show that **20** is diamagnetic in the solid-state dimeric structure.

Homometallic magnesium species [(^{Dipp}nacnac)Mg(Bu)(THF)] **22** and [(^{Dipp}nacnac)Mg(TMP)] **23** were prepared and structurally defined and their reactivity towards 1,3-benzoazoles has been assessed. Reactions of **22** and **23** with benzoxazole allowed the isolation in both cases of [(^{Dipp}nacnac)Mg{O(*o*-C_6H_4)NC}(THF)] **24** resulting from ring cleavage of benzoxazolyl anion. Benzothiazole (Btz) was magnesiated at the C2 position by the amido derivative to form [{(^{Dipp}nacnac)Mg(Btz*)}$_2$] **25** (Btz*= 2-benzothiazolyl), however when **22** was reacted with Btz a novel activation of Btz occurred in a cascade reaction involving magnesiation, C-C coupling and ring opening resulting in [(^{Dipp}nacnac)Mg{(Btz*)C(H)=N(2-C_6H_4-1-S)}] **26**. Complex **23** when reacted with nitrogen derivative methylbenzimidazole (MeBIm) promotes the magnesiation at the C2 position to yield [{(^{Dipp}nacnac)Mg(MeBIm*)}$_2$] **27**. In contrast alkyl derivative **22** only coordinated to MeBIm through the lone pair on the N to yield [(^{Dipp}nacnac)Mg(Bu)(MeBIm)] **28**.

Studies assessing the catalytic ability of sodium magnesiates to promote the hydroamination of isocyanates and carbodiimides, show that homoleptic [$NaMg(CH_2SiMe_3)_2$] **32** can effectively catalyse at room temperature the reactions of $HNPh_2$ with several aliphatic isocyanates to yield the relevant ureas [(NHR)C(=O)(NPh_2)] (R = ^{t}Bu, **29**, R = Cy, **39**, R = Et, **43**) in yields ranging from 99 to 100%. Similarly tris(amido) complex [$NaMg(NPh_2)_3$] **30** catalyses the trimerisation of aryl isocyanates under mild reaction conditions. The isolation of key intermediates of the stoichiometric reactions provided important information to propose a possible catalytic cycle. Guanidines [(NHR)C(=NR)NPh_2] (R =Cy, **48**, R = ^{i}Pr, **49**) could be prepared in good-moderate yields (64-65%) by reacting $NHPh_2$ with RN=C=NR using **30** as a catalyst.

Publications

1. "*Magnesium-Mediated Benzothiazole Activation: A Room Temperature Cascade of C-H Deprotonation, C-C Coupling, Ring-Opening, and Nucleophilic Addition Reactions*"; V. L. Blair, W. Clegg, A. R. Kennedy, **Z. Livingstone**, L. Russo and E. Hevia, *Angew.Chem.Int.Ed.*, **2011**, 50, 9857.
2. "*Isomeric and chemical consequences of the direct magnesiation of 1,3 benzoazoles using β-diketiminate stablised magnesium bases"*; S. E. Baillie, V. L. Blair T. D. Bradley, W. Clegg, J. Cowan, R. W. Harrington, A. Hernan-Gomez, A. R. Kennedy, **Z. Livingstone**, S. D. Robertson and E. Hevia, (manuscript submitted).

Publications out with this work

1. "*New Insights into Addition Reactions of Dialklylzinc Reagents to Trifluoromethyl Ketones: Structural Authentication of a β-hydride Elimination Product Containing a Tetranuclear Zinc Chain*"; E. Hevia, A. R. Kennedy, J. Klett, **Z. Livingstone** and M. D. McCall, *Dalton Trans.*,**2010**, 39, 520.

Oral Presentations

1. "Novel N-heterocyclic activations via a sodium magnesiation with a steric support"; University of Strathclyde, Inorganic Research Day, June 2011

2. "New Sodium Magnesiates with Bulky Bis(amido) Ligands: Structural Tailoring for Deprotonation and Addition Reactions"; Universities of Scotland Inorganic Conference, Durham University, Durham, July 2010.

Poster Presentations

1. "Magnesium Mediated Benzothiazole Activation: a Room Temperature Cascade of C-H Deprotonation, C-C Coupling and Ring-Opening Reactions"; North West Organic Conference, Liverpool University, Liverpool, July 2012.

2. "Magnesium Mediated Benzothiazole Activation: a Room Temperature Cascade of C-H Deprotonation, C-C Coupling and Ring-Opening Reactions"; Universities of Scotland Inorganic Conference, Glasgow University, Glasgow, July 2011. Awarded judge's choice in poster competition.

3. "Magnesium Mediated Benzothiazole Activation: a Room Temperature Cascade of C-H Deprotonation, C-C Coupling and Ring-Opening Reactions"; RSC Dalton Division Meeting on Main Group Chemistry, London Imperial College, London, July 2011. Awarded 1st prize in poster competition.

4. "Magnesium Mediated Benzothiazole Activation: a Room Temperature Cascade of C-H Deprotonation, C-C Coupling and Ring-Opening Reactions"; International American Chemical Society Meeting, Aneheim, March 2011.

Abbreviations

Å	Ångström
Ad	adamantyl
AMMM	alkali-metal mediated metallation
AMMMg	alkali-metal mediated magnesiation
Ar	aryl
Ar*	2,6-$^{i}Pr_2$-C_6H_3
b	broad
bipy	bipyridine
Boz	benzoxazole
Btz	benzothiazole
Btz*	benzothiazolyl
Bu	butyl
^{t}Bu	*tert*-butyl
Bz	benzyl
C_6D_6	dueterated benzene
CIPE	complex-induced proximity effect
COSY	^{1}H-^{1}H correlated NMR spectroscopy
Cp	cyclopentadienyl
CSD	crystallographic structure database
Cy	cyclohexyl
DA(H)	diisopropylamine
DFT	density functional theory
Dipp	diisopropylphenyl
DoM	directed *ortho* metallation
DMAP	4-dimethylaminopyridine
DMP(H)	dimethylpiperididne
dpq	2,3-bis(2-pyridyl)quinoxaline
en	ethylenediamine
EPR	electron paramagnetic resonance
Et	ethyl

fc ferrocenyl

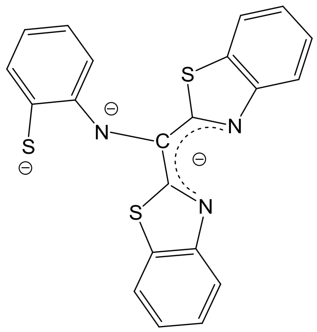
g grams

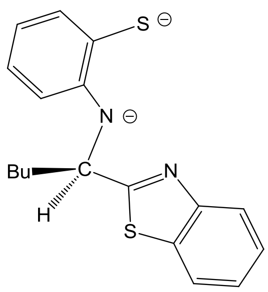
HMDS(H) hexamethyldisilazane

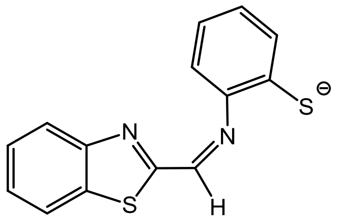
HSQC heteronuclear single quantum coherence

^{i}Pr isopropyl

IPr 1,3-bis-(2,2-diisopropylphenyl)imidazol-2-ylidene

L 

L* 

L' 

m multiplet

Me methyl

MeBIm methylbenzimidazole

MeBIm* methylbenzimidazolyl

Mes mesityl

ml millilitre

nacnac $[\{2,6\text{-}^{i}Pr_2C_6H_3)N(Me)C\}_2CH]$

NHC N-heterocyclic carbene

NMR nuclear magnetic resonance

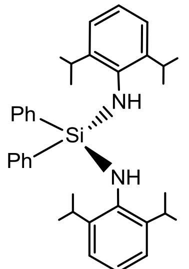
PEPPSI pyridine-enhanced precatalyst preparation, stabilization, and initiation

Ph	phenyl
ppm	parts per million
q	quartet
Qox	quinoxaline
s	singlet
TEMPO	(2,2,2,6,6-tetramethyl-1-piperidinyloxy)
d_8-THF	deuterated tetrahydrafuran
THF	tetrahydrafuran
TMEDA	tetramethylethylenediamine
TMP(H)	tetramethylpiperidine

Table of Compounds

$[Ph_2Si(NAr^*H)_2]$	**1**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(Bu)(THF)\}^-]$	**2**
$[\{Ph_2Si(NHAr^*)(NAr^*)Na\}_2]$	**3**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Al(Bu)_2\}^-]$	**4**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(CH_2SiMe_3)(THF)\}^-]$	**5**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(N(SiMe_3)_2)(THF)\}^-]$	**6**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(NPh_2)(THF)\}^-]$	**7**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(N^iPr_2)(THF)\}^-]$	**8**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(DMP)(THF)\}^-]$	**9**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)_2)Mg(TMP)\}^-]$	**10**
$[\{Na(THF)_6\}^+\{(Ph_2Si(NAr^*)(NHAr^*))Mg(NHAr^*)_2(THF)\}^-]$	**11**
$[\{(Ph_2Si(NAr^*)(NHAr^*))Mg(NC_4H_4)_2(THF)Na(THF)_2\}]$	**12**
$[\{Na(THF)_6\}^+\{Ph_2Si(NAr^*)_2)Mg(C_4H_3S)(THF)\}^-]$	**13**
$[\{Na(THF)_5\}_2{}^+\{(Ph_2Si(NAr^*)_2)Mg(MeBIm^*)\}_2{}^-]$	**14**
$[L_2Mg_2Na_2(THF)_5]$	**15**
$[L_2L^*_2Mg_3Na_4(THF)_9]$	**16**
$[(Ph_2Si(NAr^*)_2)Mg(THF)_2]$	**17**
$[LMg_2(SH)(THF)_4]$	**18**
$[(Ph_2Si(NAr^*)_2)Mg(THF)(PhN(C_2N(NPh)_2)Na(THF)_4]$	**19**
$[\{Na(THF)_6\}_2{}^+\{(Ph_2Si(NAr^*)_2)Mg(Qox^\bullet)\}_2{}^-]$	**20**
$[(Ph_2Si(NAr^*)_2)Mg(TEMPO)Na(THF)_3]$	**21**

$[(^{Dipp}nacnac)Mg(Bu)(THF)]$	**22**
$[(^{Dipp}nacnac)Mg(TMP)]$	**23**
$[(^{Dipp}nacnac)Mg\{O(o\text{-}C_6H_4)NC\}(THF)]$	**24**
$[\{(^{Dipp}nacnac)Mg(Btz^*)\}_2]$	**25**
$[(^{Dipp}nacnac)Mg\{(Btz^*)C(H){=}N(2\text{-}C_6H_4\text{-}1\text{-}S)\}]$	**26**
$[\{(^{Dipp}nacnac)Mg(MeBIm^*)\}_2]$	**27**
$[(^{Dipp}nacnac)Mg(Bu)(MeBIm)]$	**28**
$[(^tBuNH)C(=O)(NPh_2)]$	**29**
$[NaMg(NPh_2)_3(THF)_2]$	**30**
$[(THF)_3NaMg((^tBuN)C(NPh_2)(=O))_3]$	**31**
$[\{NaMg(CH_2SiMe_3)_3\}]$	**32**
$[(^tBuNH)C(=O)(NBu_2)]$	**33**
$[(^tBuNH)C(=O)(NBz_2)]$	**34**
$[(^tBuNH)C(=O)(NPy_2)]$	**35**
$[(^tBuNH)C(=O)(NHAr^*)]$	**36**
$[(CyNH)C(=O)(NBu_2)]$	**37**
$[(CyNH)C(=O)(NBz_2)]$	**38**
$[(CyNH)C(=O)(NPh_2)]$	**39**
$[(CyNH)C(=O)(NPy_2)]$	**40**
$[(CyNH)C(=O)(NHAr^*)]$	**41**
$[(EtNH)C(=O)(NHAr^*)]$	**42**
$[(EtNH)C(=O)(NPh_2)]$	**43**
$[(EtNH)C(=O)(NPy_2)]$	**44**



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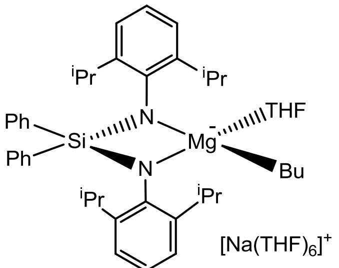

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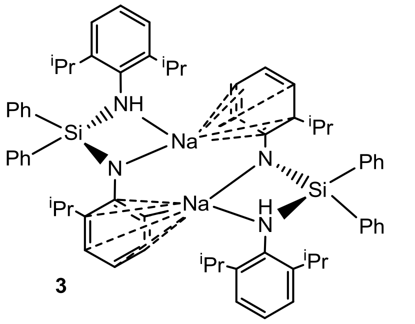

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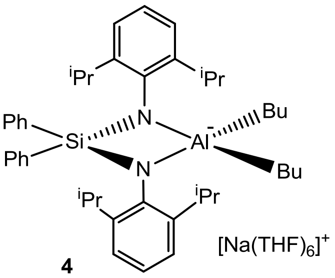

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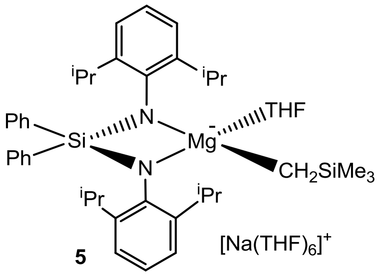

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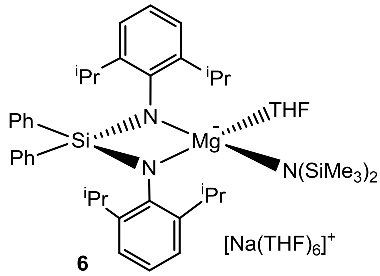

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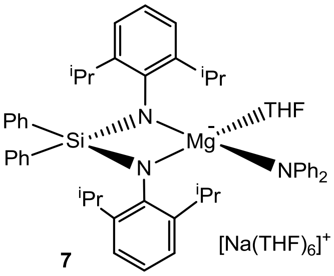

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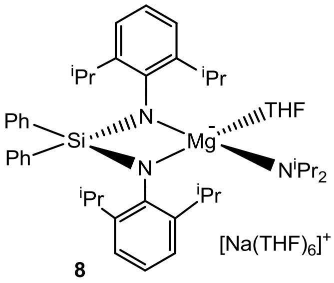

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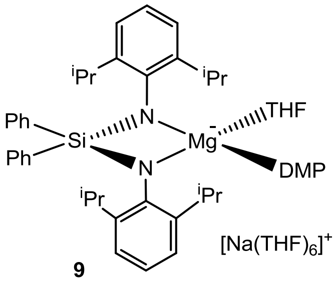

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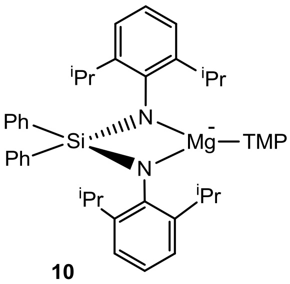

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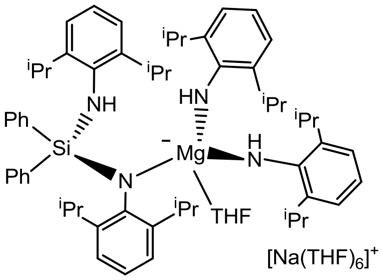

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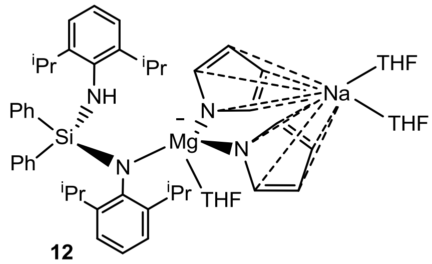

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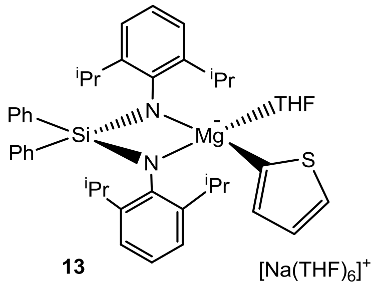

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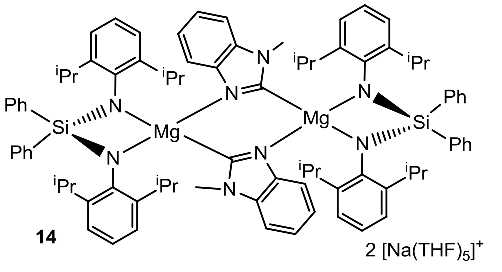

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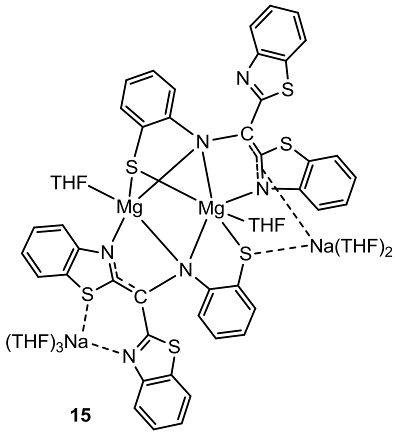

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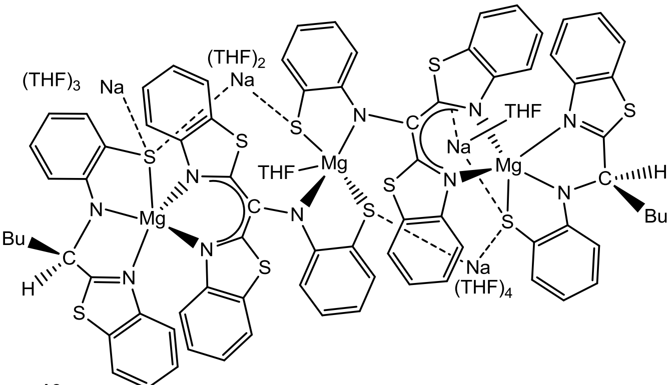

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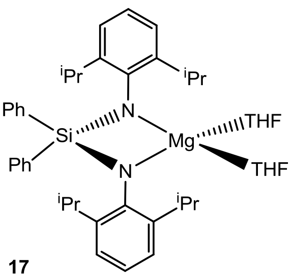

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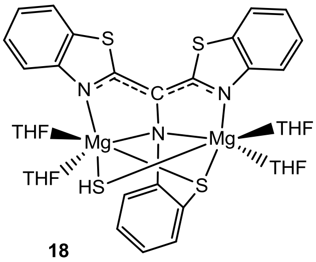

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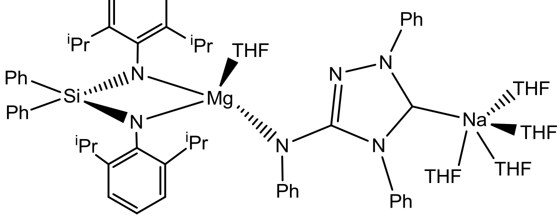

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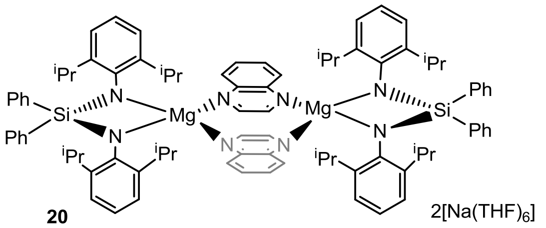

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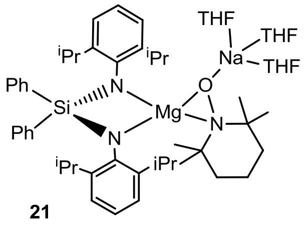

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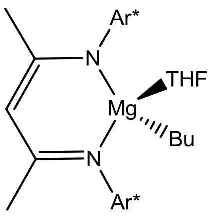

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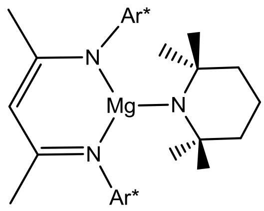

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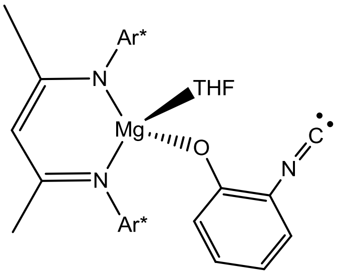

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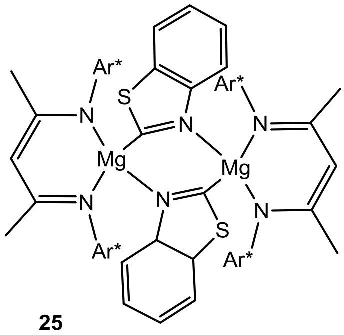

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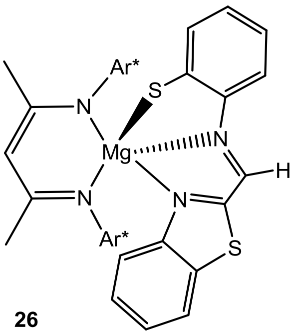

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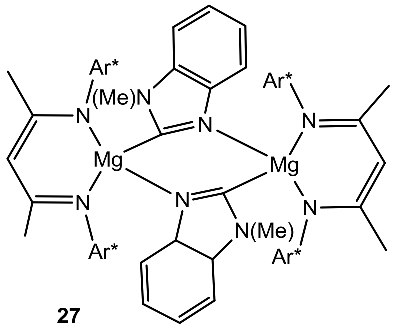

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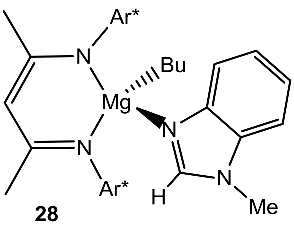

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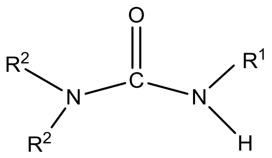
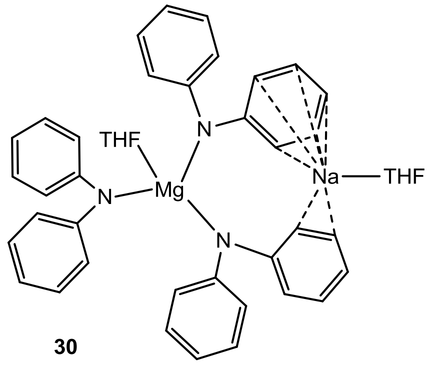


29, 33-44

R^1	R^2	compound
^{t}Bu	Ph	**29**
^{t}Bu	Bu	**33**
^{t}Bu	Bz	**34**
^{t}Bu	Py	**35**
^{t}Bu	Ar*	**36**
Cy	Bu	**37**
Cy	Bz	**38**
Cy	Ph	**39**
Cy	Py	**40**
Cy	Ar*	**41**
Et	Ar*	**42**
Et	Ph	**43**
Et	Py	**44**



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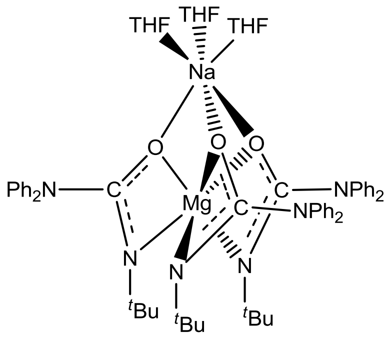

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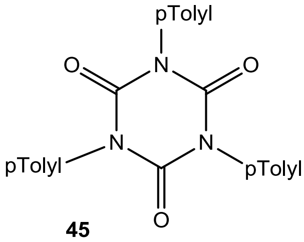

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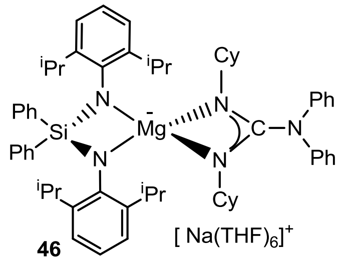

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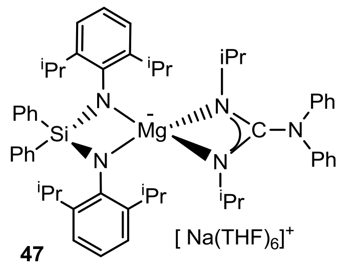

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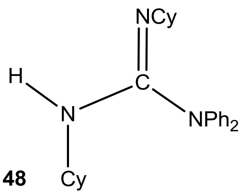

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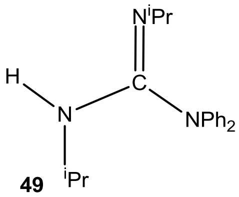

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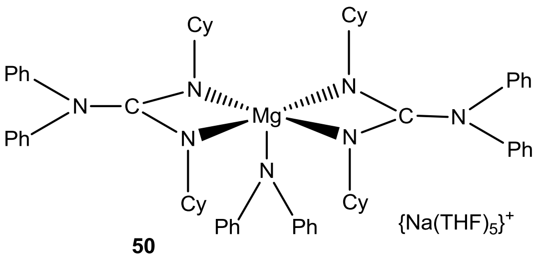

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