ENCYCLOPEDIA

of

Reagents

for

Organic

Synthesis

Editor-in-Chief

Leo A. Paquette
The Ohio State University, Columbus, OH, USA

Volume 6

N – Sin

time; must be handled under inert atmosphere; catalytic activity may decrease if impure or moist solvents are used; can be safely destroyed by slowly adding isopropanol to a suspension of the reagent in hexane with good stirring.

Catalytic Activity. K/Al_2O_3 is the most efficient among the series of alkali metals finely dispersed on alumina, although **Sodium–Alumina** (sometimes termed 'high surface sodium') essentially effects the same types of transformations. In a model system, the following order of activity for the different alkali metals supported on alumina has been established: $K \geq Rb >> Cs \approx Na$.[1a]

K/Al_2O_3 readily effects both configurational as well as positional alkene isomerizations with the following three trends being observed. Firstly, alkene groups are usually shifted (with few exceptions) towards higher degrees of substitution (eq 1).[2] Secondly, an alkene of accentuated conformational preference will accumulate; this is evidenced, for example, by the formation of the thermodynamically more stable (Z,Z)-cyclodeca-1,6-diene from (E,Z)-cyclodeca-1,5-diene (eq 2),[1] as well as by the preponderance of (–)-aristolene in the equilibrium mixture obtained upon treatment of (+)-calaren with K/Al_2O_3 (eq 3).[2] Thirdly, the double bonds in 1,n-(cyclo)alkadienes are shifted towards conjugation independent of their initial position in the starting material (eqs 4 and 5).[1,2] Similarly, 1,2,4-trivinylcyclohexane quantitatively affords 1,2,4-triethylbenzene in a highly exothermic process.[3] Although the mechanism responsible for such positional changes is not yet elucidated, allyl anion intermediates are likely.[1] This picture is supported by the observation that successive treatment of γ-**Alumina** with **Sodium Hydroxide** and Na leads to a solid superbase ($pK_b \geq 37$), which effects the same types of alkene isomerizations via allyl anion species.[8]

# Potassium on Alumina

$$K/Al_2O_3$$

[7440-09-7]   K   (MW 39.10)

(catalyst for hydrogenations,[1,7] double bond isomerizations,[1-4] dehydrations, and skeletal rearrangements;[2-4] metalating agent;[5] effects reductive decyanation[6])

Physical Data: blue powder if the metal content is in the range of 2–15%; at higher loading the reagent has a gray to black appearance. The X-ray spectrum of a 14% K on Al_2O_3 reagent shows no observable reflections due to potassium.[6] A metal content in the range of 2–15% usually leads to the highest catalytic activity.[1]

Preparative Method: by adding potassium to thoroughly dried basic or neutral alumina under argon with vigorous stirring at temperatures >100 °C until a homogeneous appearance is reached.

Handling, Storage, and Precautions: nonpyrophoric solid which can be stored under argon for extended periods of
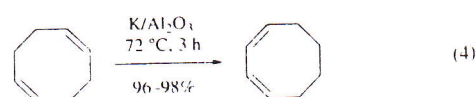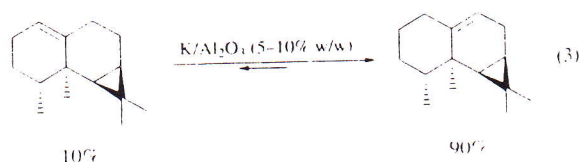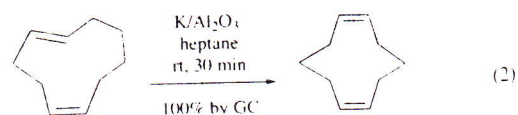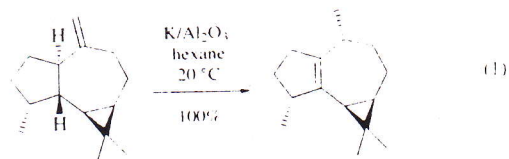
Macrocyclic 1,3-cycloalkadienes produced by isomerization of 1,n-cycloalkadienes are slowly reduced to cycloalkenes even

$$\text{(5)}$$
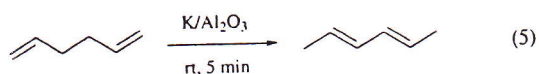
in the absence of external hydrogen.[1] Residual water or –OH groups on the alumina in combination with the adsorbed potassium may serve as the hydrogen source in this process. Under a hydrogen atmosphere (1 atm), however, this selective hydrogenation of conjugated dienes by M/Al$_2$O$_3$ (M = Na, K) is considerably accelerated, with no overreduction to the respective cycloalkane being observed.[1]

K/Al$_2$O$_3$ exhibits a distinct propensity to catalyze transannular reactions of unsaturated macrocyclic systems as well as skeletal rearrangements leading to ring contraction, as shown with (+)-longifolene as substrate.[2]

Catalytic Cascades. Six-membered rings bearing two alkene and/or cyclopropyl groups in the vicinity are smoothly aromatized when exposed to M/Al$_2$O$_3$ (M = Na, K) as catalyst by a sequence of double-bond isomerizations followed by dehydrogenation (eq 6).[2,3]


$$\text{(6)}$$
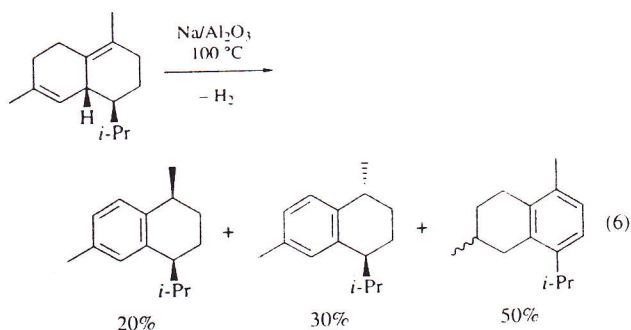
In a one-pot procedure (Z,E,E)-cyclododeca-1,5,9-triene as substrate runs through a cascade of catalytic processes induced by Na/Al$_2$O$_3$. This sequence comprises a transannular reaction, double bond isomerizations, and selective hydrogenation of the conjugated diene produced in the presence of hydrogen. Final ozonolysis of the crude reaction mixture afforded cyclododeca-1,7-dione in good yield (eq 7).[4]

$$\text{(7)}$$
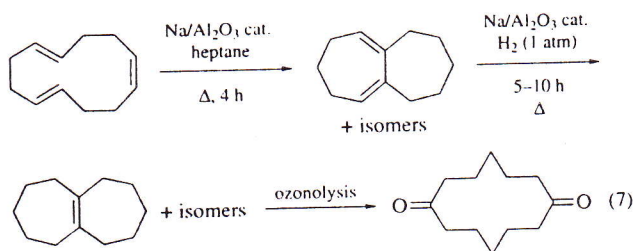
Organometallic Synthesis. K/Al$_2$O$_3$ has been used as base to metalate ketones, ethyl phenylacetate, alkyl nitriles, aldehyde-N,N-dimethylhydrazones, or N-cyclohexylketimines.[5] However, an excess of the reagent was necessary and the yields reported for alkylation of the intermediate potassium carbanions were moderate. In the case of alkyl nitriles as starting materials, the choice of solvent turned out to be decisive for the reaction path:

while deprotonation of these substrates predominates in THF, they are readily decyanated when treated with K/Al$_2$O$_3$ in hexane as the reaction medium.[6] Residual –OH groups on the alumina may be the proton sources in this reductive C–C bond cleavage. While the reaction leaves acetal groups and disubstituted alkene moieties in the substrates unaffected (eq 8), terminal double bonds are rearranged to internal ones during the decyanation process (eq 9).[6] Recently, Na/Al$_2$O$_3$ has been used as reducing agent for ketones, esters, and oximes.[9] It also serves as a catalyst for the Tischenko coupling of benzaldehyde to benzyl benzoate,[10] and may be employed for preparing activated zinc and titanium samples.[11]

$$\text{(8)}$$

$$\text{(9)}$$
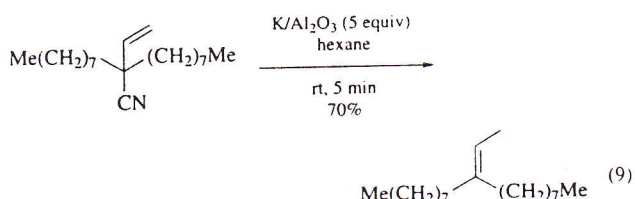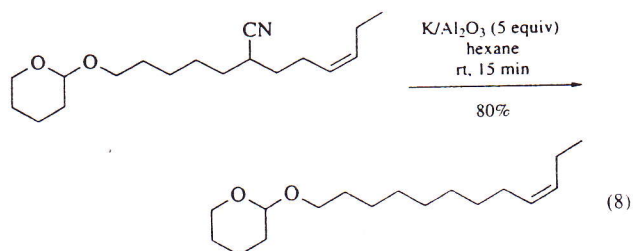
1. (a) Hubert, A. J. *JCS(C)* **1967**, 2149. (b) Hubert, A. J.; Dale, J. *JCS(C)* **1968**, 188. (c) Haag, W. O.; Pines, H. *JACS* **1960**, *82*, 387. (d) Shabtai, J.; Gil-Av, E. *JOC* **1963**, *28*, 2893.

2. Rienäcker, R.; Graefe, J. *AG(E)* **1985**, *24*, 320.

3. Ruckelshauss, G.; Kosswig, K. *CZ* **1977**, *101*, 103.

4. Alvik, T.; Dale, J. *ACS* **1971**, *25*, 1153.

5. Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *JOM* **1981**, *204*, 281.

6. Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *JOC* **1980**, *45*, 3227.

7. Tazuma, J. J.; Zadra, M. D. *J. Catal.* **1978**, *51*, 435.

8. Suzukamo, G.; Fukao, M.; Minobe, M. *CL* **1987**, 585.

9. Singh, S.; Dev, S. *T* **1993**, *49*, 10959.

10. Scott, F.; van Heerden, F. R.; Raubenheimer, H. G. *JCR(S)* **1994**, 144.

11. (a) Stadtmüller, H.; Greve, B.; Lennick, K.; Chair, A.; Knochel, P. *S* **1995**, 69. (b) Fürstner, A.; Seidel, G. *S* **1995**, 63.

Alois Fürstner
Max-Planck-Institut für Kohlenforschung, Mülheim, Germany

Potassium–Graphite Laminate

$$C_8K$$

[12081-88-8] C_8K (MW 135.18)

(powerful reducing agent for many functional groups;[1] metalating agent;[1] Lewis base;[1] hydrogenation catalyst;[1,2] catalyst for double bond isomerization and for anionic polymerization;[2] tool for preparing activated metals[1])

Physical Data: paramagnetic bronze-colored powder; $d \sim 0.73$ g cm^{-3}; interlayer distance 5.34 Å; all carbon layers are separated by one layer of potassium; space group D^6_2, $C222$.

Solubility: may be suspended in hydrocarbon and ethereal solvents; reacts violently with water, alcohols, and ammonia; THF, DME, 1,4-dioxane, and many arenes (e.g. benzene, toluene, pyridine, furan) are able to penetrate into the interlayer space, causing considerable swelling.

Preparative Methods: by stirring potassium and graphite powder at ≥ 150 °C under argon without any solvent for 5–10 min. Natural as well as synthetic graphite are suited for its preparation.

Handling, Storage, and Precautions: pyrophoric and must be handled under argon in thoroughly dried solvents. Small quantities should be weighed in a glove box; it can be stored under argon without any significant loss in activity for extended periods of time.

Introduction. Potassium–graphite laminate may be regarded as a polymeric array of naphthalenide anions and effects almost any reaction that the latter would promote. A major advantage in using C_8K as a substitute for *Lithium Naphthalenide*, for example, lies in its increased reactivity and the easy work-up, consisting of filtration of the graphite only instead of the sometimes tedious removal of naphthalene.[1] Moreover, C_8K-promoted reactions can be readily monitored by the characteristic color change from bronze of the reagent to black of the graphite host.[1]

Functional Group Reductions. Alkyl chlorides and aryl halides are generally reduced to the corresponding hydrocarbons, whereas alkyl iodides afford Wurtz-type coupled products. Alkyl bromides show a reactivity pattern between alkyl chlorides and alkyl iodides. Single-electron transfer is an important pathway in these reductions, since characteristic radical rearrangements are observed with hex-5-enyl halides as mechanistic probes (eq 1).[3] *vic*-Dihalides form alkenes in high yield (eq 2).[3,4] C_8K leads to reductive cleavage of the C–O bond of aryl ethers, whereas in sulfonate esters the S–O rather than the C–O bond is broken selectively, with formation of the parent alcohols (eq 3).[3] Aryl ether and C–Cl cleavage can be done simultaneously, thus allowing the ready destruction of toxic polyhalodibenzodioxines or -dibenzofurans at rt.[5] Vinyl sulfones and allyl sulfones afford the corresponding alkenes (the latter after initial isomerization of their double bond) (eq 4).[6] The (E):(Z) ratio in these desulfuration reactions is low, with the (E)-isomer being slightly favored.

(1)

65%   35%

(2)

(3)

(4)

$(E):(Z) = 65:35$
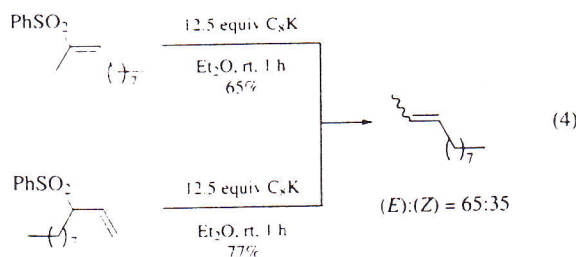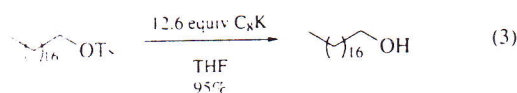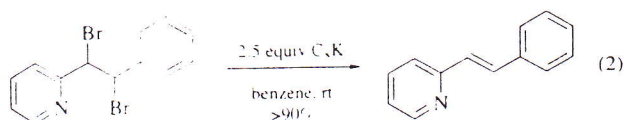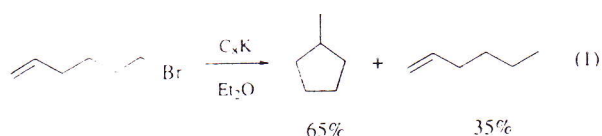
With *Hexamethyldisilazane* as cosolvent, C_8K in THF selectively reduces the double bond of enones at rt without affecting nonconjugated alkenes (eq 5).[7] α,β-Unsaturated acids are similarly reduced at 55 °C, while enoates give dimerization products. Imines afford amines in high yields with this reagent (eq 6).[7] whereas ketones may afford mixtures of alcohols and pinacols.[8] A large excess of the reagent is required to effect Birch-type reductions of arenes, as exemplified by a series of substituted naphthalene derivatives.[9] On treatment with C_8K in THF, benzil undergoes a unique coupling of the phenyl rings with formation of 9,10-phenanthrenequinone (eq 7).[10] This arene coupling can be extended to 2,3-diphenylquinoxaline and related heterocycles, which afford dibenzo[a,c]phenazine derivatives.[11]

Although C_8K was considered for a long time to be of limited value in organic synthesis due to its high reactivity,[3] it turned
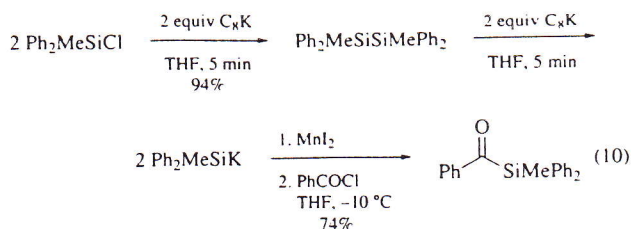

(5)

(6)

(7)
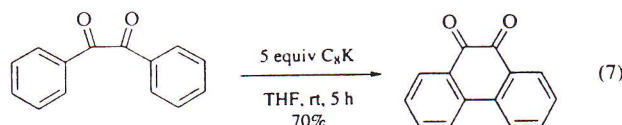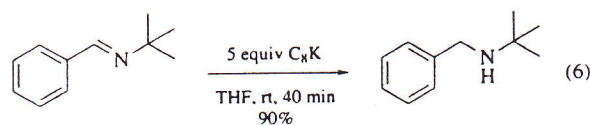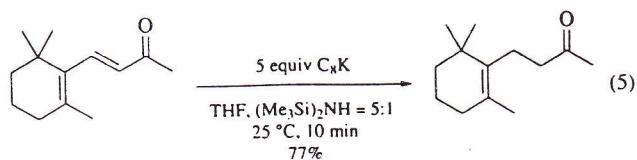
out to be the reagent of choice for the synthesis of furanoid glycals in terms of yield, reaction rate, and flexibility. The intermediate potassium alcoholates, formed upon treatment of 2,3-O-alkylidene glycosyl halides with C_8K in THF at low temperature, can be protected in situ with a wide variety of electrophiles (eq 8).[12] Aryl thioglycosides can also be reduced to the corresponding glycals by means of C_8K.[12b] Comparable reaction sequences consisting of C_8K-induced fragmentations followed by trapping of the intermediate alcoholates have also been carried out successfully with a series of carbohydrate-derived primary halides (eq 9).[13]

(8)

(9)
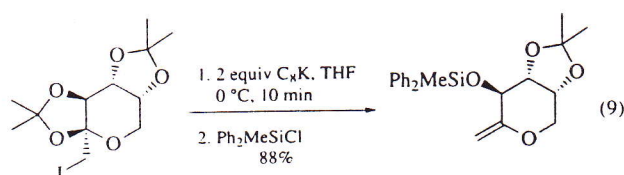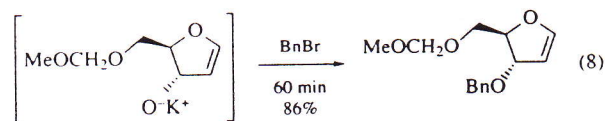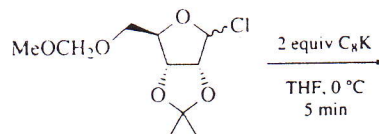
Chlorosilanes are rapidly converted by C_8K to disilanes in high to quantitative yields in THF at ambient temperature.[14] Phenyl-substituted disilanes may be further reduced to the corresponding silyl potassium reagents, which can be transmetalated with various transition metal halides (*Copper(I) Iodide*, *Copper(I) Cyanide*, MnI_2, VCl_3) to highly selective nucleophilic silylating agents. They react cleanly with enoates, enones, and acid chlorides, the last affording acyl silanes in a one-pot procedure (eq 10).[14a]

C_8K as Polymeric Lewis Base. The reactivity of C_8K towards Brønsted acids is substrate size dependent.[3] C_8K has been used to achieve selective monoalkylation of alkyl nitriles and phenylacetic acid esters (substrate:C_8K:alkyl halide = 1:2:2) at

Avoid Skin Contact with All Reagents

$$2\ Ph_2MeSiCl \xrightarrow[\substack{THF, 5\ min \\ 94\%}]{2\ equiv\ C_xK} Ph_2MeSiSiMePh_2 \xrightarrow[THF, 5\ min]{2\ equiv\ C_xK}$$

$$2\ Ph_2MeSiK \xrightarrow[\substack{2.\ PhCOCl \\ THF, -10\ ^\circ C \\ 74\%}]{1.\ MnI_2} Ph\overset{O}{\underset{}{\overset{\|}{C}}}SiMePh_2 \quad (10)$$

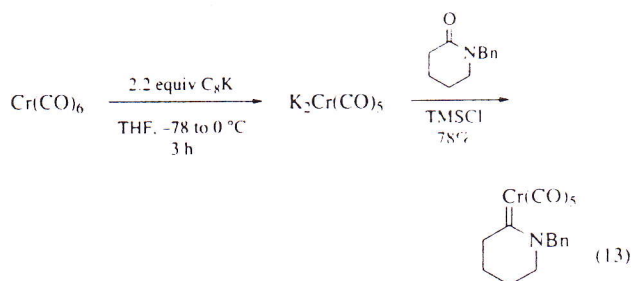–60 °C in 40–70% yield, with only small amounts of dialkylated products (0–7%) interfering.[15] Imines and dihydro-1,3-oxazine derivatives can likewise be deprotonated by this reagent at rt, followed by exclusive C-alkylation of the azaallyl anion (eq 11).[16] Some examples of selective dehydrohalogenations in the carbohydrate series due to the basisity of C_8K have also been reported (eq 12).[17]
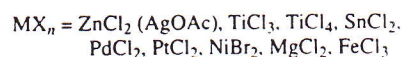
$$Ph\diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!\diagdown O \quad (11)$$

$$(12)$$
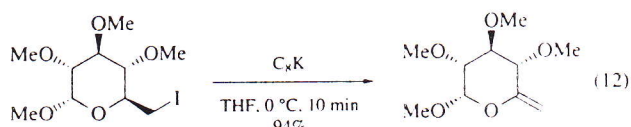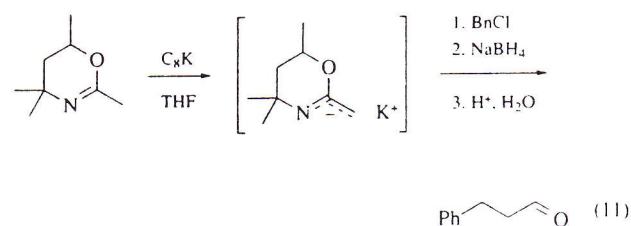
Organometallic Chemistry. C_xK is an effective reducing agent for transition metal compounds.[1] Particularly relevant to organic synthesis is the ready reduction of **Hexacarbonylchromium** to $K_2Cr(CO)_5$, which forms chromium carbenes upon reaction with amides or esters in presence of **Chlorotrimethylsilane** (eq 13). This procedure allows an improved entry into the rich chemistry of chromium carbenes, with a comparative study clearly pointing out the superiority of C_xK as reducing agent over naphthalenide anions.[18] Moreover, C_xK is the only reagent that cleanly reduces $[CpNi_2(CO)]_2$ to the highly nucleophilic nickelate $[Cp(CO)Ni]^- K^+$, which affords allylnickel complexes on reaction with **Allyl Bromide**.[19]

$$Cr(CO)_6 \xrightarrow[\substack{THF, -78\ to\ 0\ ^\circ C \\ 3\ h}]{2.2\ equiv\ C_8K} K_2Cr(CO)_5 \xrightarrow[\substack{TMSCl \\ 78\%}]{} \quad (13)$$

Metal–Graphite Reagents.[1] C_xK may be used to reduce metal salts in ethereal solvents to metal–graphite reagents (eq 14). Due to the even distribution and small size (usually in the

range of 2–10 nm in diameter) of the metal particles adsorbed on the surface of the graphite support, these reagents exhibit very high and sometimes unprecedented degrees of reactivity and are easily removed by simple filtration after use.[1] Almost any metal may be activated by this technique.

$$MX_n + n\,C_8K \longrightarrow M^* \text{ on graphite} + n\,KX \quad (14)$$

$$MX_n = ZnCl_2\ (AgOAc),\ TiCl_3,\ TiCl_4,\ SnCl_2,$$
$$PdCl_2,\ PtCl_2,\ NiBr_2,\ MgCl_2,\ FeCl_3$$

Zinc–Graphite doped with 10 mol % **Silver** exhibits an exceptionally high reactivity and wide scope. This reagent promotes Reformatsky reactions at temperatures well below 0 °C with different kinds of halo esters, including the rather unreactive chloroalkanoates (see also **Ethyl Bromozincacetate**).[20] Tandem reactions comprising a Reformatsky step followed by glycidate formation or a Peterson elimination, respectively, have been carried out.[21] Zn/Ag–graphite transforms glycosyl halides to the corresponding glycals under aprotic conditions, independent of the ring size and the protecting groups employed (eq 15).[22] Deoxyhalosugar derivatives are reductively ring opened by Zn/Ag–graphite with formation of enantiomerically pure enal building blocks of wide applicability to natural product synthesis (eq 16).[13,17,23] It is the only reagent that affords such fragmentations under essentially neutral conditions in anhydrous ethereal solvents, exhibits excellent tolerance towards a wide range of functional groups in the substrates, and is therefore well suited for selective transformations of polysubstituted molecules.[24] This was shown in a total synthesis of 9-dihydro-FK-506 (eq 17).[25] Zn/Ag–graphite is also suitable for metalating functionalized aryl halides at rt.[31]

$$(15)$$

$$(16)$$

$$(17)$$
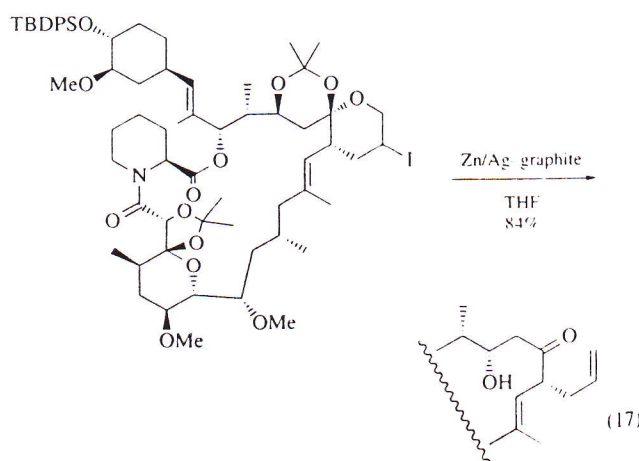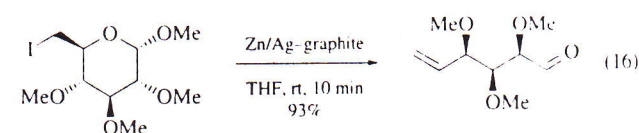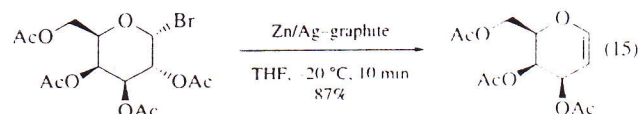
Titanium on graphite deserves special emphasis as one of the most efficient reagents for all kinds of carbonyl coupling reactions. It promotes both inter- as well as intramolecular McMurry reactions of (di)ketones and (di)aldehydes (eq 18),[26–28] cyclizes oxo esters to cyclanones,[26] and was successfully applied to polyoxygenated substrates in cases when other titanium reagents failed to effect any conversion (eq 19).[28] Recently, it was used to cyclize acyloxycarbonyl and acylamidocarbonyl compounds to furans, benzo[b]furans, and indoles (eq 20), respectively.[29] This new entry to aromatic heterocycles by reductive C–C bond formation of easily accessible precursors is compatible with a variety of other reducible sites in the substrates.[29]
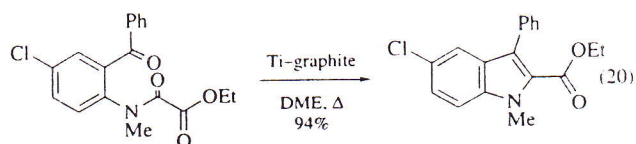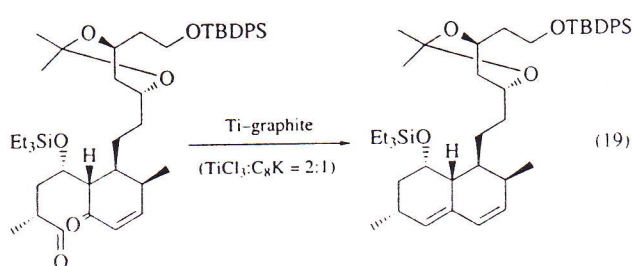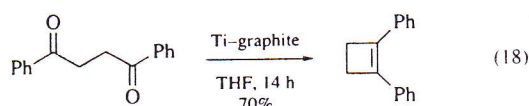
The performance of magnesium–graphite in reductive carbonyl coupling processes compares favorably to all other kinds of pinacol-forming agents described so far (eq 21).[26b] Metal–graphite combinations of platinum, palladium, and nickel have been used as highly efficient and selective catalysts for hydrogenation reactions as well as for catalytic C–C bond formations.[30] Preparative advantages have also been drawn from the use of other graphite reagents in organic and organometallic synthesis.[1,27a]
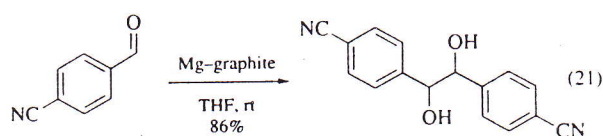
Related Reagents. Nickel–Graphite; Palladium–Graphite; Platinum on Carbon; Zinc–Graphite.

1. (a) Fürstner, A. AG(E) 1993, 32, 164. (b) Csuk, R.; Glänzer, B. I.; Fürstner, A. Adv. Organomet. Chem. 1988, 28, 85. (c) Savoia, D.; Trombini, C.; Umani-Ronchi, A. PAC 1985, 57, 1887. (d) Setton, R. In Preparative Chemistry Using Supported Reagents. Laszlo, P., Ed., Academic: New York, 1987; p 225.

2. Ebert, L. B. J. Mol. Catal. 1982, 15, 275.

3. Bergbreiter, D. E.; Killough, J. M. JACS 1978, 100, 2126.

4. Rabinovitz, M.; Tamarkin, D. SC 1984, 14, 377.

5. (a) Lissel, M.; Kottmann, J.; Lenoir, D. Chemosphere 1989, 19, 1499. (b) Lissel, M.; Kottmann, J.; Tamarkin, D.; Rabinovitz, M. ZN(B) 1988, 43, 1211.

6. (a) Savoia, D.; Trombini, C.; Umani-Ronchi, A. JCS(P1) 1977, 123. (b) Ellingsen, P. O.; Undheim, K. ACS 1979, B33, 528.

7. Contento, M.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. S 1979, 30.

8. (a) Setton, R.; Beguin, F.; Piroelle, S. Synth. Met. 1982, 4, 299. (b) Lalancette, J.-M.; Rollin, G.; Dumas, P. CJC 1972, 50, 3058.

9. Weitz, I. S.; Rabinovitz, M. JCS(P1) 1993, 117.

10. Tamarkin, D.; Benny, D.; Rabinovitz, M. AG(E) 1984, 23, 642.

11. Tamarkin, D.; Cohen, Y.; Rabinovitz, M. S 1987, 196.

12. (a) Fürstner, A.; Weidmann, H. J. Carbohydr. Chem. 1988, 7, 773. (b) Fürstner, A. LA 1993, 1211.

13. (a) Fürstner, A.; Koglbauer, U.; Weidmann, H. J. Carbohydr. Chem. 1990, 9, 561. (b) Fürstner, A. TL 1990, 3735. (c) Fürstner, A.; Praly, J. P. AG(E) 1994, 33, 751.

14. (a) Fürstner, A.; Weidmann, H. JOM 1988, 354, 15. (b) Müller, H.; Weinzierl, U.; Seidel, W. Z. Allg. Anorg. Chem. 1991, 603, 15.

15. Savoia, D.; Trombini, C.; Umani-Ronchi, A. TL 1977, 653.

16. Savoia, D.; Trombini, C.; Umani-Ronchi, A. JOC 1978, 43, 2907.

17. Fürstner, A.; Weidmann, H. JOC 1989, 54, 2307.

18. (a) Hegedus, L. S. PAC 1990, 62, 691. (b) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. OM 1990, 9, 2814.

19. Fischer, R. A.; Behm, J.; Herdtweck, E.; Kronseder, C. JOM 1992, 437, C29.

20. (a) Csuk, R.; Fürstner, A.; Weidmann, H. CC 1986, 775. (b) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. JOC 1983, 48, 4108.

21. (a) Fürstner, A. JOM 1987, 336, C33. (b) Fürstner, A.; Kollegger, G.; Weidmann, H. JOM 1991, 414, 295.

22. (a) Csuk, R.; Fürstner, A.; Glänzer, B. I.; Weidmann, H. CC 1986, 1149. (b) Pudlo, P.; Thiem, J.; Vill, V. CB 1990, 1129.

23. (a) Fürstner, A.; Jumbam, D. N.; Teslic, J.; Weidmann, H. JOC 1991, 56, 2213. (b) Fürstner, A.; Baumgartner, J.; Jumbam, D. N. JCS(P1) 1993, 131. (c) Fürstner, A.; Baumgartner, J. T 1993, 49, 8541.

24. Ireland, R. E.; Wipf, P.; Miltz, M.; Vanasse, B. JOC 1990, 55, 1423.

25. Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Gleason, J. L. JOC 1992, 57, 5071.

26. (a) Fürstner, A.; Weidmann, H. S 1987, 1071. (b) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. JCS(P1) 1988, 1729.

27. (a) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. JOM 1985, 280, 307. (b) Clive, D. L. J.; Zhang, C.; Murthy, K. S. K.; Hayward, W. D.; Daigneault, S. JOC 1991, 56, 6447. (c) Burger, P.; Brintzinger, H. H. JOM 1991, 407, 207.

28. Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; daSilva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. JACS 1990, 112, 3018.

29. (a) Fürstner, A.; Jumbam, D. N. T 1992, 48, 5991. (b) Fürstner, A.; Jumbam, D. N. CC 1993, 211. (c) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. JOC 1994, 59, 5215. (d) Fürstner, A. T 1995, 51, 773.

30. (a) Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. JOC 1981, 46, 5340 and 5344. (b) Savoia, D.; Trombini, C.;

Umani-Ronchi, A.; Verardo, G. *CC* **1981**, 540 and 541. (c) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *JOM* **1984**, *268*, 97. (d) Fürstner, A.; Hofer, F.; Weidmann, H. *J. Catal.* **1989**, *118*, 502.

31. Fürstner, A.; Singer, R.; Knochel, P. *TL* **1994**, *35*, 1047.

Alois Fürstner

Max-Planck-Institut für Kohlenforschung, Mülheim, Germany