



Photocatalytic Hydrogen Atom Transfer (HAT) in Organic Synthesis

Davide Ravelli

PhotoGreen Lab, Department of Chemistry
University of Pavia, viale Taramelli 12, 27100 Pavia

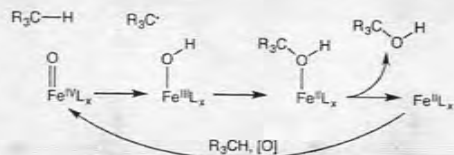
e-mail: davide.ravelli@unipv.it
website: www.unipv.it/photogreenlab

Napoli, September 22, 2018

Hydrogen Atom Transfer - HAT

A simple, yet fundamental, process: from biology to synthesis

The "Oxygen-rebound Mechanism": pathway for the hydroxylation of organic compounds by iron-containing oxygenases. These enzymes all utilize Fe-O centers that convert C-H bonds into C-OH groups.



Groves, J. T.

JBIC Journal of Biological Inorganic Chemistry **2017**, *22*, 185

Applications in SYNTHESIS

HALOGENATION

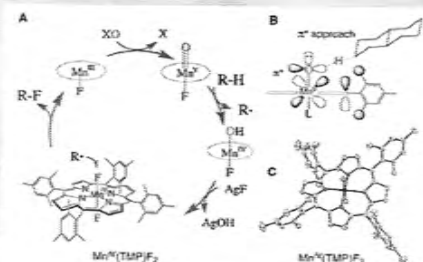
Groves, J. T. *Science* **2012**, *337*, 1322
Alexanian, E. J. *Chem. Sci.* **2018**, *9*, 5360

OXIDATION

Costas, M. *ACS Cent. Sci.* **2017**, *3*, 196
White, M. C. J. *Am. Chem. Soc.* **2017**, *139*, 14586

MECHANISM

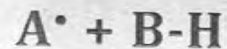
Bietti, M. *Acc. Chem. Res.* **2015**, *48*, 2895



Hydrogen Atom Transfer - HAT

A simple, yet fundamental, process: from biology to synthesis

Hydrogen atom transfer (HAT), a concerted migration of a proton and electron from a donor to an acceptor molecule in a single kinetic step



Mayer, J.M.

Acc. Chem. Res. **2011**, *44*, 36

Shaik, S.

Angew. Chem. Int. Ed. **2012**, *51*, 5556

Hammes-Schiffer, S.

ChemPhysChem. **2002**, *3*, 33



Source: scottlab.info

Cytochrome P450 (from IUPAC):

Member of a superfamily of heme-containing monooxygenases involved in xenobiotic metabolism, cholesterol biosynthesis, and steroidogenesis, in eukaryotic organisms found mainly in the endoplasmic reticulum and inner mitochondrial membrane of cells.

Photocatalytic Reactions

The combined use of a catalyst and light



Photocatalyst - PC
(IUPAC definition)



- Catalyst able to produce, upon absorption of light, chemical transformations of the reaction partners.

Deactivated PC

Reactive Intermediate

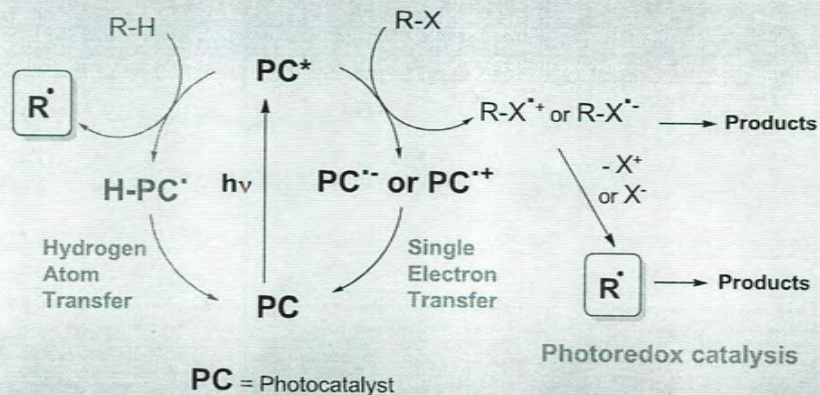
The excited state of the photocatalyst repeatedly interacts with the reaction partners forming reaction intermediates and **regenerates itself after each cycle of such interactions.**

Product

Chem. Rev. **2007**, *107*, 2725; *Chem. Soc. Rev.* **2009**, *38*, 1999; *Chem. Rev.* **2016**, *116*, 9850

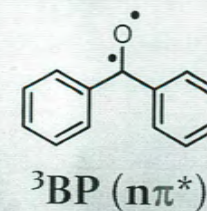
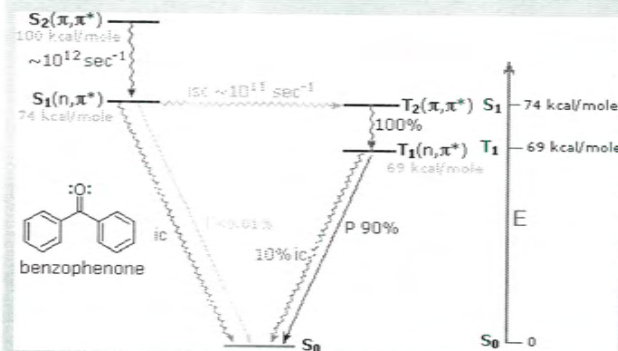
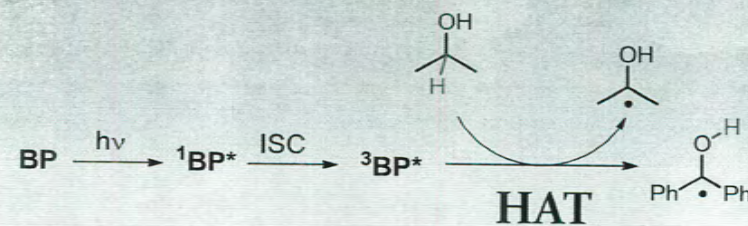
Photocatalytic Reactions in Synthesis

Modes of action of a Photocatalyst

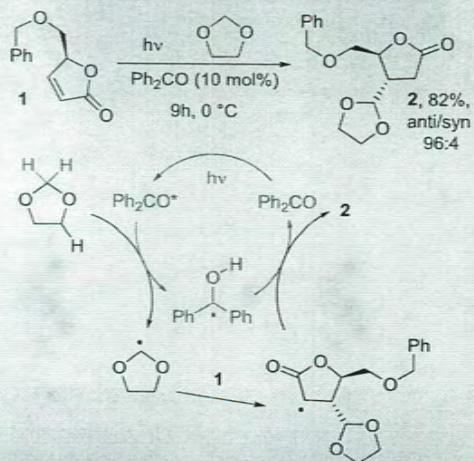


HAT via Photocatalytic Reactions

The case of Benzophenone (BP)

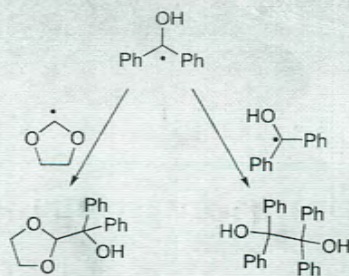


Aromatic ketones as Photocatalysts



Ghosh, A. K. *J. Org. Chem.* 2004, 69, 7822

Competitive pathways



For a review, see:

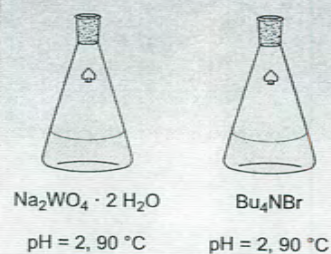
Kamijo S. (2018) C-H Activation via Radical Processes Using Photo-Excited Ketones. In: Landais Y. (eds) Free-Radical Synthesis and Functionalization of Heterocycles. Topics in Heterocyclic Chemistry, vol 54. Springer, Cham

POM (Wikipedia Definition): In chemistry, a polyoxometalate (abbreviated POM) is a polyatomic ion, usually an anion, that consists of three or more transition metal oxyanions linked together by shared oxygen atoms to form a large, closed 3-dimensional framework.

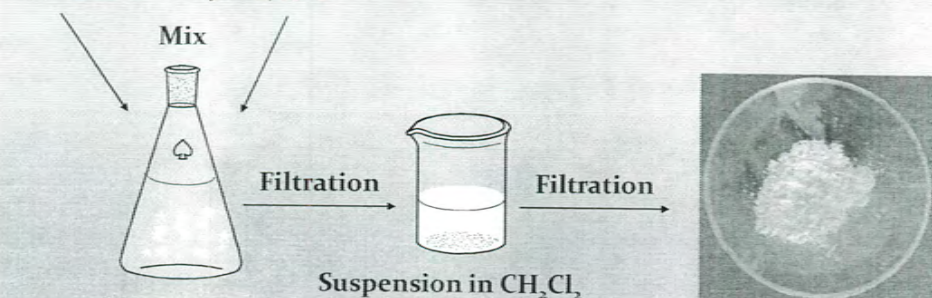
Photoactive POMs

- Keggin phosphotungstate $[\text{PW}_{12}\text{O}_{40}]^{3-}$
- Lindqvist tungstate $[\text{W}_6\text{O}_{19}]^{2-}$
- Decatungstate anion $[\text{W}_{10}\text{O}_{32}]^{4-}$

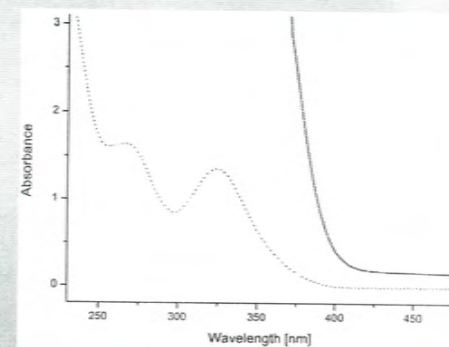
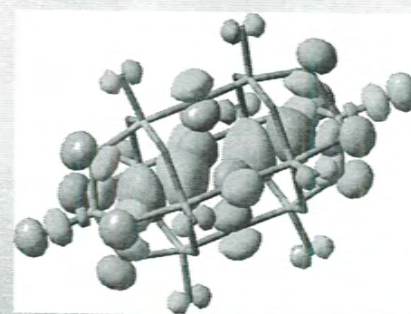
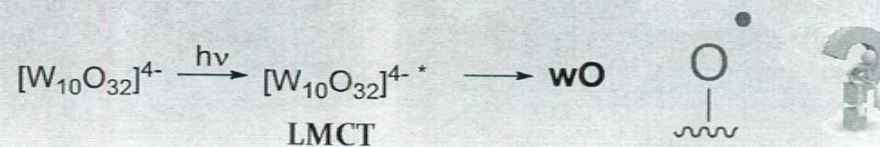
Preparation of $(n\text{Bu}_4\text{N})_4[\text{W}_{10}\text{O}_{32}]$ (TBADT)



Easily prepared
Cheap

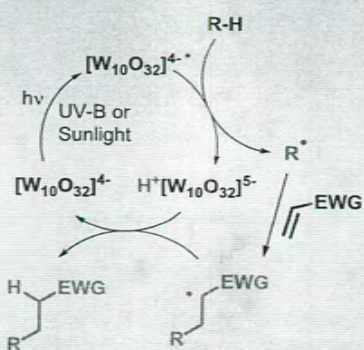


Excited $[\text{W}_{10}\text{O}_{32}]^{4-}$ An unknown player behaving like an oxyl radical



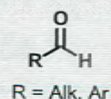
ACS Catal. 2016, 6, 7174

Applications in Organic Synthesis C-C Bond Formation via Conjugate Radical Addition

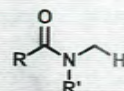


□ **Functionality-specific C-H bonds**

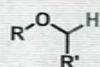
Aldehydes



Amides



Ethers (Acetals)



□ **Unactivated C(sp³)-H bonds**

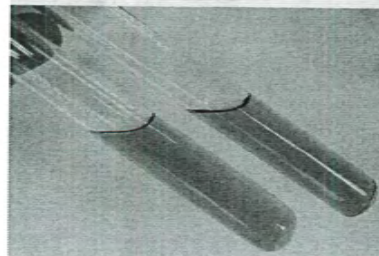
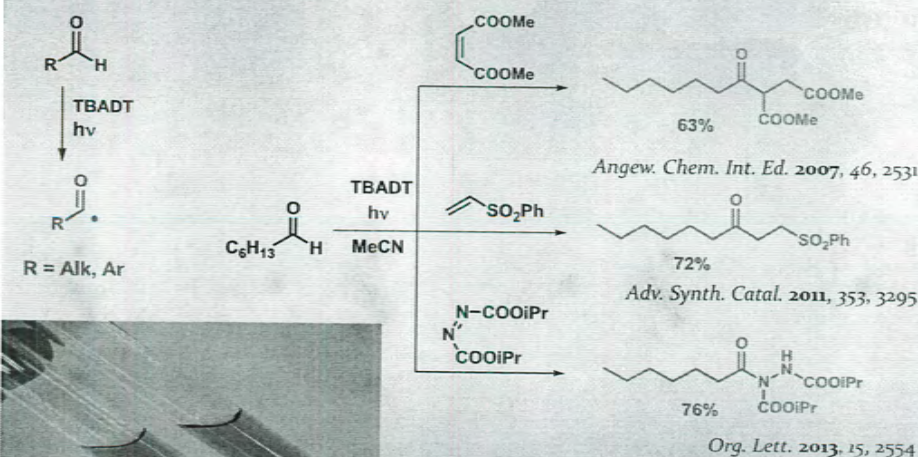
Alkanes

Atom economy
= 100% !

Acc. Chem. Res. 2016, 49, 2232

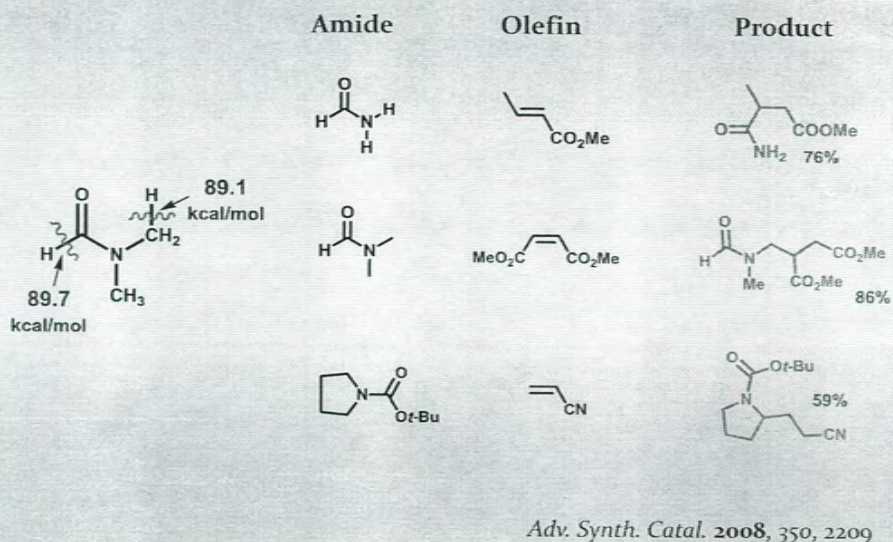
Orfanopoulos, M. Chem. Soc. Rev. 2009, 38, 2609

Formyl C-H Activation in Aldehydes A straightforward access to acyl radicals



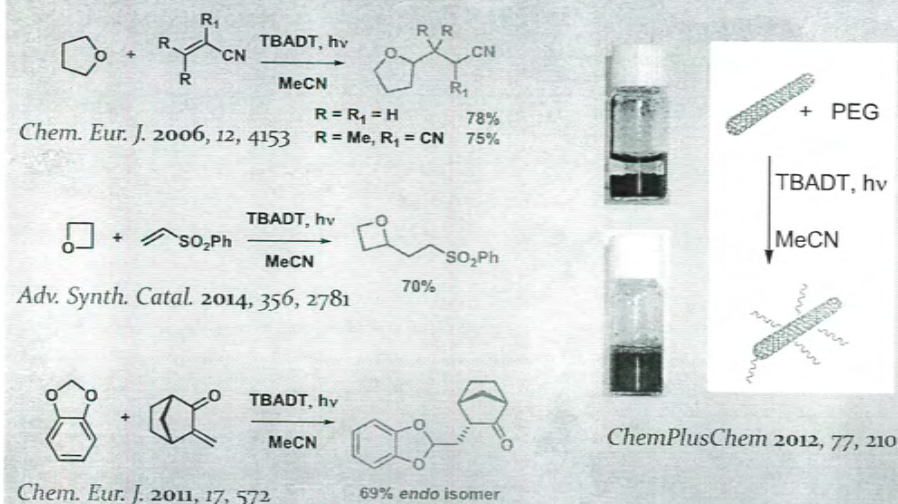
Activation of C-H bonds in Amides

Chemoselective C-H Cleavage



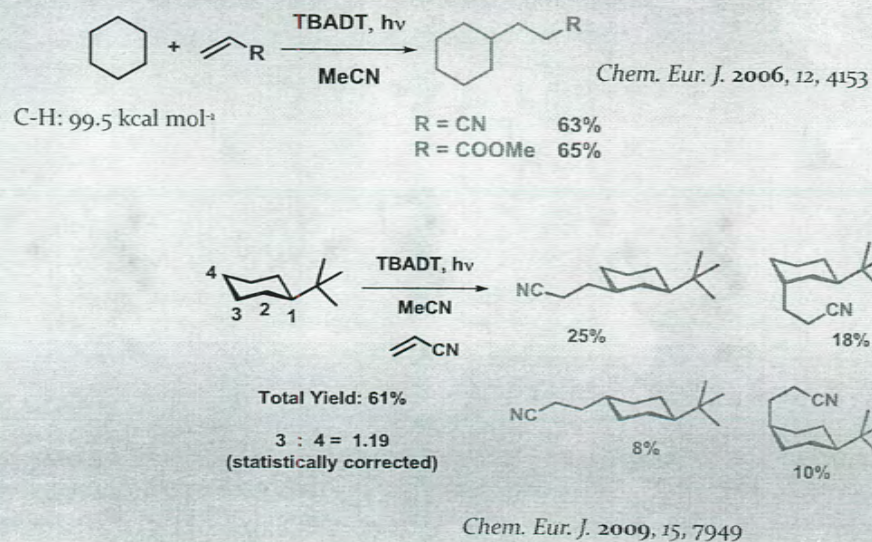
C-H Activation in oxygenated derivatives

HAT for the generation of α -oxy radicals



Photocatalytic HAT in Alkanes

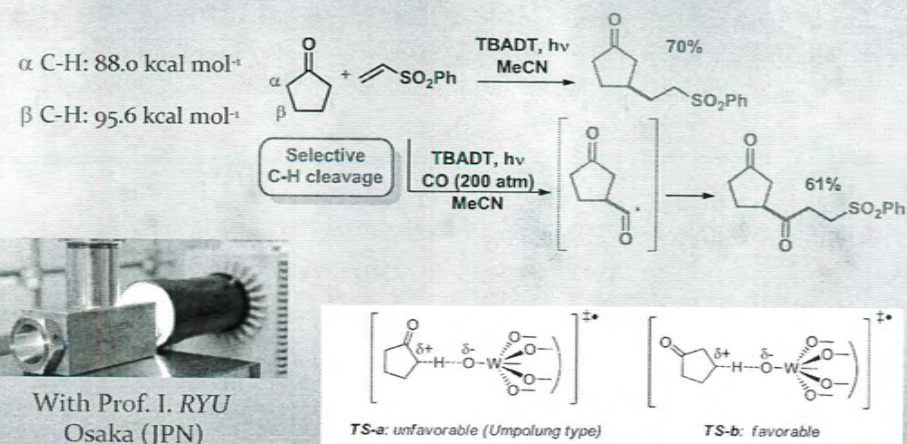
Exploiting steric effects in radical chemistry



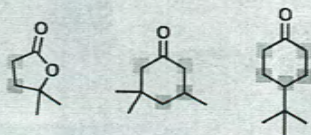
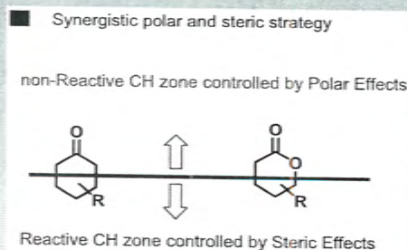
β -Alkylation of Cyclopentanones

Exploiting polar effects in radical chemistry

- High Selectivity towards the abstraction of Nucleophilic Hydrogens:



Combining Polar and Steric Effects



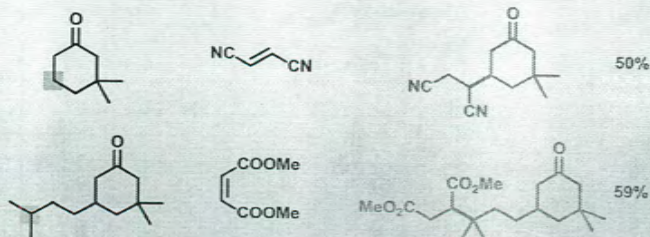
NO Reaction!



Cycloalkanone

Olefin

Product



50%

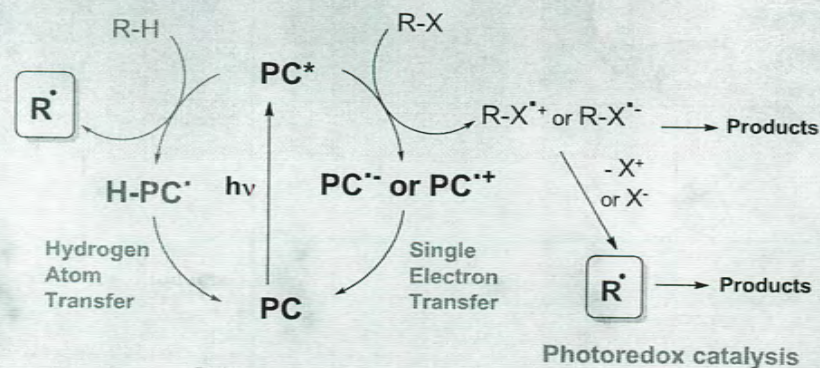
59%

ACS Catal. 2018, 8, 701

Chem. Eur. J. 2017, 23, 8615

Photocatalytic Reactions in Synthesis

Modes of action of a Photocatalyst



HAT reactions: the problem of the photocatalyst (limited in number, UV light absorbing!)

Wu, J. *Angew. Chem. Int. Ed.* 2018, 57, 8514

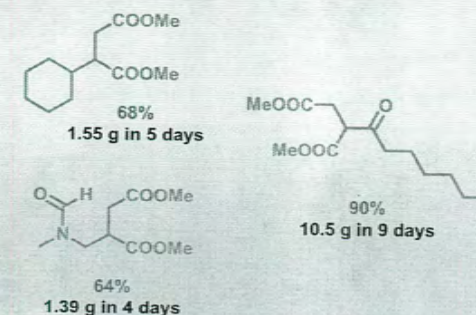
Solar Light Photocatalysis

A Green Approach to Synthesis - *Window-Ledge Chemistry*



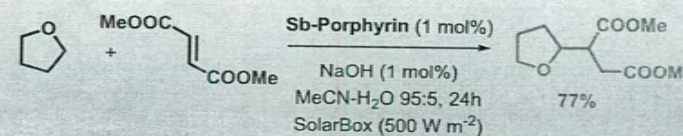
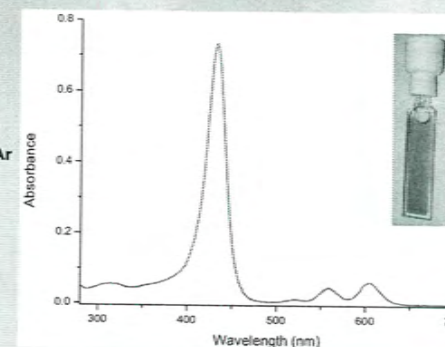
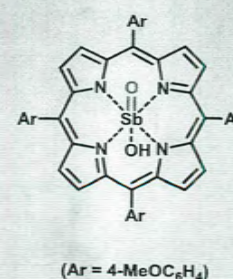
Reaction Mixture (Volume: 100 mL)

Chem. Commun. 2009, 7351



Visible light photocatalysts for HAT

Antimony-oxo porphyrins



With Prof. G. Knör, JKU Linz (Austria), *Unpublished results*

Conclusions & Perspectives

- TBADT offers a unique HAT reactivity:
 - Inexpensive;
 - Robust (in most cases a 2-4 mol% amount is used);
 - Versatile (different C-H bonds can be functionalized);
 - Offers peculiar, yet interesting, selectivities;

- Visible light absorbing photocatalysts represent a promising tool for HAT reactions



Proposal Title: Organic Synthesis via
Visible Light Photocatalytic
Hydrogen Transfer
Proposal Code: RBS1145Y9R



*Thank you for
your attention*

*SYNFORM 2010,
02, A13-A15*

*Cats sleep anywhere, any table, any chair.
Top of piano, **window-ledge**, in the middle, on the edge.
Open draw, empty shoe, anybody's lap will do.
Fitted in a cardboard box, in the cupboard with your frocks.
Anywhere! They don't care! Cats sleep anywhere.*

rhyme by Eleanor Farjeon