at −78 °C. The solution turned light yellow after addition was complete. Stirring was continued for 40 min at −78 °C, and then the reaction mixture was treated with saturated aqueous $(NH_4)_2SO_4$. The organic phase was removed, and the aqueous phase was washed with methylene chloride. The combined organic phases were dried, filtered, concentrated, and molecularly distilled [40 °C (0.005 torr)]. The distillate was chromatographed on silica with methylene chloride as eluent. The eluted product (R_f 0.39) was molecularly distilled at 40 °C (0.005 torr) to give ethyl 5-chloro-2-hydroxypentanoate (4) as a liquid (660 mg): IR ($CHCl_3$) λ_{max} 2.90, 5.79 μm; ^1H NMR ($CDCl_3$) δ 4.20 (q, J = 7 Hz, 2 H), 4.07 (m, 1 H), 3.4–3.7 (m, 2 H), 3.00 (s, 1 H), 1.7–2.1 (m, 4 H), 1.30 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 174.9 (s), 69.9 (d), 61.8 (t), 44.7 (t), 31.6 (t), 28.2 (t), 14.2 (q); MS, m/e (relative intensity) 165 (1), 163 (3), 127 (4), 109 (15), 107 (44), 71 (100). Anal. Calcd for $C_7H_{13}ClO_3$: C, 46.54; H, 7.25; Cl, 19.63. Found: C, 45.99; H, 7.21; Cl, 19.51.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

Registry No. 1, 86633-06-9; 2, 20462-00-4; 3, 86633-07-0; 4, 86633-08-1; 1-bromo-3-chloropropane, 109-70-6; lithium diisopropylamide, 4111-54-0.

Coupling Reactions of Higher Order Cuprates with Primary Halides: Extremely Mild and Efficient Substitution Reactions of Bromides and Chlorides

Bruce H. Lipshutz,*[1] David Parker,[2] and
Joseph A. Kozlowski

*Department of Chemistry, University of California,
Santa Barbara, California 93106*

Robert D. Miller

IBM Research Laboratory, San Jose, California 95193

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Among the many uses of organocuprate reagents in synthesis, the coupling between primary halides and ligands bound to copper constitutes one of the most common procedures for carbon–carbon bond construction.[3] Typically, primary iodides are the substrates of choice in terms of reactivity and efficiency, with tempertures as low as −78 °C routinely used with Gilman reagents.[3] The corresponding bromides couple well, although considerably higher temperatures (ca. 0 °C) and larger quantities of reagent may be needed.[3,4] In some of our recent work elucidating the stereochemical consequences of substitution chemistry at secondary unactivated centers,[5] it was found that treatment of a primary iodide with n-$Bu_2Cu(CN)Li_2$ led to a mixture of products rapidly at −100 °C. This result suggested that primary *bromides* might react with higher order, mixed cuprates $R_2Cu(CN)Li_2$ (1) under conditions normally characteristic of iodides with lower order species. In view of the difficulties oftentimes surrounding the preparation and handling of iodides in general (e.g., light sensitivity), we have investigated the possibility of utilizing a more stable bromide as a functional equivalent (reactivity-wise) of an iodide toward displacement by simply switching from copper halide to CuCN-based technology. We now report that, indeed, both chlorides and, in particular, bromides readily react in high yields with reagents 1 at remarkably reduced tempertures relative to those called for under the influence of R_2CuLi (2).[3,4]

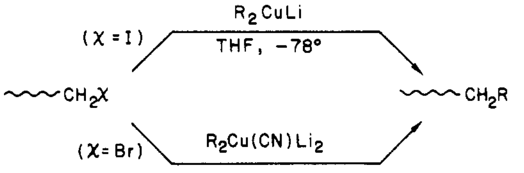
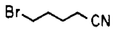
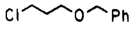
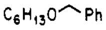
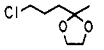
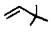
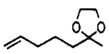
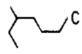
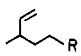
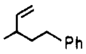
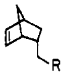
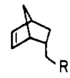
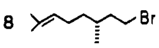
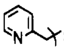
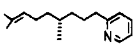
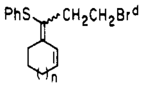
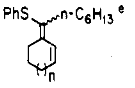


Table I. Reactions of $R_2Cu(CN)Li_2$ with Primary Halides

entry	substrate	cuprate/ conditions	equiv	product(s)	yield, %
1		n-$Bu_2Cu(CN)Li_2$ THF, −50°, 2.5h	1.3	$C_8H_{17}CN$	92[b]
2		n-$Pr_2Cu(CN)Li_2$ THF, 0°, 6h	2.0		81[b]
3		n-$Bu_2Cu(CN)Li_2$ THF, −50°, 2.5h	2.0	$C_{11}H_{24}$	95[a]
4		 $_2Cu(CN)Li_2$ THF, rt, 24h	4.0		58[a]
5		s-$Bu_2Cu(CN)Li_2$ THF, −78°, 0.75h	1.1		89[a]
6		$Ph_2Cu(CN)Li_2$			
	a, R = Br	THF, rt, 6h	2.0		91[a]
	b, R = OTs	THF, rt, 24h	2.0		95[a]
7		n-$Bu_2Cu(CN)Li_2$			
	a, R = Br	THF, 0°, 3.5h	1.7	R′ = n-Bu	91[a]
	b, R = OTs	THF, 0°, 21 h	2.0	R′ = n-Bu	30[a]
	c, R = OMs	THF, rt, 7h	2.0	R′ = OH	c
8		 $_2Cu(CN)Li_2$ THF, −50°, 3h	1.4		93[b]
9		n-$Bu_2Cu(CN)Li_2$ THF, −35°, 20h	2.0		
	a, n = 1				74[b]
	b, n = 2				72[b]

[a] By quantitative VPC. [b] Isolated yield of chromatographically pure product. [c] Only the alcohol was isolated. [d] See ref 7a. [e] See ref 7b.

A fairly broad sampling of functionalized substrates was examined as illustrated in Table I. Insofar as primary bromides are concerned, most reactions took place at −50 °C or below where alkyllithium-derived cuprates were involved (entires 1, 3, and 8). Thus, in addition to a straight-chain example (entry 3), clean displacement of bromide in 5-bromovaleronitrile (entry 1) afforded pelargononitrile in 92% isolated yield. Substituted pyridines could also be prepared by using the reagent formed from lithiated picoline[6] and CuCN (entry 8). Less reactive reagents (e.g., 1, R = Ph, entry 6a) required higher temperatures, in this case room temperature for 6 h, without, however, compromising reaction efficiency. Likewise,

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[1] Recipient of an American Cancer Society Junior Faculty Research Award, 1981–1983.

[2] Recipient of University of California Reagents Fellowship, 1981–1982.

[3] Posner, G. H. *Org. React.* (*N.Y.*) **1975**, *22*, 253.

[4] Whitesides, G. M.; Fischer, W. F.; San Fillippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

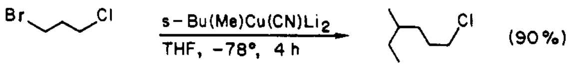
[5] Lipshultz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696.

[6] Lithiated 2-picoline was prepared following the basic recipe of Danishefsky et al. for the metalation of 2,6-lutidine, substituting n-BuLi as base in place of PhLi; Danishefsky, S.; Cain, P. *J. Org. Chem.* **1974**, *39*, 2925.

highly hindered halides, e.g., a norbornene derivative (entry 7a), called for 0 °C for 3.5 h while still affording an excellent yield of the desired hydrocarbon. Thioenol ethers (entry 9)[7a] tended to be quite sensitive to reaction temperatures as well, although under carefully controlled conditions good isolated yields of products were realized.[7b]

Primary chlorides generally couple with 1 at ca. 0 °C. For example, the benzyl ether of 3-chloro-1-propanol (entry 2) reacted with n-Pr$_2$Cu(CN)Li$_2$ to give benzyl n-hexyl ether (81%, isolated). This ca. 50° difference in reactivity between bromides and chlorides could be used to advantage in the case of 1-bromo-3-cloropropane, which underwent substitution with 1, R = *sec*-Bu at −78 °C exclusively at the carbon-bearing bromine to afford the primary chloride. Entry 4, which cites the reaction between a less reactive chloro ketal with a relatively sluggish vinyl cuprate (1, R = vinyl) led to at best a 58% yield of olefinic ketal, in spite of the large excess of reagent and higher temperature used. It should be noted, however, that while this particular result is not in line with the other entries in the table, the corresponding reaction employing 2 (R = vinyl), under otherwise identical conditions, gave less than 2% of the expected product.

In order to briefly examine the selectivity of transfer[8] of two different ligands attached to copper [i.e., $R_TR_{R'}$Cu(CN)Li$_2$, where R_T = a (potentially valuable) transferable residue, $R_{R'}$ = a nontransferable, second "dummy" ligand], we have prepared the reagent *sec*-Bu(Me)Cu(CN)Li$_2$, 3, via sequential addition of MeLi and *sec*-BuLi to CuCN. Reaction of 3 (1.3 equiv) with 4 afforded chloride 5 in 90% (VPC) yield with 100% selectivity of transfer of the *sec*-Bu ligand.[9]



4 5

Sulfonates were briefly investigated as they are oftentimes convenient reaction partners.[3] Sterically uncongested tosylates (e.g., entry 6b) appear to undergo displacement in high yields, while more demanding situations (e.g., entry 7b) lead to poor yields of product. Mesylates appear to suffer elimination, returning the alcohol portion essentially quantitatively. Thus, it is interesting that where higher order cuprates are concerned, primary bromides tend to be the preferred substrates over *both* iodides and tosylates, a phenomenon quite unexpected and contrary to CuI-based cuprate chemistry.[3,10]

In summary, this study demonstrates that primary bromides and chlorides may serve as equivalents of primary iodides and bromides, respectively, in coupling reactions with organocopper reagents by simply chosing an alternative source of the Cu(I) salt (namely, CuCN over CuX). This method permits and encourages use of the more manageable bromides over iodides, especially now that their reactivity and/or reaction efficiency in substitution processes are no longer in question.

Experimental Section

All glassware and syringes were dried in an oven (120 °C overnight prior to use. Ethereal solvents (Et$_2$O, THF) were freshly distilled from sodium/benzophenone. Methyllithium was purchased from Aldrich, while n-butyllithium, *sec*-butyllithium, and phenyllithium were purchased from Ventron; n-propyllithium was prepared from n-propyl chloride; vinyllithium was obtained from Organometallics; all commercial lithium reagents were titrated by the method of Watson and Eastham.[11] IR spectra were recorded on a Perkin-Elmer Model 283 infrared spectrophotometer. NMR data were obtained on a Varian T-60, FT-80, or XL-100 spectrometer. VPC analyses were conducted on a Hewlett-Packard Model 5880 A gas chromatograph. All runs were carried out with a 6 ft × $^1/_8$ in. column packed with 20% SE-30 on Chromosorb W. TLC analyses were conducted with 0.25-mm glass plates purchased from Baker. Column chromatography was performed by using silica gel-60 from Merck, 70–230 mesh.

Representative Procedures for Substitution Reactions. Pelargononitrile. Copper cyanide (0.0896 g, 1.0 mmol) was placed in a 25-mL, two-necked round bottomed flask, evacuated with a vacuum pump, and purged with argon, and the procedure was repeated three times. THF (1.0 mL) was injected via syringe and the resulting slurry cooled to −75 °C where n-butyllithium (0.8 mL, 2.0 mmol) was added dropwise. Subsequent warming to 0 °C produced a tan solution, which was immediately recooled to −50 °C, followed by dropwise addition, via syringe, of 5-bromovaleronitrile (0.089 mL, 0.77 mmol). The reaction was stirred at this same temperature for 2.5 h followed by quenching with 5 mL of 9:1 saturated NH$_4$Cl/concentrated NH$_4$OH solution. Extraction with Et$_2$O (3 × 5 mL), drying over Na$_2$SO$_4$, and evaporation of the solvent in vacuo resulted in a light yellow oil. This was then chromatographed on silica gel with 15% Et$_2$O/pentane to yield 0.099 g (92%) of a clear liquid: TLC R_f 0.5 (20% Et$_2$O/pentane); NMR and IR data were identical when compared with that of pelargononitrile (Aldrich).

Benzyl *n*-Hexyl Ether. To 89 mg (1.0 mmol) of dry CuCN in a two-necked flask under Ar was added 1.0 mL dry THF, and the slurry was cooled to −78 °C. n-PrLi (1.0 mL, 2 mmol, 1.96 M) in hexane was added and the mixture warmed to 0 °C whereupon a solution resulted. The flask was recooled to −78 °C, and the chloride, dissolved in 0.5 mL THF, was added via canula, followed by warming to 0 °C and stirring at this temperature for 7 h. Quenching with 10% concentrated NH$_4$OH/90% saturated NH$_4$Cl at 0 °C followed by an extractive workup (Et$_2$O) and filtration of the residue through SiO$_2$ with 2.5% Et$_2$O/pentane afforded 75 mg (78%) benzyl n-hexyl ether plus 3.3 mg of the starting material (81% based on recovered chloride): IR (neat) cm^{-1} 3038, 1210, 1110; NMR (CDCl$_3$) δ 0.87 (3 H, unresolved t), 1.05–1.83 (8 H, m), 3.42 (2 H, t, J = 6 Hz), 4.44 (2 H, s), 7.25 (5 H, s); mass spectrum, m/e (relative intensity), 192 (M$^+$, 0.47), 92 (58), 91 (100); exact mass calcd for C$_{13}$H$_{20}$O 192.1514, found 192.1509.

Acknowledgment. Financial support from the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the American Cancer Society (JFRA No. 37 to B.H.L.) is gratefully acknowledged. We thank Dr. H. Webb for recording the mass spectral data.

Registry No. 1 (R = n-Bu), 80473-69-4; 1 (R = n-Pr), 80473-72-9; 1 (R = vinyl), 80473-65-0; 1 (R = *sec*-Bu), 86646-53-9; 1 (R = Ph), 80473-66-1; 1 (R = 2-picolinyl), 86668-10-2; 4, 109-70-6; 5, 86646-45-9; Br(CH$_2$)$_4$CN, 5414-21-1; Cl(CH$_2$)$_3$OCH$_2$Ph, 26420-79-1; Br(CH$_2$)$_6$CH$_3$, 629-04-9; H$_2$C=CHCH(CH$_3$)(CH$_2$)$_2$OTs, 86646-40-4; (CH$_3$)$_2$C=CH(CH$_2$)$_2$CH(CH$_3$)(CH$_2$)$_2$Br,

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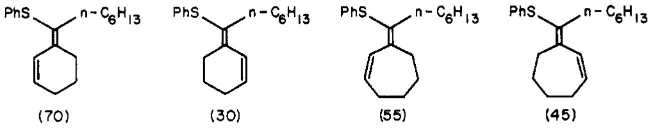
[7] (a) Miller, R. D.; McKean, D. R.; Kaufmann, D. *Tetrahedron Lett.* **1979**, 587. (b) Isomer ratios were determined by NMR and are very similar to those of the starting bromides. For case a, a 70:30 mixture is seen, case b, a 55:45 ratio, the stereochemistry tentatively assigned as shown below on the basis of NMR data.



[8] Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 400.

[9] The use of a methyl group as the $R_{R'}$ ligand was anticipated from the difference in conditions required for effecting substitution at secondary centers; cf.: Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. The details on the use of these more highly mixed higher order cuprates will be forthcoming in our full account of the substitution chemistry of reagents 1.

[10] Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777, 7783.

[11] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

10340-84-8; $H_2C{=}CHCH(CH_3)(CH_2)_2Br$, 59822-10-5; $C_8H_{17}CN$, 2243-27-8; $C_6H_{13}OCH_2Ph$, 61103-84-2; $C_{11}H_{24}$, 1120-21-4; $H_2C{=}CHCH(CH_3)(CH_2)_2Ph$, 42524-30-1; 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, 5978-08-5; 5-(bromomethyl)bicyclo[2.2.1]hept-2-ene, 17016-12-5; 5-(tosyloxymethyl)bicyclo[2.2.1]hept-2-ene, 50626-34-1; 5-(mesyloxymethyl)bicyclo[2.2.1]hept-2-ene, 86646-41-5; (*E*)-[[(2-bromoethyl)-2-cyclohexen-1-ylidenemethyl]thio]benzene, 86646-42-6; (*E*)-[[(2-bromoethyl)-2-cyclohepten-1-ylidenemethyl]thio]benzene, 86646-43-7; 2-methyl-2-(4-penten-1-yl)-1,3-dioxolane, 86646-44-8; 5-pentylbicyclo[2.2.1]hept-2-ene, 22094-82-2; bicyclo[2.2.1]hept-2-ene-5-methanol, 95-12-5; (*R*)-2-[4,8-dimethylnon-8-en-1-yl]pyridine, 86646-46-0; (*E*)-[[(2-cyclohexen-1-ylidene)hexylmethyl]thio]benzene, 86646-47-1; (*Z*)-[[(2-cyclohexen-1-ylidene)hexylmethyl]thio]benzene, 86646-48-2; (*E*)-[[(2-cyclohepten-1-ylidene)hexylmethyl]thio]benzene, 86646-49-3; (*Z*)-[[(2-cyclohepten-1-ylidene)hexylmethyl]thio]benzene, 86646-50-6; (*Z*)-[[(2-bromoethyl)-2-cyclohexen-1-ylidenemethyl]thio]benzene, 86646-51-7; (*Z*)-[[(2-bromoethyl)-2-cyclohepten-1-ylidenemethyl]thio]benzene, 86646-52-8.

Conversion of Acetals and Ketals to Carbonyl Compounds Promoted by Titanium Tetrachloride

Geneviève Balme and Jacques Goré*

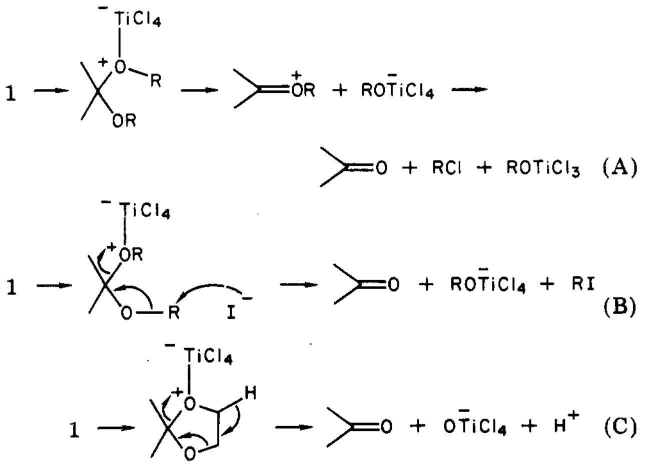
Laboratoire de Chimie Organique 1, ERA 611 du CNRS, Université de Lyon I, ESCIL, 69622 Villeurbanne, France

Received December 20, 1982

If many solutions have been proposed in the recent years for the conversion of thioketals into ketones under mild conditions,[1,2] only a few works were concerned with the deprotection of acetals and ketals and more particularly of dioxolanes, which remain the most usual protecting group for the ketone functionality. Generally, the carbonyl moiety is regenerated from acetals and ketals by aqueous acid hydrolysis or by strong-acid-catalyzed exchange with acetone.[2] However, such conditions are very often incompatible with the presence in the molecule of some other functional group like protected hydroxyl group.

Recently, more neutral reagents were described for the hydrolysis or exchange of acetals and ketals: acidified silica gel,[3] lithium tetrafluoroborate in wet acetonitrile,[4] acetone in the presence of pyridinium tosylate.[5] At least two nonaqueous methods have also been proposed for the deprotection of acetals and ketals with the exception of dioxolanes: the first one uses phosphorus triiodide and diphosphorus tetraiodide[6] while the second one is based on the electrophilicity of trimethylsilyl iodide.[7]

Scheme I



We report now that the deprotection of acetals and ketals, including dioxolanes, can be effectively realized in mild conditions by titanium tetrachloride in diethyl ether at room temperature. The results obtained with eight acetals and ketals **1** are summarized in Table I.

The dimethyl acetal **1c** is rapidly transformed to benzaldehyde (entry 3) at room temperature by treatment with 0.5 molar equiv of $TiCl_4$ (GC analysis reveals an almost quantitative yield). However, the same conditions are inoperant with acetal **1a** derived from a saturated aldehyde after 48 h, only 10% deprotection is observed. The rate of this reaction is greatly improved by adding 1 molar equiv of lithium iodide, and the parent aldehyde is then obtained with good yield starting either from the methyl or the ethyl acetal (entries 1 and 2). The presence of this coreagent is not necessary in the case of the methyl ketal of cyclohexanone but it increases markedly the rate of the reaction (entries 4 and 5).

The other results show that the method is also effective for dioxolanes, mainly those of cyclohex-2-en-2-ones **1g** and **1h**, which are rapidly deprotected in the presence of a slight molecular excess of $TiCl_4$ (entries 9 and 10). It can be noticed that in the case of **1g**, the same deprotection–dehydration process was previously done at room temperature by 2 N hydrochloric acid,[8] but the requisite time was then 10 h and the yield was lower. This example shows the efficiency of $TiCl_4$ for such a deprotection. Also, the case of **1h**[9] is representative of the chemoselectivity of the reagent since the tetrahydropyranyloxy protective group was unaffected by conditions that remove completely the ethylene ketal group (entry 10).

If an aliphatic ketone is regenerated without any problem (entry 8), the case of the dioxolane of cyclohexanone was not completely solved. As shown by entry 6, the rate of the reaction is slow and cannot be increased: the use of a slight excess of $TiCl_4$ and the addition of lithium chloride or fluoride to the reaction mixture cause intense polymerization while lithium bromide and iodide are unefficient. In methylene chloride, a better solvent than ether for $TiCl_4$, the acetal **1e** has completely reacted after several hours at room temperature, but the reaction leads to a complicated mixture of unidentified products where cyclohexanone is absent. The best conditions for the conversion of **1e** into cyclohexanone are those described in entry 6. The yield is good, but the starting material (20%) still remaining cannot be transformed by stretching out the reaction time to 48 h.

With regard to the mechanism of these transformations of acetals and ketals to carbonyl compounds, different processes (Scheme I) can be proposed depending on the

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[1] For recent methods and review see: (a) G. A. Olah, S. C. Narang, and G. F. Salem, *Synthesis*, 657 (1980); (b) G. S. Bates and J. O'Doherty, *J. Org. Chem.*, **46**, 1745 (1981); (c) G. A. Olah, S. C. Narang, A. Garcia Luna, and G. F. Salem, *Synthesis*, 146 (1981); (d) D. Ghiringhelli, *Ibid.*, 580 (1982).

[2] T. W. Greene, "Protective Group in Organic Synthesis", Wiley, New York, 1981, p 144.

[3] F. Huet, A. Lechevalier, M. Pellet, and J. M. Conia, *Synthesis*, 63 (1978).

[4] B. H. Lipshutz and D. F. Harvey, *Synth. Commun.* 12, 267 (1982).

[5] R. Sterzycki, *Synthesis*, 724 (1979).

[6] J. N. Denis and A. Krief, *Angew. Chem., Int. Ed. Engl.*, **19**, 1006 (1980).

[7] M. E. Jung, W. A. Andrus, and P. L. Orstein, *Tetrahedron Lett.*, 4175 (1977).

[8] J. Lafontaine, M. Mongrain, M. Sergent-Guay, L. Ruest, and P. Deslongchamps, *Can. J. Chem.*, **58**, 2460 (1980).

[9] The preparation of this ketal will be described in G. Balme's Ph.D. Thesis, Lyon, 1983.

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