Notes

New Application of Aggregative Activation: A Very Efficient Epimerization of Alcohols

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Introduction

During our studies on the stereoselective reduction of ketones[1] with complex reducing agents[2,3] (MCRA's), we confirmed the suspected[2a] oxido-reductive properties of a number of these reagents. In fact oxido-reduction is expected every time a transition-metal species prone to give β-metal hydride eliminations is included in CRA's. Taking account of these observations the epimerization of alcohols as given in Scheme I may be proposed.

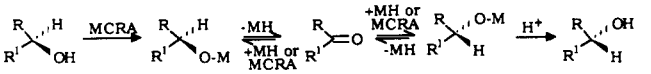
From the literature two kinds of epimerization appear. The first relates to the Merwein–Pondorff–Verley–Oppenauer (MPVO) oxido-reduction[4,5] and is performed in the presence of a ketone and of 1 equiv of aluminium alkoxide[4] or hydride.[5] The second involves the use of Raney nickel under protic or aprotic conditions.[4,6]

From previous work,[7] CRA's appeared more efficient and worked without added ketone under mild conditions. Moreover, CRA aggregates being completely different from the literature reagents, different equilibrium positions could be expected.

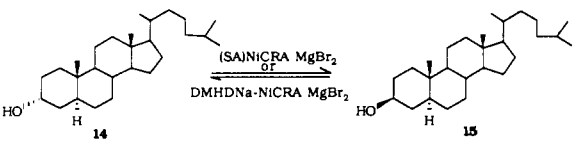
Results and Discussion

Thermodynamic Equilibration of Alcohols by MCRA's. The different factors influencing the properties of MCRA's were studied with 4-*tert*-butylcyclohexanols. We draw the following conclusions:[7b] among the known MCRA's,[2a] Mn, Co, and NiCRA's were the most efficient. The best ones were NiCRA's, which thus were chosen for the present work. Concerning NiCRA's: (i) the best conditions were found at 63 °C in THF. (ii) According to the preceding paper,[1] the sodium salt of 2,5-dimethylhexane-2,5-diol (DMHD) was found to be the best activating agent. The corresponding CRA's will be abbreviated DMHDNa–NiCRA's. On the other hand, a number of substrates to be epimerized were themselves good activating agent. These substrate-activated CRA's will be abbreviated (SA)NiCRA's. (iii) $MgBr_2$ was found as the best additive to improve the reduction of the formed ketone.

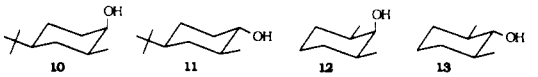
Scheme I



Scheme II



Equilibration of Unsubstituted or Alkyl-Substituted Cycloalkanols. Taking into account the above conclusions, we first studied the behavior of representative alcohols against four reagents: DMHDNa–NiCRA (reagent A); DMHDNa–NiCRA–$MgBr_2$ (reagent B); (SA)NiCRA (reagent C); (SA)NiCRA–$MgBr_2$ (reagent D). The results obtained are grouped in Table I. It appears that NiCRA's were, in many cases, much more efficient than Ni Raney or MPVO reaction. As far as the ratios of epimers are concerned NiCRA's resemble $LiAlH_4$–$AlCl_3$. Moreover, with hard to epimerize alcohols such as borneol or fenchol NiCRA's were much more efficient catalysts. It also appeared that with a few exceptions the thermodynamic equilibria were reached since the same alcohols ratios were obtained when starting from either epimer. During the reduction of 2-methylated ketones, epimeization of the methyl group was observed.[8d] So epimerization of alcohols **10**–**13** was undertaken.



The results observed may be summarized as follow: (i) Starting from **10** or **11** and whatever the NiCRA used, the epimerization of the methyl group never exceeds 2 to 12% while the hydroxyl group was completely epimerized. (ii) Selective hydroxyl epimerization of **12** and **13** was unsuccessful, 30 to 50% of methyl epimerization was observed.

Finally, as an application of the above results, we performed the epimerization given in Scheme II. Starting from **14** or **15** an equilibrium ratio **15**/**14** of 96/4 was obtained after 3 h with a 96% yield. MPVO led to 84/16[8b] while $LiAlH_4$–$AlCl_3$ to 100/0.[8c]

Equilibration of Cycloalkanols 16 Possessing an Oxygen or Nitrogen Atom in the Neighborhood of the Hydroxyl Group. From unreported works, it appeared

(1) Fort, Y.; Feghouli, A.; Vanderesse, R.; Caubère, P. *J. Org. Chem.*, accompanying paper in this issue.

(2) (a) Caubère, P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 599. In this paper we have adopted the following convention: a MCRA (metal atom specified) prepared from NaH, RONa, and Mx_n will be abbreviated MCRA ($x/y/z$). In the same way a MCRA–$MgBr_2$ prepared from NaH, RONa, MX_n, and $MgBr_2$ will be abbreviated MCRA–$MgBr_2$ ($x/y/z/t$) where molar ratio NaH/RONa/MX_n/$MgBr_2$ (in that order) is equal to $x/y/z/t$. (b) Caubère, P. 8th FECHEM on Organometallics, VESZPREM, HUNGARY, 8/1989.

(3) See, for example: (a) Vanderesse, R.; Brunet, J. J.; Caubère, P. *J. Org. Chem.* **1981**, *46*, 1270. (b) Fort, Y.; Vanderesse, R.; Caubère, P. *Tetrahedron Lett.* **1985**, *26*, 3111. (c) Fort, Y.; Vanderesse, Caubère, P. *Tetrahedron Lett.* **1986**, *27*, 5487.

(4) See, for example: (a) Chiurdoglu, G.; Masschelein, W. *Bull. Soc. Chim. Bel.* **1961**, *70*, 767. (b) Wicker, R. J. *J. Chem. Soc.* **1956**, 2165.

(5) Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367.

(6) (a) Eliel, E. L.; Schroeter, H. S. *J. Am. Chem. Soc.* **1965**, *87*, 5031. (b) Eliel, E. L.; Schroeter, H. S.; Brett, T. J.; Biros, F. J.; Richer, J. C. *J. Am. Chem. Soc.* **1966**, *88*, 3327 and references cited therein.

(7) (a) Feghouli, G.; Vanderesse, R.; Fort, Y.; Caubère, P. *Tetrahedron Lett.* **1988**, *29*, 1383. (b) Feghouli, G. Thèse de l'Université de Nancy I, France, 1989.

(8) (a) Coulombeau, A.; Rassat, A. *Bull. Soc. Chim. Fr.* **1965**, 3338 and references cited therein. (b) Nace, H. R.; O'Connor, G. L. *J. Am. Chem. Soc.* **1951**, *73*, 5824. (c) Wilcox, C. F.; Sexton, M.; Wilcox, M. F. *J. Org. Chem.* **1963**, *28*, 1079. (d) Eliel, E. L.; Ro, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 5992. (e) Eliel, E. L.; Haubenstock, H. *J. Org. Chem.* **1961**, *26*, 3504. (f) Eliel, E. L.; Nasipuri, D. *J. Org. Chem.* **1965**, *30*, 3809.

0022-3263/90/1955-5916$02.50/0

Table I. Thermodynamic Equilibration[a] of Alcohols by MCRA's

entry	alcohol	reagent	time (h)	yield, %[b,c]	alcohols ratio, %[b-d]	ketone, %[b,c]	alcohols ratio, % (lit.)[d]
1	*cis*-4-*tert*-butylcyclohexanol (1)	A	18	97 97	98/2 98/2	2 2	79/21 MPVO[e], (8d)
2		B	18	99 99	98/2 98/2	tr *tr*	96–97/4–3 LiAl[f] (5)
3		C	18	95 97	98/2 98/2	4 2	72.5/27.5 NiR[g] (6b)
4		D	18	99 99	98/2 98/2	tr *tr*	
5	*cis* 2-methylcyclohexanol (2)	A	5	91 97	94/6 94/6	tr *tr*	83/17 MPVO (8d)
6		B	24	99 98	94/6 94/6	tr tr	82/18 NiR (6b)
7		C	18	90 99	94/6 94/6	6 *tr*	
8		D	18	92 99	93/7 93/7	4 *tr*	
9	*trans*-3-methylcyclohexanol (3)	A	3	91 99	94/6 92/8	tr *tr*	79/21 MPVO (8d)
10		B	5	99 99	94/6 94/6	tr *tr*	94/6 LiAl (8d)
11		C	24	85 99	92/8 90/10	14 *tr*	78–72.6/22–27.4 NiR (6b)
12		D	18	98 99	90/10 90/10	tr *tr*	
13	*cis*-4-methylcyclohexanol (4)	A	5	99 99	90/10 91/9	tr *tr*	68.5/31.5 MPVO (8d)
14		B	3	99 99	90/10 90/10	tr *tr*	92/8 LiAl (5)
15		C	18	78 96	90/10 91/9	15 2	70–75/30–25 NiR (6b)
16		D	4	98 99	90/10 90/10	tr *tr*	
17	*cis*-2-ethyl cyclohexanol (5)	A	66	95 96	80/20 80/20	3 *tr*	77.8/22.2 MPVO (6b)
18		B	0.5 (3)[h]	99 99	81/19 79/21	tr *tr*	77/23 NiR (6b)
19		C	66	97 96	80/20 80/20	tr *tr*	
20		D	66	95 96	80/20 80/20	3 *tr*	
21	*trans*-3,3,5-trimethylcyclohexanol[h] (6)	A	5	90 99	97/3 98/2	10 *tr*	94/6 MPVO (8e)
22		B	44	98 99	98/2 98/2	2 *tr*	100/0 LiAl (8f)
23		C	18	50 86	97/3 97/3	45 *tr*	93/7 NiR (6b)
24		D	4	94 99	98/2 98/2	5 *tr*	
25	*endo*-norborneol (7)	A	4	91 99	89/11 90/10	2 *tr*	80/20 MPVO (6b)
26		B	4	99 99	90/10 90/10	tr *tr*	89/11 LiAl (8c)
27		C	18	96 99	88/12 90/10	2 *tr*	82.4/17.6 NiR (6b)
28		D	18	99 99	90/10 90/10	tr *tr*	
29	*exo*-borneol (8)	A	42	96 97	76/24 81/19	2 2	79/21 MPVO (6b)
30		B	28	99 99	78/22 80/20	tr *tr*	LiAl: side reactions (8c)
31		C	5	98 99	71/29 79/21	2 *tr*	
32		D	18	94 99	79/21 80/20	4 *tr*	
33	*exo*-fenchol (9)	A	3 (18)[h]	92 97	48/52 79/21	7 5	equilibration never obtained (8a)
34		B	4	95 99	80/20 91/9	3 4	
35		C	18	99 99	52/48 88/12	2 *tr*	
36		D	5 (18)[h]	90 97	81/19 81/19	5 2	

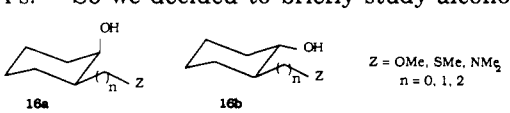
[a] Reactions performed at 63 °C in THF on a 10-mmol scale with 4/1/1 or 4/1/1/1 molar ratio reagents. [b] Starting from less stable alcohol (normal characters). [c] Starting from more stable alcohol (italic characters). [d] Ratio of more stable alcohol/less stable alcohol in percent. [e] MPVO: Meerwein–Pondorff–Verley–Oppenhauser method using $(Pr^iO)_3Al$. [f] LiAl: $LiAlH_4$–$AlCl_3$ procedure. [g] NiR: Raney nickel method. [h] Reaction time with more stable alcohol.

Table II. Equilibration of Cycloalkanols[a] Possessing an Oxygen or a Nitrogen Atom in the Neighborhood of the Hydroxyl Group

	16						
entry	*n*	Z	reagent[b]	time (h)	yield, %[c,d]	alcohol ratio, %[c-e]	ketone, %[c,d]
1	0	MeO	B	72	84 99	68/32 75/25	5 *tr*
2	0	MeO	D	66	94 99	69/31 71/29	tr *tr*
3	0	NMe_2	B	36	94 97	76/24 90/10	2 *tr*
4	0	NMe_2	D	24	90 93	88/12 88/12	tr *tr*
5	1	MeO		demethoxylation			
6	1	NMe_2	B	2	80	80/20	tr
7	1	NMe_2	D	1	81	86/14	tr
8	2	MeO	B	3	98 94	80/20 90/10	tr 4
9	2	MeO	D[f]	18	89 99	81/19 80/20	7 *tr*

[a] Reactions performed at 63 °C in THF on a 10-mmol scale. [b] Reagent B (DMHDNa)NiCRA–$MgBr_2$: 4/1/1/1. Reagent D (SA)NiCRA–$MgBr_2$: 4/1/1. [c] Starting from less stable alcohol (normal characters). [d] Starting from more stable alcohol (italic characters). [e] Ratio of more stable alcohol/less stable alcohol in percent. [f] Reaction performed at 63 °C in THF on a 5-mmol scale.

that heteroatoms modify considerably the behavior of MCRA's.[9a] So we decided to briefly study alcohols **16**.

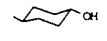
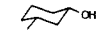
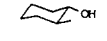
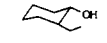
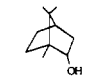
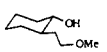


As expected,[9] sulfur atom was not tolerated. Such substrates poisoned NiCRA's and/or were desulfurized. On the contrary, with a few exceptions, oxygen- or nitrogen-substituted cyclalkanols were easily epimerized without side reactions (Table II). Curiously, the equilibrium was reached only with reagents D. Substituent on the 2 position (entries 1–4) considerably slowed the epimerization and addition of $MgBr_2$ was necessary to obtain reasonable results. When n = 1 and Z = OMe the only product formed was 2-methylcyclohexanol. On the contrary, epimerization succeeded with Z = NMe_2. When n = 2, epimerization occurred very slowly (entry 9); thus the use of an excess of reagent was preferable.

Easy Access to Less Stable Alcohols from Most Stable Ones. During exploratory experiments with DMHDNa–NiCRA, it was found that to a decrease in the

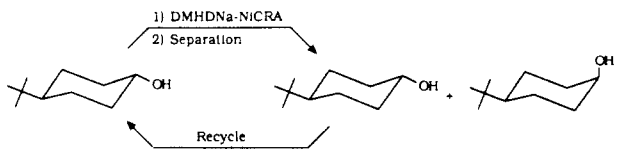
(9) (a) Feghouli, A. Thèse de l'Université de Nancy I, France, 1989. (b) Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* **1989**, *54*, 4848.

Table III. Epimerization of More Stable Alcohols by Reagents B[a] at 63 °C

entry	substrate	time (h)	yield,[b] %	less stable alcohol, %	ketone,[c] %
1		18	90	29[d]	5
2		28	92	30[d]	6
3		4	93	20[e]	5
4		18	94	34[e]	5
5		1	92	30[e]	4
6		1	70	30[d]	30
7		18	87	32[d]	9
8	5α-cholestan-3β-ol	4	88	32[d]	12

[a] NaH/DMHDNa/Ni(OAc)$_2$/MgBr$_2$/substrate = 2/1/1/1/1. [b] Total yield of alcohols determined by GC analysis. [c] Determined by GC analysis. [d] Isolated yields.

Scheme III



amount of NaH corresponds an increase of the amount of the less stable isomer. The only drawback was the formation of larger amounts of the corresponding ketones. However, this kind of epimerization could be of use to transform given alcohols into their thermodynamically less stable epimer (Table III). To confirm the potential preparative interest of these reactions, we performed the reactions symbolized in Scheme III.

Thus starting from *trans*-4-*tert*-butylcyclohexanol and after four separations and epimerization of the recovered trans alcohol, the cis isomer was obtained in 80% yield, besides 15% of the trans isomer and 5% of ketone.

Conclusion

This study displays that NiCRA's are very efficient for epimerization of alcohols and may be situated among the best reagents known till now. They are devoid of a number of disadvantages of usual systems. NiCRA's work under mild conditions without added ketone and in stochiometric amounts relative to the substrate. It is shown that with a few exceptions the thermodynamic equilibria corresponding to our conditions were reached. Finally, NiCRA's may be used to transform a given alcohol into its thermodynamically less stable epimer.

Experimental Section

The following instruments were used. For GC analyses, Girdel 330 FID (150-ft Carbowax 20M capillary, 9 ft × 0.25 in. 10% SE30 or 3% UCON Polar 6% KOH columns); for IR, Perkin-Elmer Model 580B; for NMR, Bruker AW80 (80 MHz) and Bruker AM 400 (400 MHz); for preparative HPLC, Waters 500A. Melting points were determined on Tottoli capillary apparatus.

NaH (Fluka 55–60% in oil) was used after three washings with THF under nitrogen. Ni(OAc)$_2$ (Aldrich) was dried in vacuo for 12 h at 120–130 °C. 2,5-Dimethyl-2,5-hexanediol was used without further purifications. Anhydrous MgBr$_2$ was prepared by a reported procedure.[10] *cis*- and *trans*-4-*tert*-butyl, 2-methyl-, 3-methyl-, 4-methyl, and 2-ethylcyclohexanols were separated by HPLC from commercially available mixtures. *cis*- and *trans*-3,3,5-trimethylcyclohexanols were prepared by reduction of the ketone by ZnCRA–Si[1] and were separated by HPLC. *endo*- and *exo*-norborneol, borneol, and isoborneol were commercially available from Aldrich. *endo*- and *exo*-1,3,3-trimethyl-2-norbornanol were prepared by reduction of fenchone by LiAlH$_4$[11a] and separated by HPLC. 5α-Cholestan-3β-ol is commercially available (Aldrich), 5α-cholestan-3α-ol is obtained by inversion of the 5α,3β epimer.[11b] The two isomers were separated by HPLC. *cis,cis*- and *trans,trans*-4-*tert*-butyl-2-methylcyclohexanols were obtained by reduction by LiAlH$_4$[11c] of the corresponding ketone.[11d,e] *cis,cis*- and *trans,trans*-2,6-dimethylcyclohexanols were separated by HPLC from a commercially available mixture (Aldrich). The cis,trans isomer was obtained by reduction of the trans ketone by NaBH$_4$.[11d,e] *cis*-2-Methoxycyclohexanol was prepared by reduction of the corresponding ketone (Aldrich) by LiAlH$_4$.[11f] The trans isomer is obtained by opening of cyclohexene oxide by BF$_3$–Et$_2$O in methanol.[11f] *cis*-2-(Dimethylamino)-cyclohexanol was prepared by reduction with L-Selectride[11g] of the corresponding ketone.[11h] The trans isomer was uniquely prepared by action of dimethylamine on cyclohexene oxide at 120 °C.[11h] *cis*- and *trans*-2-(methoxymethyl)cyclohexanols were prepared by reduction with a ZnCRASi[9a] of the corresponding ketone.[11i,j] The two isomers were separated by their benzoate derivatives. *cis*-Benzoate: ^{1}H NMR (400 MHz) 5.35 (s, 1 H, C*H*OCOC$_6$H$_5$). *trans*-Benzoate: ^{1}H NMR (400 MHz) 4.90 (m, 1 H, C*H*OCOC$_6$H$_5$). Anal. Calcd for C$_8$H$_{16}$O$_2$: C, 66.67; H, 11.12; O, 22.21. Found: C, 66.67; H, 11.41; O, 21.92. *cis*-2-[(Dimethylamino)methyl]cyclohexanol was prepared by reduction with L-Selectride[11g] of the corresponding ketone.[11k,l] The trans epimer was prepared by Lattess' procedure.[11m] The two isomers were separated by recrystallization of their benzoates[11n] derivatives. *cis*- and *trans*-2-(2-methoxyethyl)cyclohexanols were obtained by reduction of the corresponding ketone[11j] and were separated by HPLC. Authentic samples of ketone were either commercially available or prepared by recognized procedures (vide supra and ref 9a).

General Procedures. Preparation of DMHDNa–NiCRA (4/1/1) (Reagent A). A solution of 2,5-dimethylhexane-2,5-diol (DMHD) (10 mmol) in 10 mL of THF was added dropwise under N$_2$ to a suspension of degreased NaH (60 mmol) and anhydrous Ni(OAc)$_2$ (10 mmol) in refluxing THF (20 mL). After 2 h of stirring at 63 °C, the reagent was ready for use and the substrate could be added in THF (10 mL).

Preparation of DMHD–NiCRA–MgBr$_2$ (4/1/1/1) (Reagent B). The above procedure was employed and 10 mmol of MgBr$_2$–2THF was added after the 2 h of stirring at 63 °C and 0.5 h before the addition of the substrate.

Preparation of (SA)–NiCRA (4/1) (Reagent C). Under N$_2$, a solution of the substrate activant (SA) in 10 mL of THF was added dropwise to a suspension of degreased NaH (50 mmol) and anhydrous Ni(OAc)$_2$ (10 mmol) in refluxing THF (20 mL).

Preparation of (SA)–NiCRA–MgBr$_2$ (4/1/1) (Reagent D). The above procedure was employed and 10 mmol of MgBr$_2$–2THF was added after 2 h of stirring at 63 °C and 0.5 h before the addition of substrate.

The reactions were monitored by GC analysis of small aliquots. After completion of the reaction, the excess of NaH was carefully destroyed by dropwise addition of EtOH at 25 °C. After traditional workup, products were separated by flash chromatography. Isolated yields were in accordance with those of GC

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analysis (±5%). Spectral and physical data (^{1}H NMR, IR, bp, mp) were in agreement with the literature data or with those of authentic samples (commercially available or prepared by recognized procedures).

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Base Catalysis in Imaging Materials. 1. Design and Synthesis of Novel Light-Sensitive Urethanes as Photoprecursors of Amines

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The ability to photogenerate active species has led to significant advances in areas as varied as organic synthesis, with the use of photolabile protecting groups, microelectronics with photoresists, and coating technology with photocurable polymers. In imaging techniques such as those used for microlithography, numerous systems have relied on the use of photogenerated acid[1] for their success.[2] In contrast, the use of photogenerated base has essentially not been explored with a few notable exceptions.[3] The reason for this dichotomy is not the lack of applicable chemistry, since base catalysis is widely applicable to numerous reactions but the fact is that photogenerated bases are not readily available.

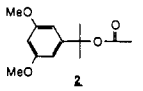
A survey of the literature reveals a few examples of photochemical reactions in which amines are liberated, albeit in low yields, from organic precursors.[4] Typical of these reports are processes in which the amine photoproducts are trapped in solution in their protonated form as they are formed. In the context of systems that require base catalysis, such processes are usually of little practicality as the reactive free amines are not obtained. Most useful perhaps are the classical metal–ammine complexes, which have been used to photogenerate ammonia in a quantum efficient process.[3,5] A significant limitation of such metal–ammine complexes is their inorganic nature, which leads to low solubility in organic systems. Our objectives in this study were to develop efficient organic photoprecursors of simple amines. The design criteria included ease of synthesis, solubility in organic media, and the ability to produce *free* amines by photocleavage using UV irradiation.

Results and Discussion

A simple system, shown in eq 1, is based on the use of a photolabile amino protecting group.

$$R_1R_2N\text{–}PG \xrightarrow{h\nu} R_1R_2NH + PG' \qquad (1)$$

Of the wide range of photosensitive protecting groups available for the amino function,[6] we consider the (α,α-dimethyl-3,5-dimethoxybenzyloxy)carbonyl group (Ddz, **2**) to be the masking group of choice. The Ddz group,[7] as developed for peptide applications,[8] combines the photolability of the (3,5-dimethoxybenzyloxy)carbonyl group[9] with the acid sensitivity of the (α,α-dimethylbenzyloxy)-carbonyl moiety.[10] Removal of the Ddz group from protected amino acid **3** affords the zwitterionic amino acid **4** together with a four-membered photodimerization product, **5**, of 3,5-dimethoxy-1-(2-propenyl)benzene[7] as shown in Scheme I.



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The preferred route[7,8] for the preparation of Ddz-protected amino acids involves the reaction of the carbonyl azide or the pentachlorophenyl mixed carbonate of 3,5-dimethoxy-α,α-dimethylbenzenemethanol with the free amino acid group of the amino acid. In the context of a simple primary amine protected as in structure **6** (Scheme II), this approach amounts to disconnection A. We favor the alternate disconnection route B, which involves readily available isocyanates **7** and tertiary alcohol **8**. While the direct addition of isocyanates to tertiary alcohols is usually inefficient,[11] the reaction proceeds more satisfactorily in the presence of a lithium alkoxide catalyst.[12] The required alcohol **8** is readily prepared by a simple Grignard reaction from the commercially available methyl 3,5-dimethoxybenzoate.[7] Isocyanates were chosen for their ultimate ability to afford photoactive carbamates capable of liberating strongly basic amines upon irradiation as shown in Scheme III for compound **9**.

In contrast to the uncatalyzed reaction, which proved inefficient, the lithium alkoxide catalyzed addition of tertiary alcohol **8** to cyclohexyl isocyanate afforded a high yield (80%) of a white crystalline solid, which proved to

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