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Regioselective Copper-Catalyzed Alkylation of [2.2.2]-Acylnitroso Cycloadducts: Remarkable Effect of the Halide of Grignard Reagents

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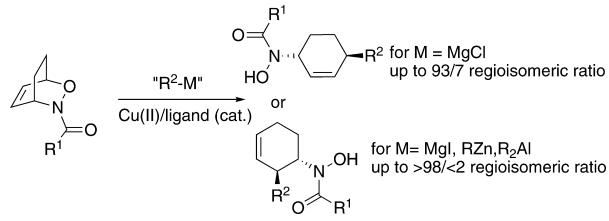
ABSTRACT



Ring opening with organometallic reagents of [2.2.2]-acylnitroso cycloadducts, including an enantioselective kinetic resolution of these compounds, has been accomplished for the first time. By the careful choice of reaction conditions, it was possible to obtain new cyclohexenyl hydroxamic acids with complete *anti*-stereoselectivity and a nice regioalternating control. A remarkable effect of the halogen of the Grignard reagent was observed during ring opening.

The use of heterobicyclic templates to obtain cycloaliphatic compounds in a regio- and stereoselective way is a valuable strategy in organic synthesis.[1] Recently, many efforts have been devoted to the nucleophilic ring-opening of hetero-Diels−Alder [2.2.1]-bicyclic adducts as an efficient strategy toward the synthesis of functionalized cyclopentenes.[2,3] However, little interest can be found in analogous reactions involving the less strained [2.2.2]-cycloadducts notwithstanding the possibility to access valuable nitrogen-substituted cyclohexenes by their ring openings. The ring opening of [2.2.2]-acylnitroso adducts is more often effected by N−O bond cleavage to give amino alcohols.[4] On the other hand, their nucleophilic ring-opening has been realized so far only with heteronucleophiles (alcohols, water) in Lewis acid catalyzed solvolytic conditions and showed a poor regiocontrol.[5] The C−O bond cleavage is of particular interest because it allows the generation of a hydroxamic acid moiety, a key structural element in a wide range of biologically active compounds.[3,5]

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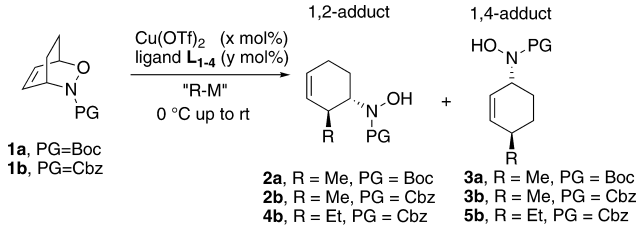
We report here unprecedented ring-openings of [2.2.2]-acylnitroso cycloadducts with organometallic reagents to give new substituted cyclohexenyl hydroxamic acids with a definite stereo- and regiochemistry.

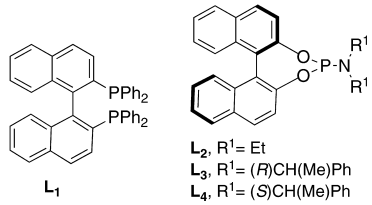
In our continued interest in the reactivity of small-medium ring heterocycles with carbon nucleophiles, we examined a variety of organometallic reagents for the ring-opening of compounds **1a**,**b**. For this purpose, we examined the use of organozinc and organoaluminium reagents which were found to be effective in the related alkylation of the [2.2.1]-bicyclic system.[6] In preliminary experiments, we were disappointed by the scarce reactivity (<5% conversion) of compounds **1a** and **1b** with Et_2Zn in the presence of catalytic amounts of copper- and phosphorus-containing ligands. On the other hand, the $Cu(OTf)_2$-(±)-binap (**L_1**)-catalyzed addition of organoaluminium reagents (3.0 equiv) to **1a** gave a complex mixture of products with removal of the protecting group, while the addition to **1b** proved to be rather slow (data not shown in Table 1).[7] Aiming to have a clean 1,2-arylation of the bicyclic framework, we turned our attention to the mixed organoaluminum reagent obtained from a dialkylaluminum chloride reagent and PhLi. When we used Me_2AlCl with the Cbz-protected substrate **1b**, we obtained the corresponding addition products **2b** and **3b** with a moderate yield but a good 1,2-regioselectivity (Table 1, entry 1). To our surprise, these compounds derived from the attack of the methyl moiety, with only marginal formation (<7%) of the corresponding phenylated adducts. This result deviates from the normal exclusive or predominant addition of the phenyl moiety from a reagent of this kind.[8] Moreover, and without any reasonable explanation, when the transmetalation with PhLi was performed with the more common Et_2AlCl or with $MeAlCl_2$ no addition took place (entry 2). To overcome the scarce reactivity of Me_2Zn with **1a**, a solution was found by the addition of $Sc(OTf)_3$ (10 mol %) as an external Lewis acid. In this way, we were able to obtain the 1,2-adduct with complete regio- and anti-stereoselectivity, albeit with a moderate conversion (entries 3−5 and 7).

The use of racemic phosphoramidite type ligand **L_2** (12 mol %) gave an improved conversion, together with a complete regioselectivity (entry 4). The propensity of the present addition reaction to stop halfway prompted us to explore a kinetic resolution of acylnitroso cycloadducts **1a**,**b**. It is worth mentioning that [2.2.2]-acylnitroso cycloadducts in enantioenriched form have been obtained by means of a chiral auxiliary approach,[9] probably because catalytic enantioselective intermolecular acylnitroso Diels−Alder reactions are very difficult processes.[10] The kinetic resolution of acylnitroso cycloadducts **1a**,**b** with Me_2Zn using (3.0 mol %) of chiral ligand (*R*,*R*,*R*)-**L_3** showed modest but significant levels of enantiomeric enrichment (36% ee for **1a**, entry 5) and (70% ee for **1b**, entry 6). Diastereoisomeric phosphoramidite (*S*,*R*,*R*)-**L_4** gave an inferior result (14% ee at 38% conversion, entry 7). A significant increase in the efficiency of the kinetic resolution ($s = 8.3$) was found in the reaction of Cbz-derivative **1b** with 2.0 equiv of $AlEt_3$ using (3.0 mol %) of (*R*,*R*,*R*)-**L_3** and carrying out the reaction at −20 °C (entry 8).[11]

In order to have a more robust and versatile entry to alkylated cyclohexenyl hydroxamic acids, we also examined the reactions of Grignard reagents with [2.2.2]-cycloadducts (Table 2).[12] The addition of 3.0 equiv of ethereal MeMgBr to **1a** and **1b** in CH_2Cl_2 from 0 °C to rt for 18 h gave mixtures of the methylated adducts with a preference for 1,4-addition adducts and consistent amounts (22% for **1a** and 43% for **1b**) of the corresponding

Table 1. Copper-Catalyzed Ring Opening of Cycloadducts **1a**,**b** with Organozinc and Organoaluminium Reagents[a]





N	sub (% ee)	R-M	L	convn[b] (%)	ratio 1,2/1,4[b]	yield[c] (%)
1	**1b** (Na)	$PhAlMe_2$	**L_1**	95	85/15	55[d]
2	**1b** (Na)	$PhAlEt_2$	**L_1**	<5	Nd	Nd
3[e]	**1a** (Na)	$ZnMe_2$	**L_1**	45	>98/<2	(**2a**) 35
4[e]	**1a** (Na)	$ZnMe_2$	**L_2**	70	>98/<2	(**2a**) 58
5[e]	**1a** (36)	$ZnMe_2$	**L_3**	48	>98/<2	(**2a**) 40
6	**1b** (70)	$ZnMe_2$	**L_3**	75	97/3	(**2b**) 50
7[e]	**1a** (14)	$ZnMe_2$	**L_4**	38	>98/<2	Nd
8[f]	**1b** (49)	$AlEt_3$	**L_3**	42	94/6	(**4b**) 30

[a] Reaction conditions: **1a** or **1b** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol for entries 1−4, 0.006 mmol for entries 5−8), ligand (0.024 mmol for entries 1−3, 0.04 mmol for entry 4, and 0.012 mmol for entries 5−8), RM (1.2 mmol, 3.0 equiv), CH_2Cl_2 (2.0 mL), from 0 °C to rt for 18 h. [b] Determined by ^1H NMR of the crude mixture. [c] Isolated yields after chromatographic purification of the indicated product. [d] Inseparable mixture of **2b** and **3b**. [e] Addition of $Sc(OTf)_3$ (10 mol %). [f] Reaction carried out at −20 °C for 24 h in anhydrous toluene with 2.0 equiv of $AlEt_3$.

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(7) It is known that phosphoramidite ligands readily react with organoaluminium reagents leading to aminophosphine ligands; see: Bournaud, C.; Falciola, C.; Lecourt, C.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581.

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(9) (a) Kirby, G. W.; Nazeer, M. *Tetrahedron Lett.* **1988**, *29*, 6173. (b) Miller, A.; Paterson, T. Mc. C.; Procter, G. *Synlett* **1989**, 32. (c) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1043. (d) Behr, J.-B.; Defoin, A.; Pires, J.; Streith, J.; Macko, L.; Zehnder, M. *Tetrahedron* **1996**, *52*, 3283.

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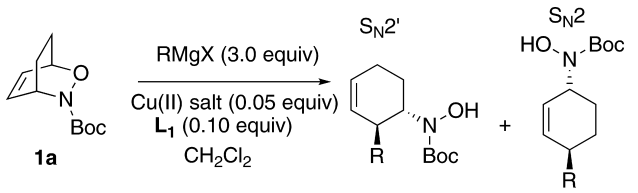
(11) Stereoselectivity factor (*s*) determined by the following equation: $s = \ln[(1 - c)(1 - ee)]/\ln[(1 - c)(1 + ee)]$ where *c* is the conversion of **1a**,**b** and ee is the enantiomeric excess of remaining **1a**,**b**.

Table 2. Ring Opening of Cycloadduct **1a** with Grignard Reagents[a]



entry	temp (°C)	Grignard	ratio 1,2/1,4[b]	yield[c] (%)
1	0 to rt	MeMgBr	33/67	(**2a**) 18, (**3a**) 45
2	−78	MeMgBr	17/83	(**2a**) 10, (**3a**) 65
3	−78	MeMgCl	15/85	Nd
4[d]	−78	MeMgCl	7/93	(**3a**) 75
5	0 to rt	MeMgI	93/7	(**2a**) 85
6	−78	EtMgBr	80/20	(**4a**) 65
7[d]	−78	EtMgCl	33/67	(**5a**) 52
8[d]	−78	*i*-PrMgCl	60/40	(**6a**) 45, (**7a**) 26
9	−78	EtMgI	94/6	(**4a**) 85
10	0 to rt	EtMgI	98/2	(**4a**) 94
11	−78	PhMgBr	30/70	(**8a**) 18, (**9a**) 40
12	0 to rt	PhMgI	66/34	(**8a**) 45, (**9a**) 22

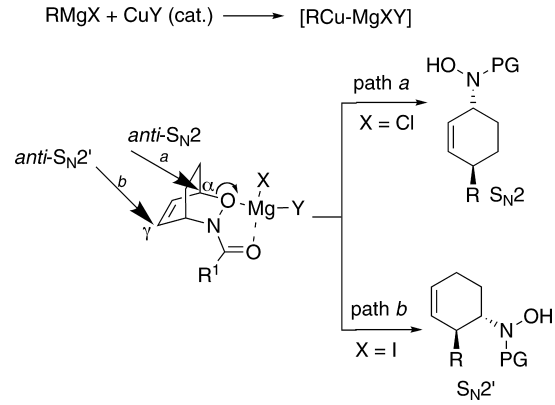
[a] Reaction conditions: **1a** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol), (±)-$\mathbf{L_1}$ (0.24 mmol), Grignard (1.2 mmol of a 2.0 M solution in Et_2O), CH_2Cl_2 (2.0 mL) for 18 h, unless stated otherwise. [b] Determined by ^1H NMR of the crude mixture. [c] Isolated yields of the indicated product after chromatographic purification. [d] Anhydrous $CuCl_2$ (0.02 mmmol) was used.

deprotected bicyclic oxazines. Next, our efforts concentrated on N-Boc derivative **1a** because the corresponding alkylated adducts were separable by chromatographic purification. The N-deprotection pathway and the presence of minor amounts of other methylated adducts were suppressed when the reaction was carried out in the presence of catalytic amounts of $Cu(OTf)_2$ (5 mol %) and (±)-binap ($\mathbf{L_1}$) (6 mol %) (Table 1, entry 1). An increase of the 1,4-adducts **3a**, deriving from a direct *anti*-S_N2 cleavage of the C−O bond, was observed when the alkylation was performed at −78 °C (entries 2 and 3).[13] The maximization of the *anti*-S_N2 addition pathway was realized by means of chlorine-based Grignard reagents using anhydrous $CuCl_2$ as the copper salt (entry 4). To our surprise, switching to the iodo Grignard reagent MeMgI dramatically reversed the position selectivity of the methyl addition in favor of the 1,2-adduct **2a** that derives from an *anti*-S_N2' cleavage of the C−O bond (entry 5). The use of other Grignards showed a predominant S_N2-addition pathway, revealing the complex nature of the catalytic system (entries 6−8). However, the addition of iodide-based Grignard was still highly regioselective (entries 9 and 10). Aryl nucleophiles reacted efficiently but displayed poor regioselectivity (entries 11 and 12).

A critical influence of the halogen of a Grignard reagent on the regioselectivity of the addition process has been described elsewhere.[14] However, to the best of our knowledge, a regioalternating control of this kind has no precedents in ring-opening reactions.

In particular, it was possible to change the native uncatalyzed S_N2 regioselectivity observed with methyl Grignard reagents and to obtain with a high regioselectivity the corresponding 1,2-adducts deriving from a S_N2' pathway. Probably, the influence of the halide stems from their relative coordinating potency to copper within the magnesium cuprate structure (i.e., the RCuMgXY species formed in situ) that is in competition with the coordination of the phosphine ligand to copper. Thus, the use of an uncatalyzed Grignard addition and/or the use of harder chlorine based Grignard reagents in combination with copper(II) salts preferentially gave 1,4-adducts (path *a*, Scheme 1). The decreased acidity of the corresponding magnesium salts, makes it possible for the softer iodo magnesium cuprates to react with a high selectivity at the softer site γ-position of the double bond giving the 1,2-adduct (path *b*).

Scheme 1. Copper-Catalyzed Position Selective Ring Opening of **1a** with Different Grignard Reagents



In conclusion, we successfully accomplished the ring-opening by C−O bond cleavage of 1,3-cyclohexadiene−acyl nitroso cycloadducts with organometallic reagents including a kinetic resolution of these compounds. The position selective installation of carbon based nucleophiles can be tuned by the appropriate choice of reaction conditions, thus opening a new regio- and stereocontrolled access to a variety of cyclohexenyl hydroxamic acids.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For the addition of Grignard reagents to [2.2.1]-acylnitroso cycloadducts, see: (a) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Tetrahedron Lett.* **2002**, *43*, 1131. (b) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *J. Org. Chem.* **2002**, *67*, 4115.

(13) The regio- and stereochemistry of the 1,2- and 1,4-adducts were demonstrated by 2D NMR (COSY, HSQC, NOE) and 1D homodecoupling experiments.

(14) For example, see: Kobayashi, Y.; Nakata, K.; Ainai, T. *Org. Lett.* **2005**, *7*, 183.