2224 J. Am. Chem. Soc. 1987, 109, 2224-2225

Organocerium Additions to SAMP-Hydrazones: General Synthesis of Chiral Amines

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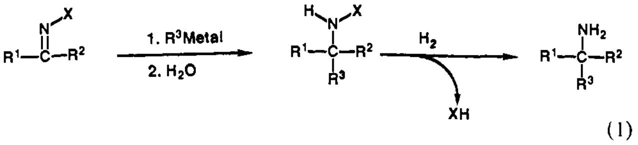
Received December 15, 1986

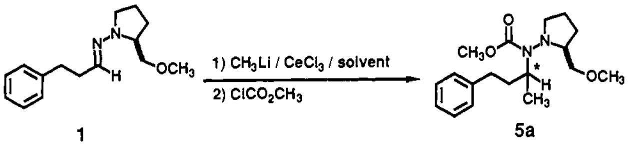
The addition of carbon nucleophiles to the imine function and its derivatives (oximes, hydrazones) constitutes an important method for the preparation of amines[2] (eq 1). A particularly



(1)

attractive feature of this construct is the potential for asymmetric synthesis using chiral imine derivatives.[3] The problems which have traditionally plagued this approach, (1) poor electrophilicity, (2) enolization of substrates with α-hydrogens, and (3) limited stereochemical control, have stimulated a variety of solutions. The first two problems have been addressed by (1) employing activated imine derivatives (iminium salts,[4c,b] acyliminium ions,[4c] sulfonylimines,[4d] and nitrones[4e]) and (2) by the use of less basic reagents such as allylboranes,[5] allylboronates,[6] allylstannanes,[5b,7] alkylcoppers,[8a] alkyl cuprates,[8b] and various metal enolates (Li,[9a,b] Et_2Al,[9c] Cl_3Ti,[9d] Zn[9e]). The issue of stereocontrol has been addressed by chiral modification of the substrates which produce optically active amines with good diastereo- and enantioselectivity. However, these methods are limited to either allylic nucleophiles[5] or aryl (nonenolizable) imines[10] and hydrazones.[11,12] We wish to report a new method for the preparation of amines in optically active form which provides a highly general solution to these problems.

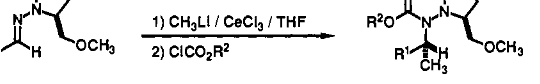
Table I. Optimization of $CH_3Li/CeCl_3$ Addition to Hydrazone 1[a]



entry	CH_3Li, equiv	$CeCl_3$, equiv	solvent	yield,[b] %	de[c]
1	1.2	1.2	THF	d	
2	2.0	2.0	THF	80	98:2
3	5.0	5.0	THF	61	*e*
4	3.0	1.0	THF	75	89:11
5[f]	3.0	1.0	THF	28	94:6
6	2.0	2.0	DME	80	86:14
7	2.0	2.0	Et_2O	44	95:5

[a] For details, see ref 16. [b] Yield after chromatography. [c] Determined by capillary GC analysis (50 m, OV-17). The minor diastereomer was identified. [d] Mostly unreacted starting material was recovered. Up to 25% of unprotected hydrazine could be isolated by quenching with H_2O. [e] Diastereomeric excess not determined. [f] $CeCl_3$ was stirred with 1 at room temp for 2 h then treated at -78 °C with CH_3Li.

Table II. $CH_3Li/CeCl_3$ Addition to SAMP-Hydrazones 1-4[a]



hydrazone	R^1	R^2	product	yield,[b] %	de[c]	confign[d]
1	$PhCH_2CH_2$	Me	**5a**	81	98:2	R
2	$PhCH_2$	Me	**6**	66[e]	96:4	R
3	Ph	Me	**7**	59[e]	91:9[f]	R
4	(*E*)-$CH_3CH{=}CH$	Me	**8**	82	96:4	R[g]

[a] See ref 18 for a comparison to CH_3Li alone. [b] Yield after chromatography. [c] Determined by capillary GC analysis (50 m, OV-17). The minor diastereomer was identified. [d] See ref 19 for assignment. [e] The benzyl carbamates ($R^2 = PhCH_2$) were formed in higher yield: **6** (83%); **7** (75%) with similar diastereomeric excesses. [f] Determined by HPLC analysis (5 μm SiO_2, 250 × 4.5 mm). [g] The assignment is by analogy.

In the context of an unrelated synthetic project we observed the diastereoselective addition of *n*-BuLi to an aldehyde SAMP-hydrazone[13,14] as a byproduct of enolization. Extensive attempts to improve the addition using various organometallic reagents (RLi, RMgX, R_2CuLi) alone and in conjunction with additives ($BF_3 \cdot OEt_2$, TMEDA) were disappointing (0-43%). However, we have discovered that *organocerium reagents* prepared in situ according to Imamoto[15] add to SAMP-hydrazones in good yield with high diastereoselectivities. Since the resulting hydrazines were prone to air oxidation, the reactions were quenched with

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(14) After submission of this manuscript a report from Enders' laboratories appeared describing the additions of *alkyllithiums* to a selection of SAMP-hydrazones (Enders, D.; Schubert, H.; Nubling, Ch. *Angew. Chem.* **1986**, *98*, 118). The failure of our original experiments with alkyllithiums apparently derives from the use of Et_2O instead of THF as solvent. For a comparison of the results of lithium vs. cerium additions see ref 18.

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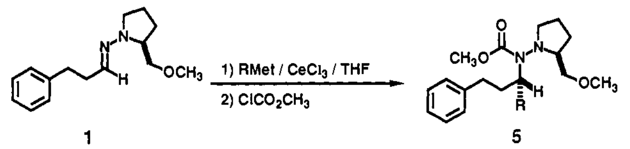
Table III. RMet/$CeCl_3$ Additions to Hydrazone **1**[a]



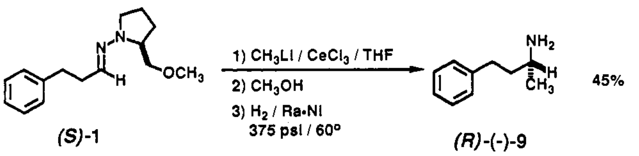
entry	R	M	product	yield,[b] %	ds,[c] %
1	Me	Li	**5a**	81	98
2	Me	MgBr	**5a**	76	97
3	*n*-Bu	Li	**5b**	71	93
4	*i*-Pr	MgBr	**5c**	67	99[d]
5	*t*-Bu	Li	**5d**[e]	72	96
6	Ph	Li	**5e**	72	96
7	*i*-$Pr_3SiCH{=}CH$	Li[f]	**5f**	74	97
8	$PhMe_2SiC{\equiv}C$	Li[g]	**5g**	0	

[a] Actual times for complete reaction vary but a standard protocol was used: (1) 1 h (−78 °C), 2–3 h (−78 °C → 20 °C); (2) 12 h (20 °C). [b] Yield after chromatography. [c] Determined by capillary GC analysis. See text for explanation. [d] GC analysis of crude hydrazine showed 15% of another material which may have been a diastereomer but did not protect. [e] **5d** is the unprotected hydrazine, incomplete reaction with $ClCO_2CH_3$. [f] For the preparation of this reagent see ref 20. [g] Generated by deprotonation with *n*-BuLi.

methyl or benzyl chloroformate to obtain the stable carbamates.

The preliminary optimization experiments were performed for the $CH_3Li/CeCl_3$ system by using hydrocinnamaldehyde SAMP-hydrazone **1** as test substrate. In all of these reactions it is imperative to slurry the freshly dried $CeCl_3$ in THF at room temperature for at least 2 h.[16] The data in Table I, entries 1–3, show that the preferred stoichiometry of reagents is RMet:$CeCl_3$:hydrazone = 2.0:2.0:1.0. Using less $CeCl_3$ led to lower selectivities (entry 4). The experiment in entry 5 suggests that organocerium reagents are involved since precomplexation of **1** with $CeCl_3$ followed by addition of CH_3Li gave poor results. The solvent of choice is THF, as DME gave good yields but poorer selectivity while the reverse was true for Et_2O (entries 6 and 7).

To survey substrate generality we selected four types of aldehyde hydrazones:[17] aliphatic (**1**), highly enolizable (**2**), aromatic (**3**), and α,β-unsaturated (**4**) and examined their reactivity toward $CH_3Li/CeCl_3$. The results are collected in Table II.[18] All of the substrates reacted readily and gave good yields of methyl adducts with high diastereomeric excesses. Of particular note is the selective 1,2-addition to hydrazone **4**. This is in keeping with the behavior of organocerium reagents with α,β-unsaturated carbonyls.[15] The diastereomeric excess and absolute configuration of the products was established for **5–7** by $LiAlH_4$ reduction of the corresponding methyl ketone SAMP-hydrazones and protection of the resulting hydrazines as their methyl carbamates. In each case a mixture of diastereomers was obtained with selectivities reversed compared to $CH_3Li/CeCl_3$ addition (**5**, 21:79; **6**, 6:94; **7**, 28:72). Enders has established the predominant *l* pathway in these reductions, i.e., SAMP → *S* amines.[14] Thus, the major products in the $CH_3Li/CeCl_3$ additions have the *R* configuration. To illustrate the utility of this process for the preparation of amines in optically active form, we have cleaved the N–N bond of the unprotected hydrazines by hydrogenolysis as shown in eq 2 and 3. The absolute configurations of the amines



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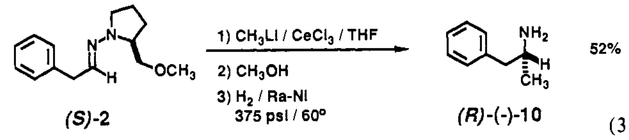

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9[19a] and **10**[19b,c] was established by comparison of $[\alpha]_D$ to literature values.

The structural diversity of the nucleophile was also surveyed for substitution level and hydridization by using hydrazone **1** as a test substrate. The results in Table III illustrate that nearly all types of simple organometallic reagents may be employed. Thus 1°, 2°, and 3° carbons give addition products. For methyl and *i*-Pr (entries 2 and 4) the Grignard reagents could be employed, while for *t*-Bu and vinyl (entries 5 and 7) only the lithium reagent would add. Only the acetylenic reagent (entry 8) has failed to add as either metal derivative thus far. The stereoselectivity of the reactions was evaluated for the purified, protected hydrazines. Since we have not prepared the diastereomers of compounds **5b–f**, the diastereoselectivities (ds) indicated are *minimal values* calculated by comparison to the next largest peak in the GC. The absolute stereochemistry of the products is assumed to derive from *re*-face attack by analogy to $CH_3Li/CeCl_3$. This assumption is also consistent with the model for asymmetric reduction with $LiAlH_4$.[14c] In this case, however, the "$RCeCl_2$" is coordinated to the methoxymethyl group and delivers R to the *re* face.

It has already been demonstrated that organolanthanide reagents have a strong propensity to be coordinated with Lewis bases.[21] This property has been invoked to explain much of their chemistry as well as their very existence in some cases.[21c] We have now demonstrated that organocerium reagents readily undergo additions to hydrazones. We suggest this is due to activation by coordination to the basic nitrogens and are investigating the importance of the complexing appendage of the auxiliary. The addition of functionalized carbanions, reactions with other imine derivatives, and synthesis of amino acids as well as the precise nature of the cerium reagent are under active study.

Acknowledgment. We are grateful to the National Science Foundation Presidential Young Investigator Program (NSF CHE-8451321). Matching funds for this project were generously provided by Smith Kline and French Laboratories.

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(16) Representative procedure: In a three-necked, round-bottomed flask fitted with N_2 inlet, thermometer, magnetic stirrer, and septum was placed $CeCl_3{\cdot}7H_2O$ (Aldrich, 2.0 equiv) which was dried [140 °C (0.5 torr)] for 2 h. The dried $CeCl_3$ was stirred in dry THF (5 mL/mmol $CeCl_3$) for 2 h at 20 °C. The suspension was cooled to −78 °C, treated with the organometallic reagent (2 equiv), and stirred at −78 °C for 1 h. A solution of the aldehyde SAMP-hydrazone (1 equiv) in dry THF (3 mL/mmol hydrazone) was added, and the suspension was stirred at −78 °C for 1 h and then allowed to warm to 20 °C over 2–3 h. To protect the hydrazine, $ClCO_2CH_3$ (4 equiv) was added and the mixture was stirred for 12 h. Aqueous extractive workup, silica gel chromatography, and bulb-to-bulb distillation afforded the pure carbamates. To obtain the amines, the reaction mixture was quenched at 20 °C with MeOH (1 mL/10 mL THF). The crude hydrazine, obtained by extractive workup and concentration, was hydrogenated (375 psi/60 °C) in MeOH with Raney nickel (Aldrich, W-2) for 18 h. The amine was isolated by the method of Enders.[14]

(17) All new compounds have been fully characterized by ^1H and ^{13}C NMR (300 MHz), IR, mass spectrometry, and elemental analysis (±0.3%).

(18) Direct comparison of alkyllithium vs. alkylcerium additions in THF gives the following results (yield, de) with CH_3Li: **5a** (59%, 98:2), 6 (0%), 8 (52%, 95:5). Hydrazone **1** gave 15% addition with *i*-PrMgBr and 0% with PhLi.

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