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Organocerium Additions to Hydrazones: Effects of Reagent Stoichiometry on Efficiency and Selectivity

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The effects of reagent stoichiometry on the efficiency and selectivity of organocerium additions to chiral and achiral hydrazones have been investigated. The reagent formed in-situ from 1 equiv of CH_3Li and 0.33 equiv of $CeCl_3$ adds efficiently (>65% yield) to *N,N*-dimethylhydrazone 1, but this same reagent reacts only sluggishly with chiral SAMEMP hydrazone 2 (<30% yield). The optimal stoichiometry of the organocerium reagent is 1:1 $CH_3Li/CeCl_3$, despite the fact that not all of the $CeCl_3$ is consumed in the transmetalation. At least 2 equiv of methyl nucleophile is required to obtain acceptable yields in additions to 2, suggesting that the auxiliary side chain inhibits the reactivity of the first equivalent of organometallic reagent and that binding of the reagent to one of the hydrazone nitrogen atoms facilitates addition. This hypothesis is supported by the observation that competitive ligands such as amines or alkoxides effectively inhibit the addition of organocerium reagents to 1. The active reagent formed at all mixing stoichiometries is proposed to be a trimethyllanthanide species on the basis of reactivity and the presence of unreacted MCl_3 at less than 3:1 CH_3Li/MCl_3 mixing ratios.

Introduction

We have been engaged in a program designed to exploit the unique reactivity of organocerium reagents with hydrazones, leading to the development of a general method for the synthesis of enantiomerically enriched α-branched amines.[1] Central to the success of this strategy has been the lower basicity and higher nucleophilicity of organocerium reagents as opposed to organolithium and Grignard reagents.[2,3] Despite their widespread use as synthetic reagents, only recently has serious attention been paid to the effects of reagent stoichiometry and/or lanthanide salt precursor on reaction efficiency and selectivity. In this paper we discuss our studies of the effects of reagent stoichiometry on the addition of $CH_3Li/CeCl_3$ to *N,N*-dimethylhydrazone 1 and SAMEMP[1b] hydrazone 2 both derived from hydrocinnamaldehyde (Scheme I).

Background

The use of organocerium reagents was pioneered by Imamoto as an alternative to alkyllithium and Grignard reagents for nucleophilic additions to carbonyls.[4] These reagents have received a great deal of attention in the literature due to their novel reactivity. Cerium(III) strongly coordinates Lewis basic atoms such as oxygen and nitrogen, and this Lewis acidic nature of Ce(III) reagents has been used to rationalize the chemistry they exhibit.[5] Alkylcerium reagents derived from anhydrous $CeCl_3$ and an organolithium or Grignard reagent react highly regioselectively with α,β-unsaturated carbonyl compounds, affording the product of 1,2-addition almost exclusively.[4a,6] These reagents are much less basic than the organolithium or organomagnesium precursor from which they are derived and afford much higher yields with highly enolizable substrates.[3,4] In addition, *n*-BuLi- and *t*-BuLi-derived cerium reagents do not readily participate in lithium–halogen exchange reactions with aryl bromides, unlike the alkyllithiums themselves.[3o]

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(6) Similarly, lanthanide salts mediate 1,2-reductions of α,β-unsaturated carbonyls with $NaBH_4$ or $LiAlH_4$; see: (a) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (c) Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1929.

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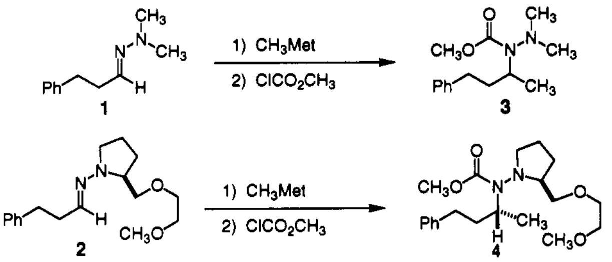
Scheme I

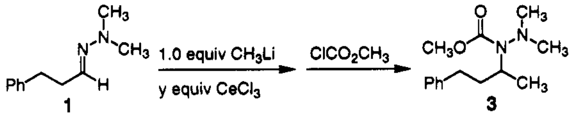


In the vast majority of cases, organocerium reagents are generated in-situ from 1 equiv each of the organometallic precursor and $CeCl_3$ or CeI_3.[7] The reagents derived from alkyllithiums are typically formed at −78 °C,[4b–g] while those derived from Grignard reagents are typically formed at 0 °C.[4a] Notably, the organocerium species obtained from each type of organometallic precursor are not identical, as alkylcerium reagents with β-hydrogens derived from alkyllithiums decompose by a β-hydride elimination mechanism at temperatures above 0 °C[3o,4a] while those derived from the corresponding Grignard reagent do not. Few reports have mentioned the use of different RM/CeX_3 ratios,[3a,r,4a] and there has been no in-depth study of the effects of reagent stoichiometry on reactivity. Several workers, however have reported that other lanthanide salts, such as $La(OTf)_3$,[3m] $Yb(OTf)_3$,[3n] and various $Ln(O\text{-}i\text{-}Pr)_3$[3c] species, show increased reactivity compared to the $CeCl_3$-derived analogs.

Two examples from the recent literature demonstrate the significant effects lanthanide species can have on the *diastereoselectivity* of nucleophilic additions as well. Molander and co-workers[3n] have reported that $Yb(OTf)_3$-mediated alkyllithium and alkylmagnesium additions to chiral cyclohexanones exhibit greatly increased diastereoselectivity for certain nucleophile/substrate combinations. This effect was attributed to the ytterbium reagents being "larger" than the lithium or magnesium reagents from which they are derived. Even more impressive is the *reversal* of diastereoselectivity observed in additions to chiral 2-acyl-1,3-oxathianes. Utimoto and co-workers[3o] have shown that YCl_3- or $YbCl_3$-mediated alkynyllithium additions to these substrates proceed with complementary diastereocontrol compared to the alkynyllithium and alkynylmagnesium reagents.

The solution structure of all of these reagents is unknown, and their existence is usually inferred by the appearance of a yellow to orange/tan color. Schumann and co-workers[8] have synthesized several *hexamethyl* derivatives of the lanthanides, although the cerium analog could not be obtained in pure form.[5,9] TMEDA is required to stabilize these complexes. A tetra-*tert*-butyl derivative of Lu(III) was also synthesized, but not fully characterized. Two (Ln = Pr, Sm) of the hexamethyl derivatives were shown to transfer their methyl ligands to α,β-unsaturated aldehydes and ketones by 1,2-addition, and the yields reported indicate that all six methyl groups are transferable. In light of Schumann's results and the lack of detailed studies of the effects of reagent stoichiometry on reactivity, we initiated a program to probe such effects.

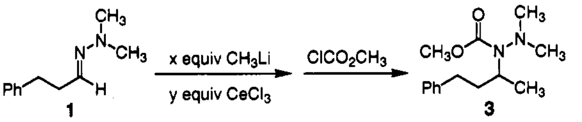
Table I. Methylation of 1 with 1 Equiv of CH_3Li[a]



entry	equiv of $CeCl_3$	yield of **3**,[b,c] %
1	1.00	64–74
2	0.83	64–72
3	0.66	57–60
4	0.50	66–73
5	0.33	63–65
6	0.20	43
7	0.16	40–41
8	0.00	23–29

[a] See Experimental Section for details. [b] Yield after chromatography. [c] Ranges indicate results from duplicate experiments.

Table II. Methylation of 1 with Variable Equivalents of CH_3Li[a]



entry	CH_3Li, equiv	$CeCl_3$, equiv	reagent composition (equiv)	yield of **3**,[b,c] %
1	1.50	1.50	1:1 (1.5)	89–90
2	2.00	2.00	1:1 (2)	86–90
3	3.00	3.00	1:1 (3)	79–80
4	3.00	2.00	1.5:1 (2)	80–86
5	2.00	1.00	2:1 (1)	78–79
6	3.00	1.50	2:1 (1.5)	78–86
7	1.50	0.50	3:1 (0.5)	78–82
8	2.00	0.66	3:1 (0.66)	76–82
9	3.00	1.00	3:1 (1)	75–75
10	6.00	2.00	3:1 (2)	79
11	2.00	0.00	1:0 (2)	66–71
12	3.00	0.00	1:0 (3)	78–81

[a–c] See Table I.

Results

***N,N*-Dimethylhydrazone 1.** To determine the optimal conditions for methylcerium additions to *N,N*-dimethylhydrazone 1, the effects of the stoichiometry of the organocerium reagent on the efficiency of nucleophile delivery and the efficiency of substrate conversion were studied. The results of this stoichiometry study are shown in Tables I and II and displayed graphically in Figures 1 and 2. The protocol used for these experiments was that reported earlier[1a] for additions to SAMP hydrazones: reagent generation for 1 h at −78 °C, followed by addition of a THF solution of the hydrazone at −78 °C and warming to room temperature after stirring for 1 h at −78 °C. Trapping of the intermediate hydrazine anion was accomplished by addition of methyl chloroformate after 2 h at room temperature followed by stirring at room temperature for 12–18 h, at which time the hydrazine intermediate was not observed by TLC analysis. Table I contains the data obtained using 1 equiv of CH_3Li and various amounts of $CeCl_3$. The goal of this study was to

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[7] Reagents with similar reactivity profiles are obtained by treating alkyl iodides with cerium amalgam or other Ln(0) species. See ref 2a–e for examples.

[8] Schumann, H.; Müller, J.; Bruncks, N.; Lauke, H.; Pickardt, J. *Organometallics* **1984**, *3*, 69.

[9] For other crystal structures of alkyllanthanide species, see: (a) Schumann, H.; Genthe, W.; Bruncks, N.; Pickhardt, J. *Organometallics* **1982**, *1*, 1194. (b) Huang, Z.; Chen, M.; Qiu, W.; Wu, W. *Inorg. Chim. Acta* **1987**, *139*, 203. (c) Heeres, H. J.; Renkema, J.; Booij, M.; Meetsma, A.; Teuben, J. H. *Organometallics* **1988**, *7*, 2495. (d) Hitchcock, P. B.; Lappert, M. F.; Smith, R. G.; Bartlett, R. A.; Power, P. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1007. (e) Mashima, K.; Takaya, H. *Tetrahedron Lett.* **1989**, *30*, 3697. (f) Hitchcock, P. B.; Lappert, M. F.; Smith, R. G. *J. Chem. Soc., Chem. Commun.* **1989**, 369. (g) Deng, D.; Qian, C.; Wu, G.; Zheng, P. *J. Chem. Soc., Chem. Commun.* **1990**, 880.

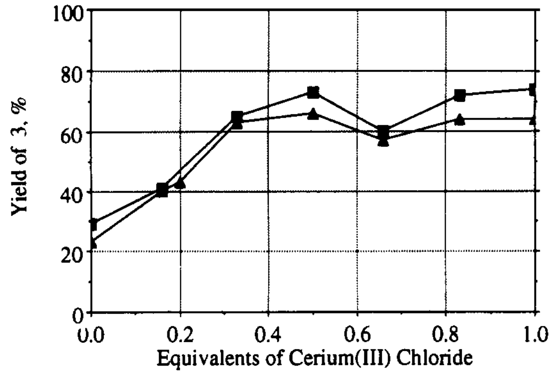


Figure 1. Additions to 1 with 1 equiv of methyllithium.

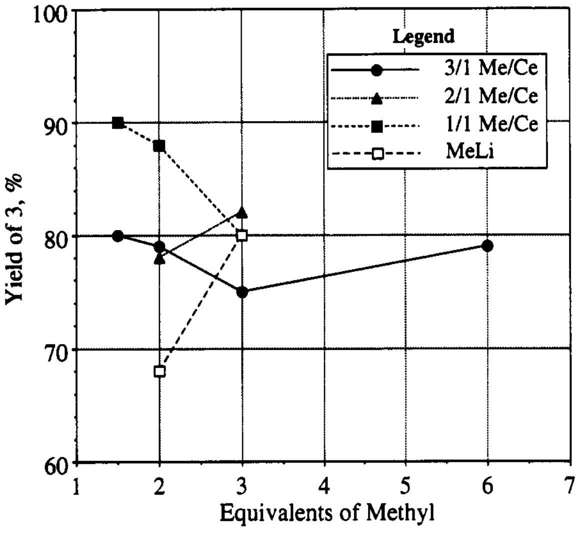
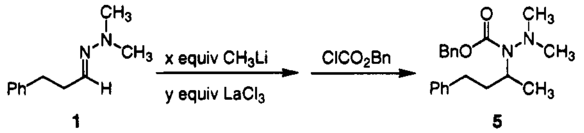


Figure 2. Effects of reagent stoichiometry on yield in additions of methylcerium reagents to 1.

establish the optimal yield based on the nucleophile. Following the general procedure, yields of between 57 and 74% were consistently obtained with 1 equiv of CH_3Li and as little as 0.33 equiv of $CeCl_3$ (Table I, Figure 1). These yields rivaled those obtained in reactions using 2 equiv of CH_3Li in the absence of $CeCl_3$ (Table II, entry 11). Lesser amounts of $CeCl_3$ lowered the yield substantially (Table I, entries 6–8). This "drop-off" point is particularly evident when depicted graphically (Figure 1). The data in Table I clearly show that 1 equiv of $CeCl_3$ per equivalent of hydrazone was *not* required to obtain good yields of addition product. These results also demonstrate that the reactivity of *N,N*-dimethylhydrazone 1 differed substantially from that of SAMP hydrazones, since the latter additions require greater than 1 equiv of the alkyllithium to proceed to completion.[1a]

The data in Table II and Figure 2 depict the effects of reagent stoichiometry using various equivalents of CH_3Li per equivalent of 1. In direct comparisons, the 1:1 reagent (entries 1–3) proved to be superior to the 3:1 reagent (entries 7–10) at every level of available methyl examined (1.5 equiv: entry 1 vs entry 7; 2 equiv: entry 2 vs entry 8; 3 equiv: entry 3 vs entry 9). The highest yields were obtained with 1.5 or 2 equiv of "CH_3CeCl_2"[10] (86–90%); indeed, adding more equivalents of this reagent did not improve the yield. In the case of both the 1:1 and the 3:1 reagents, the use of more than 2 equiv of available methyl actually lowered the yields. This result was not due to destruction of the product by excess reagent, as addition of 2 equiv of the 3:1 reagent (6 equiv of methyl, entry 10) afforded a 79% yield of **3**. The data in Table II are shown graphically in Figure 2, each line representing a different reagent stoichiometry: 1:1, 2:1, and 3:1 $CH_3Li/CeCl_3$ ratios and CH_3Li in the absence of $CeCl_3$. Clearly, the addition of $CeCl_3$ to these reactions resulted in improved yields of addition product, and the lower ratios of $CH_3Li/CeCl_3$ consistently afforded the better yields, the 1:1 reagent proving to be the best.

Scheme II



We have also investigated the response of 1 to reagents derived from $CH_3Li/LaCl_3$. Additions of methyllanthanum reagents of various stoichiometries to 1 proceeded smoothly following the procedure described above, but trapping with methyl chloroformate afforded variable yields of **3**. TLC analysis of the reaction mixtures indicated that addition had occurred in high conversion but that trapping was incomplete. It was subsequently determined that higher concentrations of hydroxide ion in older bottles of CH_3Li facilitated trapping, while the use of freshly opened bottles of CH_3Li with low hydroxide ion concentrations afforded lower yields of **3**. Attempted trapping with benzyl chloroformate, which we had previously found to give better yields in certain additions to SAMP hydrazones,[1a] also afforded variable yields of **5** (Scheme II). Qualitatively, $CH_3Li/LaCl_3$ reagents were found to exhibit a reactivity similar to $CH_3Li/CeCl_3$ reagents, but these observations could not be quantified.

Composition of Reagent. All of the reagents prepared by the standard protocol of low-temperature mixing of CH_3Li and $CeCl_3$ were heterogeneous. Even the 3:1 reagent, though darker yellow in color, still contained an undissolved solid at −78 °C. The solid remaining after combining CH_3Li and $CeCl_3$ in a 1:1 ratio in THF was found to be pure $CeCl_3$ by isolation and elemental analysis. We reasoned that the precise quantitation of this material would provide information on the number of methyl groups bound to the metal (assuming that this reagent is soluble). These studies were carried out with $LaCl_3$ at −78 °C because it has the lowest solubility in THF (at 20 °C).[11] Among four runs of 1:1 reagent stoichiometry the ratio of recovered to starting $LaCl_3$ fell in the range of 0.7231–0.9243. The theoretical recovery for the soluble reagent of composition $(CH_3)_3La$ would be 0.6667 while that for $La(CH_3)_6Li_3$ would be 0.8333.

These results proved to be qualitatively informative but the accuracy and reproducibility of the measurement precluded firm conclusions. This is in line with previous attempts to isolate and characterize the methyl adducts from Sc, Y, La, and Pr using 3:1 and 4:1 stoichiometries.[12]

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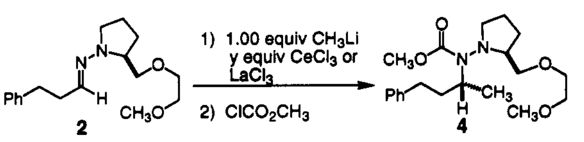
(10) The formula "$RCeCl_2$" is often used to describe organocerium reagents, but is used here only to represent the stoichiometry of the reagent. NMR spectroscopic studies of organolanthanide reagents generated in-situ have been reported, see ref 3m. NMR studies of various methyllanthanum species conducted in these laboratories have been equally inconclusive: Edwards, J. P. Ph.D. Thesis, University of Illinois, Urbana—Champaign, 1991.

(11) $LaCl_3$: 0.126 g/100 mL at 20 °C; $CeCl_3$: 0.593 g/100 mL at 20 °C; Flachsbart, I.; Hein, H.; Kirschstein, G.; Koch, E.; Kreuzbichler, I.; Kuhn, P.; Lehl, H.; Vetter, U. In *Gmelin Handbook of Inorganic Chemistry*; Bergmann, H., Hein, H., Koch, E., Merlet, P., Vetter, U., Eds.; Springer Verlag: Berlin, 1982; Sc, Y, La-Lu, Part C 4a, pp 172–173.

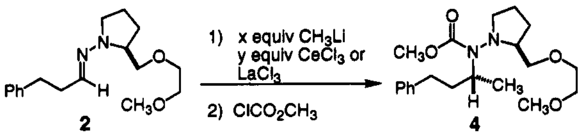
Table III. Methylation of 2 with 1 Equiv of CH_3Li[a]



entry	MCl_3 (equiv)	reagent composition	yield of 4,[b] %	de,[c] %
1	$CeCl_3$ (1.00)	1:1	30	98
2	$CeCl_3$ (0.50)	2:1	31	90
3	$CeCl_3$ (0.33)	3:1	28	88
4	none	1:0	23	90
5	$LaCl_3$ (1.00)	1:1	44	94
6	$LaCl_3$ (0.50)	2:1	27	92
7	$LaCl_3$ (0.33)	3:1	42	92

[a] See Experimental Section for details. [b] Yield after chromatography. [c] Determined by GC (50-m HP-1) or HPLC (Supelco LC-Si, hexane/EtOAc (86:14)).

Table IV. Methylation of 2 with Variable Equivalents of CH_3Li[a]



entry	CH_3Li, equiv	MCl_3 (equiv)	reagent composition	yield of 4,[b] %	de,[c] %
1	6.0	$CeCl_3$ (2.0)	3:1	86	84
2	6.0	$LaCl_3$ (2.0)	3:1	59	86
3	6.0	none	1:0	79	92
4	4.0	$CeCl_3$ (2.0)	2:1	77	88
5	4.0	$LaCl_3$ (2.0)	2:1	61	82
6	4.0	none	1:0	70	90
7	3.0	$CeCl_3$ (3.0)	1:1	89	90
8	3.0	$LaCl_3$ (3.0)	1:1	81	92
9	3.0	$CeCl_3$ (1.0)	3:1	78	86
10	3.0	$LaCl_3$ (1.0)	3:1	62	92
11	3.0	none	1:0	72	92
12	2.0	$CeCl_3$ (2.0)	1:1	85	90
13	2.0	$LaCl_3$ (2.0)	1:1	87	86
14	2.0	$CeCl_3$ (1.0)	2:1	68	90
15	2.0	$LaCl_3$ (1.0)	2:1	81	84
16	2.0	none	1:0	70	92
17	1.5	$CeCl_3$ (1.5)	1:1	59	96
18	1.5	$LaCl_3$ (1.5)	1:1	74	94
19	1.5	$CeCl_3$ (0.5)	3:1	58	88
20	1.5	$LaCl_3$ (0.5)	3:1	66	92
21	1.5	none	1:0	60	90

[a–c] See Table III.

Nonetheless, these results do point out the fallacy of ascribing reagent composition on the basis of mixing stoichiometry especially at low loadings of alkyllithium.

SAMEMP Hydrazone 2. Having established a yield dependence of the reagent stoichiometry for additions to *N*,*N*-dimethylhydrazone 1, we next examined the effects of reagent stoichiometry on similar additions to chiral SAMEMP hydrazone 2. The results of this effort are collected in Tables III and IV and Figures 3 and 4. Table III depicts the results using 1 equiv of CH_3Li and variable equivalents of both $CeCl_3$ and $LaCl_3$. Unlike the additions to 1 discussed above, methyl chloroformate reacted readily with the hydrazine anion intermediate obtained from the methyllanthanum reagents.

It is evident from the data in Table III that the reactivity of SAMEMP hydrazone 2 was not comparable to that of *N*,*N*-dimethylhydrazone 1. The most notable difference is the low yields of addition product with only 1 equiv of methyl, possibly due to the presence of the coordinating methoxyethoxy side chain (vide infra). Interestingly, the highest selectivity was observed with the 1:1 $CH_3Li/CeCl_3$ reagent (entry 1), all other ratios affording a lower diastereomeric excess (de) (entries 2–4). On the other hand, the stoichiometry of the methyllanthanum reagents had virtually no effect on reaction selectivity, although the yields were variable (entries 5–7).

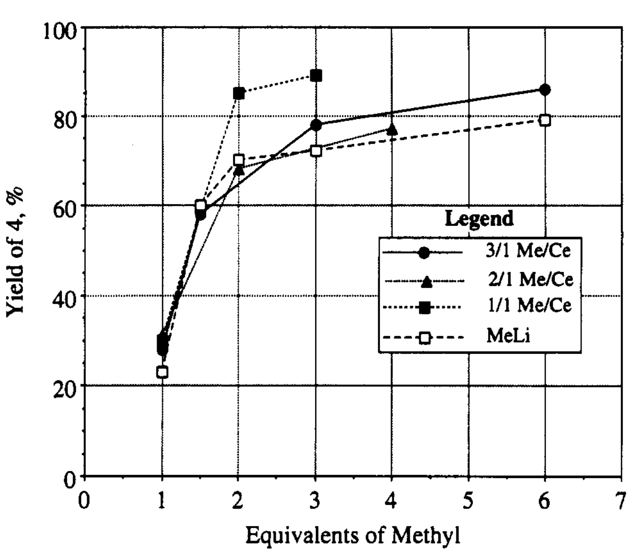


Figure 3. Effects of reagent stoichiometry on yield in additions of methylcerium reagents to 2.

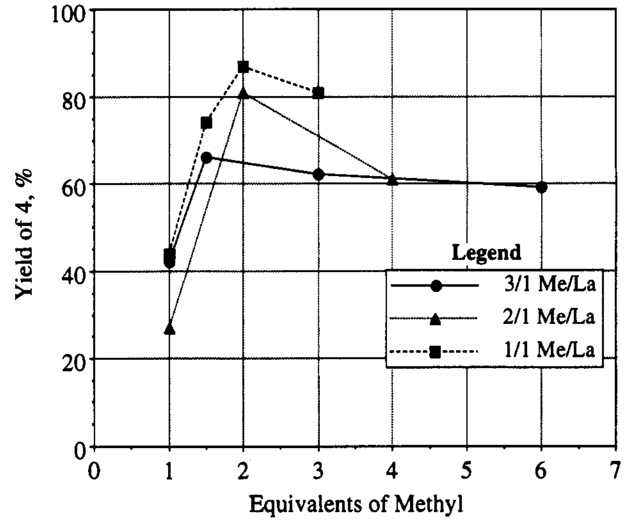


Figure 4. Effects of reagent stoichiometry on yield in additions of methyllanthanum reagents to 2.

The effects of various equivalents of serveral reagent stoichiometries on the additions to 2 were also examined, and the data are compiled in Table IV. The complexity of this system was immediately evident. However, several trends were identified by comparison of the results for various compositions of reagent derived from cerium and lanthanum. The combined results from Tables III and IV are plotted graphically in Figures 3 (Ce) and 4 (La) for yields and in Figures 5 (Ce) and 6 (La) for diastereoselectivities. Considering first the overall yield of the reaction, it is clear that the yield of 4 increased with increasing amounts of CH_3Li alone or combined in various cerium reagents. However, the use of CH_3Li alone is not recommended since the yield of 4 exceeded 72% only when

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(12) Hart, F. A.; Massey, A. G.; Saran, M. S. *J. Organomet. Chem.* 1970, *21*, 147.

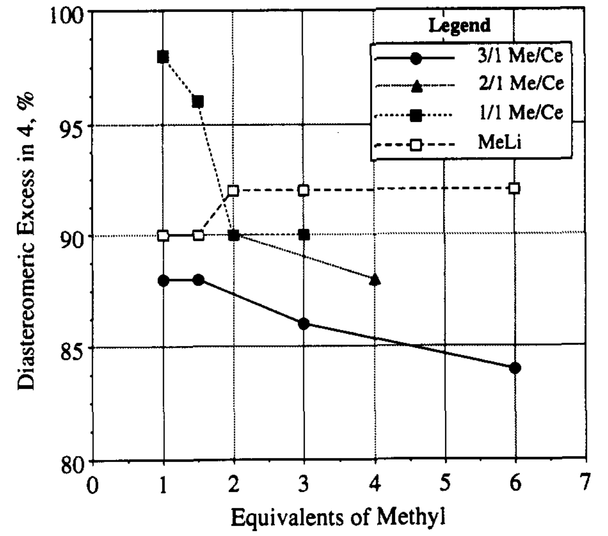


Figure 5. Effects of reagent stoichiometry on diastereoselectivity in additions of methylcerium reagents to 2.

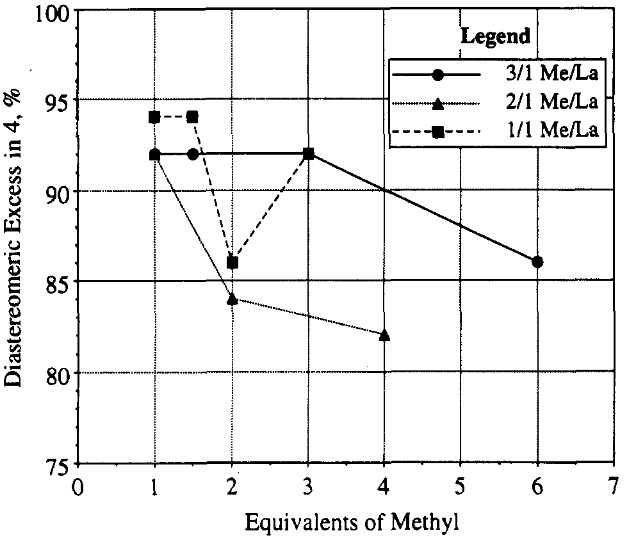


Figure 6. Effects of reagent stoichiometry on diastereoselectivity in additions of methyllanthanum reagents to 2.

6 equiv of CH_3Li were used (entry 3). In contrast, both 1:1 $CH_3Li/CeCl_3$ and 1:1 $CH_3Li/LaCl_3$ afforded greater than 85% yields using only 2 equiv of methyl (entries 12 and 13). Only the lanthanum reagents 1:1 $CH_3Li/LaCl_3$ and 3:1 $CH_3Li/LaCl_3$ afforded yields of greater than 60% with 1.5 equiv of available methyl (entries 18 and 20). However, the use of more than 2 equiv of CH_3Li to form methyllanthanum reagents resulted in reduced yields (compare entries 2, 5, and 10 vs entries 13 and 15). The methylcerium reagents did not parallel this behavior, affording only moderate yields with 1.5 equiv of methyl (entries 17 and 19). However, and more importantly, all methylcerium reagents produced higher yields of 4 at larger loadings of available methyl (Figure 3). In fact all cerium reagents containing 2 or more equiv of available methyl afforded greater than 77% yields of 4, except for the 2:1 reagent (entry 14). These data clearly demonstrate that the cerium and lanthanum reagents are not very similar in their reactivity profiles. As was indicated in the additions to 1 above, the 1:1 reagent was superior to either the 3:1 or 2:1 reagent at every level of methyl loading (entries 7 vs 9; 12 vs 14 and 17 vs 19).

Table V. Effects of Temperature on Methylation of 1 with a 3:1 Reagent

entry	reagent formation	metal	methyl equiv	yield of 3, %
1	cold[a]	Ce	2.00	76–82
2	cold[a]	Ce	3.00	75
3	warming[b]	Ce	2.00	89
4	warming[b]	Ce	3.00	78[c]
5	warming[b]	La	1.00	93
6	warming[b]	La	2.00	92
7	warming[b]	La	3.00	90

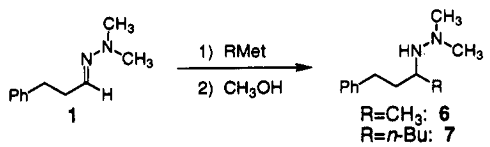
[a] Reagent prepared at −78 °C and allowed to react at −78 °C to rt. [b] Reagent prepared using a warming cycle to 0 °C. See Experimental Section. [c] An additional 12% of free, unprotected hydrazine was isolated in this experiment.

The effects of reagent stoichiometry on diastereoselectivity are also revealing. As is clearly evident from Figure 5, the number of equivalents of CH_3Li alone had little effect on the diastereomeric excess of 4 (entries 3, 6, 11, 16, and 21). A significant range of diastereoselectivities was observed (84–96% de) for the methylcerium reagents, and a definitive trend was evident from the data. For all three compositions of reagent, the diastereoselectivity decreased with increased amounts of available methyl. The 1:1 reagent showed the highest selectivities for all equivalents of available methyl. The methyllanthanum reagents behaved similarly, but trends were more difficult to discern (Figure 6). At a given level of methyl loading, the de's were similar for several compositions of reagent (entries 8 and 10, for example) and less sensitive to the amount of $LaCl_3$. However, the de was dependent upon the amount of methyl used for a given reagent stoichiometry (entries 13 and 18), and the range of diastereoselectivity observed (84–94% de) was significant. As in the case of the cerium reagents, the trend was to a lower diastereoselectivity with increasing amounts of available methyl.

Effects of Added Ligands and Temperature of Reagent Generation on Reactivity. The data in Table I and Figure 1 suggest that a trimethylcerium reagent was, if not the species obtained at all reagent stoichiometries, at least the limiting reagent stoichiometry. This result seemed to contradict the results of Schumann et al.,[8] who showed that all six methyl groups of several hexamethyllanthanide species are transferable to carbonyls. Since Schumann generated these compounds at room temperature, the effect of temperature on reagent reactivity was investigated. The results of some preliminary studies are collected in Table V along with comparison data from Table II. Thus, modification of the normal protocol to include warming the THF solution of the 3:1 $CH_3Li/CeCl_3$ reagent to 0 °C generated a homogeneous solution that, when recooled to −78 °C, consumed hydrazone 1 affording a 78–89% yield of 3. In addition, the 3:1 $CH_3Li/LaCl_3$ reagent became much more reactive (and homogeneous) when first warmed to 0 °C before adding hydrazone 1 at −78 °C, affording 90–93% yields of 3. It should be noted that this warming cycle did *not* afford homogeneous reagents when a 1:1 or 2:1 composition was employed. In addition, we found that the 6:1 reagent described by Schumann[8] was also homogenous when prepared as described above in THF. Unfortunately, this warming/recooling protocol could not be extended to other organocerium reagents.[4]

The inability of any of the reagents generated from 1 equiv of CH_3Li to add efficiently to SAMEMP hydrazone 2 suggested that the coordinating side chain was bound

Table VI. Reactivity of Various Alkylmetal Derivatives[a]



1

R=CH$_3$: **6**
R=*n*-Bu: **7**

entry	RMet	solvent	GC convn,[b] %	time, h, temp, °C
1	*n*-BuMgCl	THF	0	16, rt
2	*n*-BuMgCl	Et_2O	47	16, rt
3	*n*-BuMgCl	DMM[c]	13	16, rt
4	CH_3MgBr	THF	0	16, rt
5	CH_3MgBr	Et_2O	<1	16, rt
6	CH_3MgBr	DMM	0	16, rt
7	*n*-BuLi	Et_2O	88[d]	0.5, −78
8	*n*-BuLi	hexane	30	0.5, −78
9	*n*-BuLi	hexane[e]	99	0.5, −78
10	CH_3Li	THF	0	0.5, −78
11	CH_3Li	Et_2O	0	0.5, −78
12	CH_3Li	DMM	0	0.5, −78
13	CH_3Li	Et_2O	0	1.0, −78
14	"*n*-BuCeCl$_2$"	Et_2O	74	0.5, −78
15	"*n*-BuCeCl$_2$"	DMM	92	0.5, −78
16	"CH$_3$CeCl$_2$"	THF	70	0.33, −78
17	"CH$_3$CeCl$_2$"	THF	100	1.0, −78

[a] All reactions utilized 2 equiv of the organometallic and were quenched with methanol after the stated time at the indicated temperature. GC analysis of the crude material indicated the conversion noted. Mass balances were uniformly excellent (>90%). [b] Determined by GC: 50-m OV-17 capillary column. See Experimental Section for details. Unless otherwise noted, the only other species observed by GC was 1. [c] DMM = dimethoxymethane. [d] Approximately 6% of the crude material was unidentified byproducts. [e] Two equiv of DME was added prior to addition of *n*-BuLi.

to and attenuated the reactivity of the organometallic species. This hypothesis has been tested by conducting various methylcerium additions to *N,N*-dimethylhydrazone 1 in the presence of amine ligands. For example, addition of equimolar TMEDA to the 1:1 $CH_3Li/CeCl_3$ reagent at −78 °C followed by the addition of 0.5 equiv of 1 (2:2:2:1 $CH_3Li/CeCl_3$/TMEDA/1) afforded no addition product at −78 °C. Slow warming to room temperature resulted in complete consumption of starting material only after *12–24 h at room temperature*. Comparable results were obtained with other diamines ((*S,S*)-1,2-bis(*N,N*-dimethylamino)-1,2-diphenylethane, bis(2-(dimethylamino)ethyl ether), monoamines (2-(2-methoxyethoxy)methyl)-1-methylpyrrolidine), and metals. These results showed conclusively that chelating ligands dramatically attenuate the reactivity of organolanthanide reagents toward hydrazones.

Comparison of "RCeCl$_2$" to RLi and RMgX. A brief, noncomprehensive survey of alkylmetal additions to 1 demonstrated the facility with which alkylcerium reagents react with hydrazones compared to Grignard and lithium reagents (Table VI). Grignard reagents afforded no addition product at subambient temperatures, and only *n*-BuMgCl afforded a significant amount of adduct after 16 h at room temperature (entries 1–3). Methylmagnesium bromide afforded no adduct under these conditions (entries 4–6). The identity of hydrazines **6** and **7** was confirmed by preparative conversion to methylcarbamate **3** and acetamide **8** in separate experiments.

On the other hand, *n*-BuLi was found to add quite readily to 1, particularly as a solution in hexane in the presence of 2 equiv of DME (entries 7–9). However, in accord with previous qualitative observations during alkyllithium additions to hydrazones,[1a,13] CH_3Li afforded no addition product after 30 or even 60 min at −78 °C (entries 10–13), whereas "CH$_3$CeCl$_2$" afforded high conversion at this temperature (entries 16–17). Indeed, the only advantage of generating an organocerium reagent in the case of the *n*-butyl nucleophile (entries 14 and 15) was to achieve a cleaner reaction. No attempt was made in these experiments to distinguish between the absence of reaction and α-deprotonation of the substrate. In addition, these results were of a qualitative nature only, as the inability to obtain the unstable hydrazines in pure form precluded the determination of the relative response factors required for quantitative GC analysis. Nevertheless, the data show that alkylcerium reagents add rapidly and cleanly to 1 at low temperatures, in contrast to the Grignard reagents and CH_3Li.

Discussion

The results of the stoichiometry study using 1 equiv of CH_3Li in additions to 1 (Table I, Figure 1) clearly showed that $CH_3Li/CeCl_3$ ratios of greater than 3:1 resulted in dramatically lower yields of addition; i.e., at least 0.33 equiv of $CeCl_3$ is needed to give reactions superior to CH_3Li alone (Table I, entry 8). This implies that the reagent generated in-situ from CH_3Li and $CeCl_3$ at −78 °C in THF has the empirical formula "$(CH_3)_3CeCl_3Li_3$". This hypothesis is supported by the observation that the precipitate observed in reactions utilizing $CH_3Li/CeCl_3$ ratios less than 3:1 is $CeCl_3$. While the precise amount of MCl_3 that does not go into solution could not be accurately nor reproducibly quantified, the fraction of remaining solid indicated that the soluble reagent has between three and six methyl groups attached. On the other hand, the results of the stoichiometry study utilizing more than 1 equiv of CH_3Li in additions to 1 show that a 1:1 $CH_3Li/CeCl_3$ reagent stoichiometry affords the best yields, consistently better than the 3:1 reagent. The results of these experiments are apparently inconsistent with the hypothesis that a "trimethylcerium" reagent is the major species at all reagent stoichiometries. Although it could be argued that the excess $CeCl_3$ acts as a Lewis acid to promote addition of the 3:1 reagent, the results with the soluble "warmed" reagents (Table V) would seem to rule out this explanation. In addition, we have previously demonstrated that pretreatment of CH_3Li with $CeCl_3$ is *required* to obtain acceptable yields of addition product using SAMP hydrazones as substrates.[1a] Thus, the Lewis acidic nature of $CeCl_3$ alone is not sufficient to facilitate efficient nucleophilic addition by CH_3Li. It therefore seems reasonable to propose that the different ratios of reactants used to generate the organocerium species afford different mixtures of reagents but that a 3:1 "trimethylcerium" species seems to be the limiting stoichiometry of the organometallic that can be formed at −78 °C.

The conclusion that the limiting reagent is a "trimethylcerium" species is apparently inconsistent with the observation that in situ generated 1:1 reagents perform uniformly better than 3:1 reagents. This inconsistency disappears when the solubilized reagents are considered. The best results with the 1:1 reagent are obtained with two methyl equivalents (86–90%). Using the solubilized 3:1 reagent, again only two methyl equivalents are needed to obtain >89% yields. The discrepancy arises in the assumption that the 3:1 reagent forms stoichiometrically at −78 °C, an assumption that cannot be correct in light

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(13) Denmark, S. E.; Piotrowski, D. W. Unpublished results from these laboratories.

of the observation of unreacted $CeCl_3$ in these runs. *Thus, the lower yields of addition product obtained with −78 °C-generated 3:1 reagents must be due to undesired side reactions caused by the presence of nonmetathesized CH_3Li.*

In light of Schumann's ability to generate hexamethyl derivatives of various lanthanides[8] and the fact that we have demonstrated that a 3:1 $CH_3Li/CeCl_3$ reagent can be utilized efficiently if first solubilized by warming to 0 °C, the results of this stoichiometry study suggest that temperatures greater than −78 °C are required for CH_3Li to undergo efficient transmetalation with Ce(III). It is recognized that the addition of three anionic methyl ligands to $CeCl_3$ hypothetically generates a coordinatively saturated cerium(III) species $[(CH_3)_3CeCl_3]^{3-}$. Subsequent displacement of the chloride ions by additional methyl ligands would presumably proceed via a dissociative mechanism,[14] which may not be energetically feasible at −78 °C. Although this is only a tentative proposal based upon the data at hand, in this context it is instructive to note that Schumann generates his hexamethyllanthanide derivatives by addition of 6 equiv of CH_3Li to the $LnCl_3$ salts at −78 °C, followed by *warming to room temperature* for 2–3 h. However, the warming/recooling cycle used to generate active 6:1 reagents is not applicable to other alkyllithiums.[4] In addition, prolonged warming of alkylcerium reagents other than methyl, *tert*-butyl, or phenyl is inadvisable, as Imamoto has reported that this procedure results in β-hydride elimination for reagents generated from *n*-BuLi, *s*-BuLi, etc.[4a,g] Utimoto has made the observation[3c] that reagents derived from 1-pentynylmagnesium bromide and $YbCl_3$ become much *less* reactive with prolonged "aging" at 0 °C. It is not clear at present why this should be the case, and the extension of this work to other Grignard reagents has not been reported. However, results from these laboratories show that alkynylcerium reagents do not add to SAMP hydrazones,[1a,13] thus the significance of Utimoto's singular observation in the context of organocerium additions to hydrazones is not immediately apparent.

The results of the stoichiometry study for additions to SAMEMP hydrazone 2 demonstrate that 1 equiv of nucleophile does not add efficiently and 2 equiv affords optimal results. The chelating side chain apparently binds to the organometallic reagent and thus makes it unavailable for nucleophilic addition. This suggests that coordination of the reagent to one of the nitrogen lone pairs is needed to activate the hydrazone to nucleophilic attack and that the ability of the organocerium reagents to efficiently add to hydrazones is due to a *combination* of lower Brønsted basicity and increased Lewis acidity compared to alkyllithium and Grignard reagents.

For whatever reason, acceptable yields of addition product are attainable with *N,N*-dimethylhydrazone 1 with only 1 equiv of alkyllithium, provided that organocerium reagents are utilized. The ability to avoid the use of excess alkyllithium is an advantage in those situations where the nucleophile is precious. This is an advantage not shared by the use of alkyllithium reagents alone. Unfortunately, this does not hold for SAMP or SAMEMP hydrazones.

The use of organolanthanum reagents has significant disadvantages, as evidenced by the difficulty with which the intermediate hydrazine anion derived from 1 can be trapped. In addition, although this trapping problem apparently does not apply to additions to SAMEMP hydrazones, the yields in these reactions are significantly lower than those using organocerium reagents.

Summary

The results of this study, while unable to identify the precise nature of the organocerium reagents, should serve as a useful guide for the judicious choice of experimental conditions for organocerium additions to dialkylhydrazones. While it can be argued that the necessity of trapping the intermediate hydrazine anion as a carbamate may affect the results obtained, the facility with which this trapping occurs suggests that the yields of isolated carbamates obtained qualitatively reflects the efficiency of methyl nucleophile addition. Combined with the efficient N–N bond cleavage protocol developed recently in these[1c] and other[15] laboratories, the addition of organocerium reagents to hydrazones provides an efficient and straightforward method of preparing protected α-branched amines from readily available precursors.

Experimental Section

General Experimental Data. ^1H and ^{13}C NMR spectra were recorded at 300 MHz ^1H (75.5 MHz ^{13}C) in deuteriochloroform ($CDCl_3$) with either tetramethylsilane (TMS) (0.00 ppm ^1H, 0.00 ppm ^{13}C) or chloroform (7.26 ppm ^1H, 77.00 ppm ^{13}C) as an internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given in ppm (δ); multiplicities are indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), exch (exchangeable); coupling constants, *J*, are reported (Hz); integration is provided; and assignment is indicated. Infrared spectra (IR) were recorded in CCl_4 solution. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (weak, 0–33%), and br (broad). Mass spectra (MS) were obtained with ionization voltages of 70 and 10 eV. Data are reported in the form *m/e* (intensity relative to base = 100). Optical rotations were obtained on a JASCO DIP-360 digital polarimeter and are reported as follows: $[\alpha]^{\text{temperature}}_{\text{wavelength}}$ (concentration in g/100 mL, solvent). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates with QF-254 indicator. Visualization was accomplished by UV light, iodine, or *p*-anisaldehyde solution. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: dichloromethane (CH_2Cl_2), pentane, and hexane, $CaCl_2$; diethyl ether (Et_2O) and *tert*-butyl methyl ether (TBME), $CaSO_4/FeSO_4$; ethyl acetate (EtOAc), K_2CO_3. Column chromatography was performed using 32–63-μm silica gel (Woelm). Analytical gas chromatography (GC) was performed using a Hewlett-Packard 50-m OV-17 capillary column (column A), a Hewlett-Packard 50-m HP-5 capillary column (column B), and a Hewlett-Packard 50-m HP-1 capillary column (column C). The injector temperature was 225 °C, the detector temperature was 300 °C, and the column head pressure was 17.5 psi. Temperature programs are reported in the following form: initial temperature [time (min)], temperature ramp rate (deg/min), final temperature [time (min)]. Retention times (t_R) and integrated ratios were obtained from either a Hewlett-Packard 3390A recorder (column A) or a Hewlett-Packard 3393A recorder (columns B and C). Analytical high-pressure liquid chromatography (HPLC) was performed using a Supelco LC-Si 5-μm column (column D). The detector wavelength was set to 254 nm. Bulb-to-bulb distillations were done on a Büchi GKR-50 Kugelrohr, and boiling points (bp) correspond to uncorrected air bath temperatures. Organolith-

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(14) Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms*; Brooks/Cole: Monterey, CA, 1985; Chapter 2.

(15) Alexakis, A.; Leusen, N.; Mangeney, P. *Synlett* 1991, 625.

iums were titrated by the method of Gilman.[16] All reactions were performed under a dry nitrogen or argon atmosphere in oven- and/or flame-dried glassware. Brine refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of NH_4Cl, $NaHCO_3$, KOH, NaOH, and $Na_2S_2O_3$ are aqueous solutions. SAMEMP hydrazone 2 was prepared following the literature procedure.[1e]

(*E*)-3-Phenylpropanal *N*,*N*-Dimethylhydrazone (1). In a 15-mL one-neck flask a neat solution of hydrocinnamaldehyde (2.686 g, 20.01 mmol) was cooled to 0 °C and 1,1-dimethylhydrazine (2.30 mL, 30 mmol, 1.50 equiv) was added slowly via syringe. The reaction mixture was allowed to warm to rt, heated to 40 °C, and stirred for 18 h at 40 °C. The reaction mixture was allowed to cool to rt, diluted with EtOAc (100 mL), and washed with H_2O (2 × 100 mL) and brine (1 × 100 mL). The washings were extracted with EtOAc (2 × 100 mL). The extracts were washed with brine (1 × 100 mL). The organic layers were combined and dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 3/1) and bulb-to-bulb distillation to afford 3.477 g (95%) of hydrazone 1 as a single isomer. Data for 1: bp 100–110 °C (0.1 Torr); ^1H NMR (300 MHz) 7.29–7.17 (m, 5 H, Ph), 6.63 (t, J = 5.32, 1 H, HC(1)), 2.76 (m, 2 H, $H_2C(3)$), 2.70 (s, 6 H, $N(CH_3)_2$), 2.56 (m, 2 H, $H_2C(2)$); ^{13}C NMR (75.5 MHz), 141.29 (C(1)), 137.64 (Ph-C(1′)), 128.29 (C(2′)), 128.20 (C(4′)), 125.73 (C(3′)), 43.13 ($N(CH_3)_2$), 34.62 (C(3)), 33.98 (C(2)); IR 3028 (m), 2990 (s), 2955 (s), 2855 (m), 1497 (s), 1469 (s), 1454 (m), 1140 (m), 1030 (s); MS (70 eV) 177 (2), 176 (13), 86 (5), 85 (100), 45 (4), 44 (13); GC t_R 6.94 (column A; 135 °C isothermal); TLC R_f 0.38 (hexane/EtOAc = 2/1). Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 74.95; H, 9.06; N, 15.68.

Methyl (*N*,*N*-Dimethylamino)(1-methyl-3-phenylpropyl)carbamate (3). A 100-mL three-neck flask fitted with septum and gas inlet was charged with $CeCl_3{\cdot}7H_2O$ (2.2465 g, 6.03 mmol, 2.00 equiv) which was dried by heating to 140 °C at 0.2 Torr for 2 h. The flask was allowed to cool to rt, vented to dry nitrogen, and THF (18 mL) was added via syringe. This slurry was stirred for 2 h rt and cooled to −78 °C. To this white suspension was added CH_3Li (1.52 M in Et_2O, 3.96 mL, 6.02 mmol, 2.00 equiv) slowly via syringe, and the reaction mixture was stirred for 1 h at −78 °C. A solution of 1 (529 mg, 3.00 mmol) in THF (12 mL) was added slowly via syringe, and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was allowed to warm to rt over the course of 1 h and allowed to react for 1 h at rt. Methyl chloroformate (700 μL, 9.0 mmol, 3.0 equiv) was added via syringe, and the reaction mixture was stirred for 22 h at rt. The reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The extracts were washed with brine (1 × 100 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to afford a yellow oil. Purification by silica gel chromatography (hexane/EtOAc = 12/1) and bulb-to-bulb distillation afforded 665 mg (88%) of 3 as a clear, colorless oil. Data for 3: bp 135–140 °C (0.35 Torr); ^1H NMR (300 MHz) 7.18 (m, 2 H, HC(2′)), 7.09 (m, 3 H, HC(3′), HC(4′)), 4.01 (2 br m, 1 H, HC(2)), 3.66 (br m, 3 H, H_3CO), 2.64 (br s, 6 H, $(CH_3)_2N$), 2.50 (t, J = 8.10, 2 H, $H_2C(4)$), 1.89, 1.58 (2 m, $H_2C(3)$), 1.08 (d, J = 6.65, 3 H, $H_3C(1)$); ^{13}C NMR (75.5 MHz), 142.07 (C(1′)), 128.20, 125.64 (Ph), 53.86 (br, OCH_3), 51.86 (br, C(2)), 45.49–44.73 (br, $N(CH_3)_2$), 35.70 (C(4)), 33.07 (C(3)), 18.40 (br, C(1)); IR 2984 (s), 2949 (s), 2888 (s), 1698 (s), 1497 (m), 1441 (s), 1385 (s), 1323 (s), 1186 (s), 1105 (m), 1086 (m); MS (70 eV) 251 (M^+ + 1, 14), 250 (M^+, 83), 191 (18), 133 (14), 132 (100), 119 (9), 118 (99), 117 (67), 102 (42), 91 (55), 87 (18), 86 (23), 85 (21); TLC R_f 0.22 (hexane/EtOAc = 2/1). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.07; H, 8.78; N, 10.99.

General Procedure for the Stoichiometry Study of "$(CH_3)_xCeCl_y$" Additions to 1. All reactions were run on a 1 mmol scale based on 1 in 13–14 mL of total solvent (THF plus Et_2O from commercial CH_3Li). The procedure for 1:1:1 $CH_3Li/CeCl_3/1$ (1 equiv of the 1:1 reagent) is typical and will serve to illustrate the general procedure.

A 25-mL two-neck flask fitted with septum and gas inlet was charged with $CeCl_3{\cdot}7H_2O$ (373 mg, 1.00 mmol, 1.00 equiv) which was dried at 140 °C at 0.2 Torr for 2 h. The flask was allowed to cool to rt, vented to dry nitrogen, and THF (7 mL) was added. This slurry was stirred for 2 h at rt and cooled to −78 °C, and CH_3Li (1.43 M in Et_2O, 0.68 mL, 1.00 mmol, 1.00 equiv) was added slowly via syringe. The reaction mixture turned yellow/tan. After the mixture was stirred for 1 h at −78 °C, a solution of 1 (176 mg, 1.00 mmol) in THF (6 mL) was slowly added via syringe and allowed to stir for 1 h at −78 °C. The reaction mixture was allowed to warm to rt and stir for 2 h and then was treated with methyl chloroformate (240 μL, 3.1 mmol, 3.1 equiv) and allowed to stir for 24 h at rt. The reaction mixture was poured into H_2O (20 mL) and was extracted with EtOAc (3 × 30 mL). The extracts were washed with brine (1 × 25 mL), dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to afford a yellow oil. Purification by silica gel chromatography (hexane/EtOAc = 12/1) afforded 184 mg (74%) of 3 as a clear oil. The TLC and ^1H NMR data matched those of the previously prepared sample.

General Procedure for the Preparation of 3 from 1 and CH_3Li. The following is a modification of the Enders[17] procedure. All reactions were run on a 1 mmol scale based on 1 with 8–9 mL of solvent (THF plus Et_2O from commercial CH_3Li). The procedure for 2 equiv of CH_3Li is typical and will serve to illustrate the general procedure.

To a 15-mL, two-neck flask fitted with septum and gas inlet was added a solution of CH_3Li (1.46 M in Et_2O, 1.38 mL, 2.01 mmol, 2.00 equiv) and THF (3 mL). The reaction mixture was cooled to −78 °C, and a solution of 1 (178 mg, 1.01 mmol) in THF (4 mL) was added slowly via syringe. The reaction mixture was stirred at −78 °C for 1 h, gradually allowed to warm to rt, and stirred overnight (11 h). The reaction mixture was cooled to 0 °C, and methyl chloroformate (250 μL, 3.2 mmol, 3.2 equiv) was added slowly via syringe. The reaction mixture was allowed to warm to rt and stir for 22 h. The reaction mixture was poured into H_2O (20 mL) and was extracted with EtOAc (3 × 30 mL). The extracts were washed with brine (1 × 25 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to afford an orange oil. Purification by silica gel chromatography (hexane/EtOAc = 12/1) afforded 179 mg (71%) of the carbamate 3 as a clear oil. The TLC and ^1H NMR data matched those of the previously prepared sample.

Benzyl (*N*,*N*-Dimethylamino)(1-methyl-3-phenylpropyl)carbamate (5). A 25-mL, two-neck flask fitted with septum and gas inlet was charged with $LaCl_3{\cdot}7H_2O$ (371 g, 1.00 mmol, 1.00 equiv) which was dried by heating to 140 °C at 0.2 Torr for 2 h. The flask was allowed to cool to rt and vented to dry nitrogen, and THF (5 mL) was added via syringe. This slurry was stirred 2 h at rt and cooled to −78 °C. To this suspension was slowly added via syringe CH_3Li (1.42 M in Et_2O, 0.68 mL, 1.00 mmol, 1.00 equiv), and the reaction mixture was stirred for 1 h at −78 °C. A solution of 1 (176 mg, 1.00 mmol) in THF (5 mL) was added slowly via syringe, and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was allowed to warm to rt over the course of 1 h and allowed to react for 1 h at rt. Benzyl chloroformate (440 μL, 3.1 mmol, 3.1 equiv) was added via syringe, and the reaction mixture was stirred for 22 h at rt. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The extracts were washed with brine (1 × 20 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated to afford a yellow oil. Purification by column chromatography (hexane/EtOAc = 16/1) and bulb-to-bulb distillation afforded 245 mg (75%) of the carbamate 5. Data for 5: bp 240–245 °C (0.3 Torr); ^1H NMR (300 MHz) 7.40–7.15 (m, 10 H, Ph), 5.20 (br m, 2 H, $H_2C(4)$), 4.20 (2 br m, 1 H, HC(2)), 2.78–2.61 (3 br m, 9 H, H_3CO, $N(CH_3)_2$), 1.98, 1.68 (2 br m, $H_2C(3)$), 1.18 (d, 3 H, J = 6.64, $H_3C(1)$); ^{13}C NMR (75.5 MHz) 142 (br, C=O), 136.58, 128.63, 128.38, 128.20, 127.87, 125.67 (Ph), 67.09, 66.45 (2 br s, C(2)), 54.11 (br, C(2)), 45.84–44.78 (br, $N(CH_3)_2$), 35.66 (C(4)), 33.07 (C(3)), 18.72–18.27 (br, C(1)); IR 2947 (m), 2361 (m), 1701 (s), 1456 (m), 1394 (s), 1308 (s), 1103 (m), 1069 (m); MS (70 eV) 326 (15), 191 (28), 105 (9), 92 (10), 91 (100), 87 (33). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.51; H, 8.10; N, 8.51.

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[16] Gilman, H.; Schulze, F. *J. Am. Chem. Soc.* **1925**, *47*, 2002.

[17] Enders, D.; Schubert, H.; Nübling, C. *Angew. Chem.* **1986**, *98*, 1118; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109.

General Procedure for the Generation and the Use of the Homogeneous 3:1 $CH_3Li/CeCl_3$ Reagent. The procedure for 2.00:0.66:1.00 $CH_3Li/CeCl_3/1$ ($^2/_3$ equiv of the homogeneous 3:1 reagent) is typical and will serve to illustrate the general procedure.

In a 50-mL, two-neck flask fitted with a gas inlet tube, magnetic stir bar, and septum was placed $CeCl_3{\cdot}7H_2O$ (743.5 mg, 1.996 mmol, 0.65 equiv) which was dried (140 °C, 0.2 Torr) for 2 h. The flask was then cooled to rt and vented to dry nitrogen. The dried $CeCl_3$ was stirred in dry THF (20 mL) at rt for 0.5 h. The resulting white slurry was cooled to −78 °C, stirred for ca. 5 min, and treated dropwise with a 1.43 M solution of CH_3Li in Et_2O (4.20 mL, 6.02 mmol, 1.97 equiv/1, 3.02 equiv/$CeCl_3$). The resulting heterogeneous, yellow/tan reaction mixture was stirred for 1 h at −78 °C. At this time, no change in the physical aspect of the reaction mixture and consistency was observed. The cooling bath was then removed and the reaction mixture warmed upon stirring for 3–4 min. The yellow color became more intense, and the reaction mixture cleared. The flask was then placed in a cold bath (0–2 °C), and the reaction mixture was stirred for 5 min at which time the reaction mixture became a homogeneous, yellow solution.[18] The reagent was then cooled back to −78 °C and was stirred for ca. 5 min. A solution of 1 (538 mg, 3.05 mmol) in dry THF (4 mL) was then added dropwise via syringe. The reaction mixture turned dark brown upon addition and was allowed to stir for 1 h at −78 °C. The reaction mixture was then allowed to warm to rt and stir for 3 h. The intermediate hydrazine anion was treated with methyl chloroformate (2.30 mL, 29.8 mmol, 9.76 equiv) at 0 °C and allowed to stir at rt for 15 h. The reaction mixture was poured into H_2O (10 mL) and extracted with EtOAc (3 × 40 mL). The extracts were washed with brine (10 mL), combined, dried (Na_2SO_4), filtered through a pad of Celite, and concentrated in vacuo to afford a yellow oil. Purification by silica gel column chromatography (hexane/EtOAc = 8/1) afforded 681 mg (89%) of 3 as a pale yellow oil in addition to 36 mg (6%) of the corresponding free hydrazine (95% mass recovery). The TLC and ^1H NMR data matched those of the previously prepared sample.

Isolation and Identification of the Precipitate Resulting from the Generation of a 1:1 $CH_3Li/CeCl_3$ Reagent. A 50-mL, two-neck flask fitted with septum and gas inlet was charged with $CeCl_3{\cdot}7H_2O$ (1.013 g, 2.72 mmol) which was dried (140 °C at 0.3 Torr) for 2 h. The flask was then allowed to cool to rt and vented to dry nitrogen, and dry THF (22 mL) was added. The resulting slurry was stirred for 2 h at rt and cooled to −78 °C, and a 1.47 M solution of CH_3Li in Et_2O was added slowly via syringe (1.8 mL, 2.72 mmol, 1.00 equiv). The resulting heterogeneous, yellow/tan reaction mixture was stirred for 1 h at −78 °C. At this time magnetic stirring was ended and the reaction mixture was allowed to settle for 1 h at −78 °C. The dark brown supernatant solution was then decanted via canula, and the resulting precipitate was washed with cold, dry THF (2 × 3 mL) in a similar manner. The precipitate was dried at rt under high vacuum (0.01 Torr) for 2 days to afford a very fine white powder. A sample of this white powder was encapsulated in a glovebox and submitted for elemental analysis. Anal. Calcd for $CeCl_3$: Ce, 56.85; Cl, 43.15; Li, 0.00. Found: Ce, 56.61; Cl, 40.86; Li, 0.03.

General Procedure for the Stoichiometry Study of "$(CH_3)_xCeCl_y$" Additions to 2. Preparation of [*R*-(*R,*S**)]-Methyl [2-[(2-Methoxyethoxy)methyl]-1-pyrrolidyl](1-methyl-3-phenylpropyl)carbamate (4).** All reactions were run on a 0.5 mmol scale based on 2. The procedure for 2:2:1 $CH_3Li/CeCl_3/2$ (2 equiv of the 1:1 reagent) is typical and will serve to illustrate the general procedure.

A 50-mL, two-neck flask fitted with septum and gas inlet was charged with $CeCl_3{\cdot}7H_2O$ (341 mg, 0.92 mmol, 2.00 equiv) which was dried at 140 °C at 0.01 Torr for 2 h. The flask was then allowed to cool to rt and vented to dry nitrogen, and dry THF (9.2 mL) was added. The resulting slurry was stirred for 2 h at rt and cooled to −78 °C, and a 1.57 M solution of CH_3Li in Et_2O was added slowly via syringe (0.60 mL, 0.924 mmol, 2.02 equiv). The resulting heterogeneous, yellow/tan reaction mixture was stirred for 1 h at −78 °C. Then, a solution of 2 (133 mg, 0.458 mmol) in dry THF (4.6 mL) was slowly added via syringe and allowed to stir for 1 h at −78 °C. The reaction mixture was then allowed to warm to rt and stir for 1.5 h (reactions using 1.0–1.5 equiv of CH_3Li did not go to completion even after 23 h). The intermediate hydrazine anion was treated with methyl chloroformate (0.135 mL, 1.75 mmol, 3.81 equiv) at 0 °C and was allowed to stir at rt for 4.5 h. The reaction mixture was poured into H_2O (15 mL) and was extracted with Et_2O (3 × 30 mL). The extracts were washed with brine (10 mL), combined, dried ($MgSO_4$), filtered through a pad of Celite, and concentrated in vacuo to afford a yellow oil. This material was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford 142 mg (85%) of 4 as a yellow oil. Bulb-to-bulb distillation of this material afforded 136 mg (82%) of a pale yellow oil. Data for 4: bp 180–185 °C (0.2 Torr); ^1H NMR (300 MHz) 7.40–7.10 (m, 5 H, arom H), 4.30–3.00 (m, 16 H, ($CH_3OCC(2)$, at 3.33, s)), 2.70–2.50 (m, 2 H), 2.30–1.60 (m, 6 H), 1.16 (d, $J = 6.5$, 3 H, CCH_3); ^{13}C NMR (75 MHz) 141.78, 128.03, 125.49, 73.95, 71.63, 70.11, 62.0 (br), 58.72, 55.00 (br), 54.30, 51.88, 36.17, 32.72, 27.63, 23.41, 18.99; IR (neat) 3061w, 3026w, 2947s, 2876s, 1701s, 1605w, 1496m, 1439s, 1385m, 1319s, 1253w, 1196m, 1109s, 1049m; MS (70 eV) 364 (M^+, 1), 276 (11), 275 (100), 143 (10); TLC R_f 0.10 (hexane/EtOAc = 5/1); GC (column C; 135 °C isothermal) t_R (*R*)-4, 22.32 min (95%); t_R (*S*)-4, 23.52 min (5%); 90% de favoring the (2*S*,1*R*) diastereomer; $[\alpha]^{20}_D = -50.0°$ ($c = 1.42$, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}N_2O_4$: C, 65.90; H, 8.84; N, 7.68. Found: C, 65.85; H, 8.87; N, 7.69.

General Procedure for the Preparation of 4 from 2 and CH_3Li. All reactions were run on a 0.5 mmol scale based on 2. The procedure for 2 equiv of CH_3Li is typical and will serve to illustrate the general procedure.

A 1.57 M solution of CH_3Li in Et_2O was added slowly via syringe (0.69 mL, 1.083 mmol, 2.00 equiv) to cold, dry THF (10 mL) kept at −78 °C into a 50-mL two-neck flask fitted with septum and gas inlet. The resulting reaction mixture was stirred for 5 min, and a solution of 2 (158 mg, 0.543 mmol) in dry THF (5.4 mL) was slowly added via syringe and allowed to stir for 1 h at −78 °C. The reaction mixture was then allowed to warm to rt and stir until TLC analysis showed completion of the reaction (9.5 h). The intermediate hydrazine anion was quenched with methyl chloroformate (0.42 mL, 5.44 mmol, 5.02 equiv) at 0 °C and was allowed to stir at rt for 13 h. The reaction mixture was poured into H_2O (15 mL) and was extracted with Et_2O (3 × 30 mL). The extracts were washed with brine (10 mL), combined, dried ($MgSO_4$), filtered through a pad of Celite, and concentrated in vacuo to afford a yellow oil. This material was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to afford 135 mg (70%) of 4 as a clear yellow oil. The ^1H NMR, HPLC, and TLC data matched those of the previously prepared sample: HPLC (column D; hexane/EtOAc = 86/14; 0.8 mL/min) t_R (*R*)-4, 17.57 min (96%); t_R (*S*)-4, 23.85 min (4%); 92% de favoring the (2*S*,1*R*) diastereomer.

General Procedure for the Addition of Alkyl Metal Derivatives to 1 (Table VI). All reactions utilized 2 equiv of the organometallic reagent and were 0.10–0.15 M in 1. The procedure for the addition of *n*-BuLi to 1 in hexane (Table VI, entry 8) is illustrative.

To a 10-mL, two-neck flask was added dry hexane (1 mL) and *n*-BuLi (1.57 M in hexane, 0.32 mL, 0.50 mmol, 2.00 equiv). The reaction mixture was cooled to −78 °C, and a solution of 1 (44 mg, 0.25 mmol) in hexane (1 mL) was added dropwise via syringe. The reaction mixture was stirred for 30 min at −78 °C and quenched by the dropwise addition of CH_3OH (2 mL). The reaction mixture was allowed to warm to rt, filtered through a plug of silica gel, and analyzed by GC (column A). A 70/30 mixture of starting material to product was indicated. The labile hydrazines could not be obtained in pure form to determine relative response factors, thus, the values in Table VI are qualitative. Data for 1, 6, 7: GC, 1: t_R 4.74 (150 (5), 10, 200 (15); 6: t_R 8.24 (150 (5), 10, 200 (15); 1: t_R 6.96 (135 °C isothermal); 7: t_R 6.31 (135 °C isothermal).

3-[*N*-Acetyl-*N*-(dimethylamino)amino]-1-phenylheptane (8). To a 50-mL three-neck flask fitted with an addition

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[18] A three-neck flask fitted with a thermometer as well as a gas inlet tube and septum may be used in order to precisely follow the warmup procedure. Usually, the reaction mixture turned to a homogeneous, intense yellow solution at approximately −10 °C. The reaction mixture remained unchanged upon stirring at 0 °C for at least 30 min.

funnel was charged $CeCl_3 \cdot 7H_2O$ (1.677 g, 4.50 mmol, 1.50 equiv) which was dried at 140 °C at 0.2 Torr for 2 h. The flask was allowed to cool to rt and vented to nitrogen, and THF (15 mL) was added. The reaction mixture was stirred vigorously for 2 h at rt and cooled to −78 °C. To this suspension was added dropwise *n*-BuLi (1.60 M in hexane, 2.82 mL, 4.51 mmol, 1.50 equiv) via syringe, and the reaction mixture was stirred for 1 h at −78 °C. To this golden yellow suspension was added dropwise via addition funnel a solution of 1 (528 mg, 3.00 mmol) in THF (8 mL), and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was allowed to warm to 0 °C, and CH_3OH (2 mL) was added slowly via syringe. The reaction mixture was poured into H_2O (30 mL) and extracted with Et_2O (3 × 40 mL). The extracts were washed with brine (1 × 30 mL), combined, dried ($MgSO_4$), filtered through a pad of Celite, and concentrated. The residue was dissolved in Ac_2O (8 mL), placed in a 50-mL flask fitted with a reflux condenser, thoroughly degassed (freeze/thaw × 3), and heated to reflux for 12 h. The reaction mixture was cooled to rt and diluted with Et_2O (20 mL), and a 10% solution of $NaHCO_3$ (15 mL) was slowly added to the vigorously stirred reaction mixture. Solid $NaHCO_3$ (2 g) was added in approximately 200-mg portions. The reaction mixture was poured into H_2O (20 mL) and extracted with Et_2O (3 × 30 mL). The extracts were washed with a 10% solution of $NaHCO_3$ (1 × 25 mL) and brine (1 × 25 mL), combined, dried (K_2CO_3), filtered through a pad of Celite, and concentrated. The residue was purified by silica gel chromatography (hexane/EtOAc = 4/1) and bulb-to-bulb distillation to afford 737 mg (89%) of the amide 8 as a clear, colorless oil. Data for 8: bp 210–220 °C (0.5 Torr); ^1H NMR (300 MHz) 7.26–7.20 (m, 5 H, Ph), 3.40, 3.20 (2 m, 1 H, HC(3)), 2.88, 2.81 (2 s, 3 H, H_3CN), 2.62 (m, 2 H, $H_2C(1)$), 2.49, 2.44 (2 s, 3 H, H_3CN), 2.09 (m, 2 H, $H_2C(2)$), 2.12, 1.92 (2 s, 3 H, $H_3C(C{=}O)N$), 1.81 (m, 2 H, $H_2C(4)$), 1.35 (m, 4 H, $H_2C(5)$, $H_2C(6)$), 0.90 (m, 3 H, $H_3C(7)$); ^{13}C NMR (75.5 MHz) 173.52 (C=O), 141.99, 141.50 (*i*-Ph), 128.52, 128.40, 128.31, 128.18, 126.07, 125.81 (Ph), 61.42, 53.27 (C(3)), 45.08, 44.79, 44.03 ($(CH_3)_2N$), 35.11, 34.12 (C(1)), 33.78, 33.00 (C(2)), 32.73, 32.19 (C(4)), 29.85, 29.01 (C(5)), 23.80, 22.99 ($CH_3(C{=}O)N$), 22.93, 22.83 (C(6)), 14.13, 14.07 (C(7)); MS (70 eV) 277 ($M^+ + 1$, 1), 276 (M^+, 7), 234 (13), 233 (58), 129 (88), 128 (25), 117 (12), 105 (20), 102 (37), 101 (14), 91 (92), 86 (19), 85 (12), 60 (64), 59 (100); TLC R_f 0.55 (hexane/EtOAc = 1/1). Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.76; H, 10.29; N, 10.08.

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