Efficient Transformation of Azides to Primary Amines Using the Mild and Easily Accessible $CeCl_3\cdot 7H_2O/NaI$ System[†]

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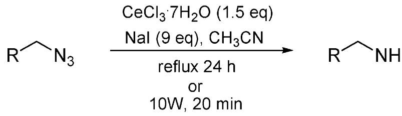

Because of the nitrogen functionality, the azido group plays an important role in the synthesis of amines, and numerous reduction methods of azides to primary amines are reported. Recent reports have highlighted the capability of NaI as a useful reagent for this transformation when it is used in combination with a Lewis acid promoter. However, these methods often suffer from harsh reaction conditions; for this reason, the development of a simple and efficient protocol using NaI in presence of inexpensive and readily available cerium salts Lewis acids would extend the scope of this organic transformation. In continuation of our interest on the use of the $CeCl_3\cdot 7H_2O/NaI$ system, in this paper we report how azides undergo reduction by NaI in the presence of $CeCl_3\cdot 7H_2O$ in refluxing acetonitrile under neutral conditions to produce the corresponding primary amines. The rate and yield of the reaction are considerably improved by employing this microwave-assisted procedure, and this may be of value for the preparation of densely functionalized molecules having biological and pharmaceutical activities.

1. Introduction

One of the best methods for synthesizing primary amino derivatives starts from the corresponding oxy counterparts and involves a two-step process: the derivative is first transformed into a good leaving group followed by reaction with an azide anion.[1] The obtained azides are then transformed into the desired amines in good yields. Thus, an azido group is used as a primary amine precursor in organic synthesis.[2]

Even though there are reports describing one-pot sequences for the transformation of alcohols to amines via azide intermediates promoted by metal catalysts,[3] it is preferable to carry out a more lengthy procedure that demands the separation of the azide intermediates since it is known that especially heavy metal azides are dangerous explosives.[4] There are many methods available for the preparation of azide compounds,[5] and one of the most common methods is the nucleophilic substitution of the sulfonate or bromide group by the azide ion.[6] However, as methods to improve the synthetic entry of these nitrogen-containing organic compounds were developed, the need arose for a general protocol for the conversion of functionalized azides to the corresponding amines in high yields and purities, with nontoxic and cheap reagents. A wide variety of reducing agents have been reported in the literature[7] for conversion of azides

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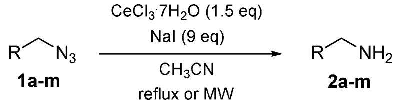
into amines, and over the years, the most prominent have employed triphenylphosphine[8] or its excellent alternative with hydrogen sulfide in pyridine.[9] The majority of these reducing agents have some disadvantages related to their lack of selectivity and drastic conditions, such as highly basic conditions. In fact, several attempts to chemoselectively reduce the azides to corresponding amines via a Staudinger reaction were problematic. Staudinger reduction using triphenylphosphine with a variety of azides is not able to give a reaction,[10] and the use of the highly reactive trialkylphosphine is necessary to have complete consumption of the azides and formation of the phosphazine ylides. These could extrude nitrogen to deliver the intermediate iminophosphoranes; however, addition of a strong base to the reaction mixture is required to obtain the hydrolysis of these stable intermediates.[11] As a result, there is always considerable interest in finding more selective methods.

Over the past years, it has been shown as NaI in combination with a Lewis acid such as $TiCl_4$ offers a useful alternative to existing methods for the reduction of both amine *N*-oxides and nitrones.[12] These mild reductive properties of the $TiCl_4$/NaI reagent system prompted Kamal et al. to try the $FeCl_3$/NaI combination as an efficient complex for the transformation of azides to the corresponding amines,[13] even if some neglected reaction details need to be considered. The $FeCl_3$, in combination with different reagents, has also been reported for several other reductions,[14] above all for its Lewis acid ability under mild and nonbasic conditions.[15] The above benefits are, however, accompanied by drawbacks. The major drawback associated with the use of $FeCl_3$ is that it is messy, very acidic, and corrosive, and the commercial grades also contain varying and often variable amounts of free hydrochloric acid.[16] The current requirements for green and efficient Lewis acid promoters in modern organic chemistry have increased attention to several environmentally friendly[17] and atom-economical organic transformations.[18] Recent reports have highlighted the applications of cerium trichloride as a green and efficient Lewis acid in modern organic synthesis.[19] Notably, studies by us and by others have resulted in the development of methodologies involving the $CeCl_3{\cdot}7H_2O$/NaI system for providing new means for promoting organic transformations in a variety of systems.[20]

As a result of our efforts, we can now report a new $CeCl_3{\cdot}7H_2O$/NaI-promoted azide-transformation for producing exclusively primary amines.[21] Its compatibility with a wide variety of other sensitive functional groups, and the fact that $CeCl_3{\cdot}7H_2O$ Lewis acid is not deactivated[22] or trapped[23] by the basic nitrogen of amine adducts, allow us to believe that our method represents a valuable alternative to the existing protocols reported in literature. Another improvement in our $CeCl_3{\cdot}7H_2O$/NaI-promoted organic transformation of azides to primary amines is the opportunity to reduce reaction time and to increase product yield by using microwave technology (eq 1). In fact, the use of microwave-assisted reaction is an area of increasing interest in both academic and industrial laboratories.[24]



(1)

2. Results and Discussion

Because of the broad range of applications of the $CeCl_3{\cdot}7H_2O$/NaI system as catalyst in many organic transformations in solvent-free conditions,[20] we decided to apply our Lewis acid combination impregnated over inorganic support such as SiO_2 or Al_2O_3[25] to facilitate the azide transformation in amines. Our initial efforts focused on examining benzyl azide (**1a**) as the

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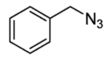
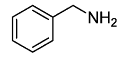
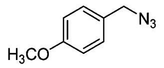
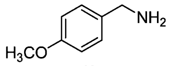
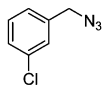
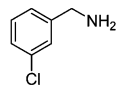
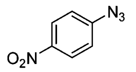
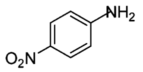
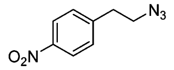
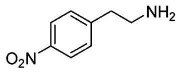
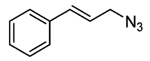
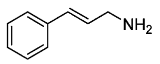
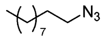
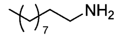
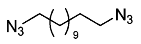
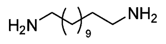
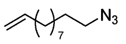
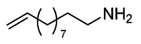
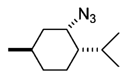
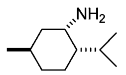
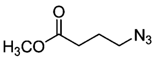
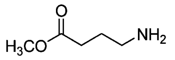
model azide substrate[26] in the presence of $CeCl_3{\cdot}7H_2O$ (1.5 equiv) and NaI (1.5 equiv) supported on SiO_2. The reaction was inefficient at room temperature, and all attempts to achieve the optimum conditions to increase the yield of amine **2a** have failed. Only with 9 equiv of NaI and with an external temperature of 100 °C[27] for 24 h were very moderate yields of adduct and many side products observed. Under these harsh conditions, decomposition of the products can occur; we have investigated the most appropriate solvent for this transformation of **1a** to the corresponding amine **2a** promoted by our $CeCl_3{\cdot}7H_2O$/NaI combination.

Although the reaction in acetonitrile has been inefficient at room temperature, good conversion has been obtained at reflux temperature. Under these conditions with approximately 0.1 M concentration and stirring for 24 h with $CeCl_3{\cdot}7H_2O$/NaI/azide in a ratio of 1.5:9:1, acetonitrile turned out to be the most appropriate among solvents evaluated according to the yields of the isolated amines. In fact, the order, in terms of efficiency, has been as follows (yields in parentheses): acetonitrile (86%), toluene (55%), THF (50%), Et_2O (42%), DMF (58%), and nitromethane[28] (40%). Having optimized the promoter system and the solvent, we have applied the procedure to various organoazides. As shown in Table 1, most reactions with different substrates reach an acceptable yields, and several examples give clear final reaction mixture with practically almost quantitative yields of the amines.

The first clear point to underline is that the electronic properties of the aromatic group in several benzyl azides can influence the transformation. We have observed that the efficiency of the procedure is increased by the presence of a substituent on the aromatic ring, even if no difference in reactivity has been observed when performing the transformation with electron-donating or electron-withdrawing substituents (Table 1, entries 1−4). It has been observed, moreover, that in the case of 4-methoxybenzylazide (**1b**) our procedure gives, contrary to the result of previously published with $FeCl_3$ as promoter,[13b] a good yield of 4-methoxybenzylamine (**2b**) without demethylation of the substituent on the aromatic ring (Table 1, entry 2).[13a] Given these results, a wide range of structurally varied alkyl azides have been subjected to reduction with our $CeCl_3{\cdot}7H_2O$/NaI system. The procedure allows us to provide the corresponding primary amines in good yields. Interestingly, in the case of azides bearing a carbon−carbon double bond, attack of the olefinic moiety does not occur (Table 1, entry 9). The same strategy applied to allyl azides led to allylic amines (Table 1, entry 6), and this transformation does not involve allylic rearrangement, a well-known process of allyl azides through sigmatropic [3,3]-shifts.[29] The alkyl azides have selectively been converted into the corresponding amines in the presence of other functional groups such as ester function (Table 1, entry 11). Then, our procedure can be successfully applied to a variety of aliphatic and aromatic azides, and various functional groups such as ester, nitro, halogen, and carbon−carbon double bond are compatible under the reaction conditions. Further, it is known that the $CeCl_3{\cdot}7H_2O$/NaI system allows the reactions to be carried out in close to neutral conditions and thus allows the survival of a large variety of functional groups or protecting groups sensitive to acidic hydrolysis.[19,20c] Azides bearing stereogenic centers (Table 1, entry 10) can be converted giving the amines with complete retention of the original configuration. The azide **1l** obtained

TABLE 1. Conversion of Azides 1a−m into Primary Amines 2a−m by NaI and $CeCl_3{\cdot}7H_2O$ in Acetonitrile at Reflux for 24 h[a]

Entry	Starting Material[b]	Product[c]	Yield (%)[d]
1	 **1a**	 **2a**	65
2	 **1b**	 **2b**	80
3	 **1c**	 **2c**	75
4	 **1d**	 **2d**	80
5	 **1e**	 **2e**	75
6	 **1f**	 **2f**	75
7	 **1g**	 **2g**	82
8	 **1h**	 **2h**	55
9	 **1i**	 **2i**	85
10	 **1l**	 **2l**	75
11	 **1m**	 **2m**	90

[a] Reactions performed in the presence of 9 equiv of NaI and 1.5 equiv of $CeCl_3{\cdot}7H_2O$ in acetonitrile (10 mL/mmol of azides **1**). [b] All starting materials were commercially available or were prepared by ref 26. [c] All products were identified by their IR, NMR, and GC/MS spectra. [d] Yields of products isolated.

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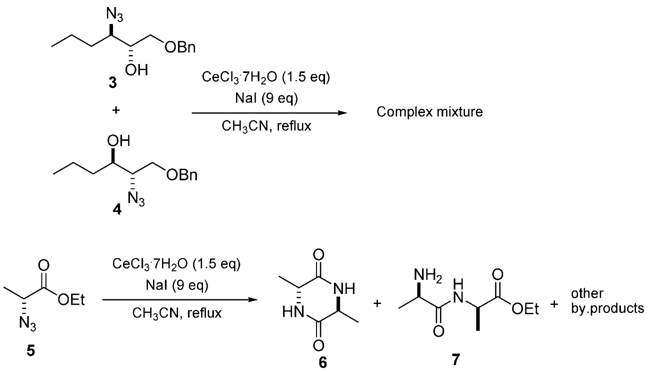
[26] Although multiple methods for the preparation of organic azides for different purposes are known (Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599), we prefer Kotsuki's procedure by conversion of alcohols to corresponding sulfonates and subsequent nucleophilic substitution by azide anion (Kotsuki, H.; Araki, T.; Miyazaki, A.; Iwasaki, M.; Datta, P. K. *Org. Lett.* **1999**, *3*, 499−502). This methodology does not use dichloromethane as solvent, and then it avoids the presence of an explosive byproduct, the bis-azidomethane, that it could form by reaction of dichloromethane with the nucleophilic azide. See: Hassner, A.; Stern, M.; Gottlieb, H.; Frolow, F. *J. Org. Chem.* **1990**, *55*, 2304−2306.

[27] Mixing pure liquids without solvents to dissipate any exothermic decomposition of the reagents or products may be dangerous on a large scale.

[28] Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Marcantoni, E.; Procopio, A. *Synlett* **2001**, 1897−1900.

[29] Mc Manus, M. J.; Berchtold, G. A.; Jerina, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 2977−2978.

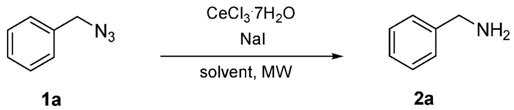
SCHEME 1



from L-menthol via stereospecific S_N2 displacement[30] undergoes smooth conversion to the corresponding chiral amine **2l**, but in less than optimal yields.[31] The formation of other byproducts has been evident, the identity of which remains unknown. It should also be noted that the reduction by $CeCl_3$•$7H_2O$/NaI system has not been efficient for chiral azido alcohols for obtaining chiral α-amino alcohols (Scheme 1). Treatment of a mixture of the two regioisomeric *trans*-azido alcohols **3** and **4**, in which the latter largely predominated (21:79),[32] gave rise, in our experimental conditions, to a complex mixture of products. By GC−MS analysis of the reaction mixture, besides the presence of traces of amino alcohol targets, we have observed the formation of unknown fragmentation products other than corresponding epoxide and aziridine. The formation of the latter one can be assumed on the basis of our $CeCl_3$•$7H_2O$/NaI one-pot conversion of a hydroxy group into an iodo group[33] and subsequent cyclization to aziridine.[34] Likewise, a α-azido ester **5**[35] has been transformed into the corresponding α-amino ester, but under our conditions coupling products, due the propensity of free amino esters to polymerize, were observed.[36] The adduct **6** and **7** have been identified by GC−MS.

Having established the conditions for the selective conversion of azido group of various alkyl azides to corresponding primary alkyl amines, we have also investigated the possibility of reduction of aryl azides. Reduction of *p*-nitrophenyl azide (**1d**) to *p*-nitroaniline (**2d**) has shown that reduction of the azido group can be carried out without nitro group reduction (Table 1, entry 4).[37] This transformation of aryl azides into anilines has not been widely investigated with our procedure because, generally, the preparation methods for aryl azide substrates are mainly based on the replacement of diazonium salts. Direct coupling of aryl halides with sodium azide has been reported to be possible, but it gave low yields because completion of the reaction needed a higher reaction temperature, which caused decomposition of the aryl azides.[38] However, we have shown that this $CeCl_3$•$7H_2O$/NaI promoted procedure provides an efficient methodology for a selective deprotection of aryl azides when the azido group is considered as protecting group of aniline derivatives.[39]

TABLE 2. Microwave-Assisted Benzylazide (1a) Transformation to Benzylamine (2a) under Different Experimental Conditions[a]



entry	NaI (equiv)	$CeCl_3$•$7H_2O$ (equiv)	conditions/ time (min)	T (°C)	yields[b] (%)
1	1.00	1.50	5 W; EtOH/30	90	31
2	2.00	1.50	5 W; EtOH/30	70	20
3	2.00	1.50	40 W; EtOH/30	90	35
4	9.00	1.50	40 W; EtOH/30	100	36
5	9.00	1.50	40 W; H2O/60	100	0
6	2.00	1.50	40 W; CH_3CN/30	100	38
7	9.00	1.50	10 W; CH_3CN/20	100	86

[a] All reactions were carried out by irradiation in a PowerMax Cooling microwave oven with a mixture of **1a** and reagent system at a given power for the selected times. [b] All yields refer to pure isolated compounds.

Another improvement introduced by our transformation of azides to primary amines is the diminution of the reaction time by using microwave technology. We have thought that these reactions can be greatly accelerated by the application of focused microwave irradiation, a useful technique that it has become a routine component of modern organic synthesis programmes.[40] Recently, two papers using microwave-assisted reaction promoted by $CeCl_3$•$7H_2O$ appeared in the literature,[41] and these results prompted us to synthesize amines by reduction of azides under microwave irradiation in the presence of our $CeCl_3$•$7H_2O$/NaI combination. For this reason, we have investigated the microwave-assisted reaction of benzyl azide **1a** under typical treatment using $CeCl_3$•$7H_2O$ and NaI in order to establish the optimal conditions. The results are summarized in Table 2, and certainly the transfer of our reaction under focused microwave irradiation needs special attention. Thus, we have decided to try a microwave control of temperature/time (the microwave controls the irradiation power to maintain the fixed temperature) by using a single mode microwave reactor equipped with a cooling system for automatic microwave power regulation.[42] By screening the various conditions, we have observed that the use of acetonitrile as solvent in this reaction gives the desired amine with better yield (Table 2, entry 7). We have also investigated the possibility to reduce the amounts of NaI, but

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(30) Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. *Synthesis* **1999**, 1373−1385.

(31) The chiral amine **2l** was hypothesized to be (1*S*,2*S*,5*R*)-configurated as reported in the literature (Smith, H. E.; Gordon, A. W.; Bridges, A. F. *J. Org. Chem.* **1974**, *39*, 2309−2311).

(32) Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463−1469.

(33) Di Deo, M.; Marcantoni, E.; Torregiani, E.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 2830−2833.

(34) Crotti, P.; Chini, M.; Uccello-Barretta, G.; Macchia, F. *J. Org. Chem.* **1989**, *54*, 4525−4529.

(35) Hoffmann, R. V.; Kim, H.-O. *Tetrahedron Lett.* **1990**, *31*, 2953−2956.

(36) Hoffmann, R. V.; Kim, H.-O. *Tetrahedron* **1992**, *48*, 3007−3020.

(37) (a) Liu, C.-Y.; Knochel, P. *J. Org. Chem.* **2007**, *72*, 7106−7115. (b) Rao, H. S. P. *Synth. Commun.* **1994**, *24*, 549−555.

(38) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888−889.

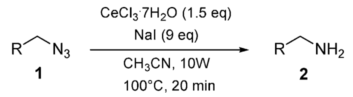
(39) Pinney, K. G.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 3125−3133.

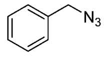
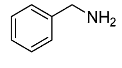
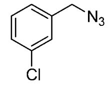
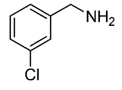
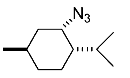
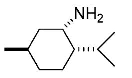
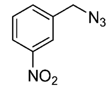
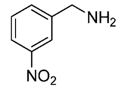
(40) (a) Razzaq, T.; Kappe, C. O. *Tetrahedron Lett.* **2007**, *48*, 2513−2517. (b) Smith, C. J.; Iglesias-Sigüenza, F. J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 2758−2761. (c) Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 1141−1150. (d) Hesse, S.; Perspicace, E.; Kirsch, G. *Tetrahedron Lett.* **2007**, *48*, 5261−5264.

(41) Microwave irradiation experiments were conducted using a CEM Discover monomode reactor with the temperature monitored by a built-in infrared sensor. This reactor is equipped with PowerMax technology that allows simultaneous cooling of a reaction with compressed gas while irradiating it with microwave energy (enhanced microwave synthesis). Thus, energy can be continuously applied while keeping the bulk temperature at a set level: this feature prevents unwanted side reactions and allows for cleaner and faster reactions. For details, see http://www.cemsynthesis.

(42) (a) Jia, C.-S.; Dong, Y.-W.; Tu, S.-J.; Wang, G.-W. *Tetrahedron* **2007**, *63*, 892−897. (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S. K.; Sabitha, R. G. *Synlett* **2001**, 1134−1136.

TABLE 3. Conversion of Azides into Amines by under Microwave-Assisted Irradiation Conditions



Entry	Starting Material^b	Product^a	Yield (%)^b
1	 **1a**	 **2a**	86
2	 **1c**	 **2c**	91
3	 **1l**	 **2l**	73
4	 **1n**	 **2n**	96

^{a} All products were fully characterized by IR, NMR, and MS Spectra. ^{b} Yields of products isolated.

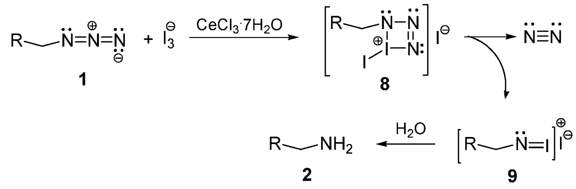
unsuccessfully: the reaction proceeds with good yield when the molar ratio of azide, $CeCl_3$•$7H_2O$, and NaI is still 1:1.5:9 with a power microwave irradiation of 10 W for 20 min.

To test if $CeCl_3$•$7H_2O$ is also responsible for this conversion of azide **1a** to amine **2a**, the reaction has been performed without cerium(III) salt. There has been no change in the starting material even after exposure to microwave irradiation for several hours. Finally, we sought to find out if the microwave-assisted azide reduction has been a mere reflection of thermal conditions. Therefore, azide **1a** and $CeCl_3$•$7H_2O$/NaI system in a ratio of 1:1.5:9 were heated in an oil bath. In this case, decomposition of the thermolabile azido group in starting material has only been observed even after heating for 20 min, and no traces of corresponding amine **2a** has been recovered. For this reason, we believe that to reduce the reaction time and to have less harsh reaction conditions, microwave-assisted is a necessary condition. By comparison of the data in Table 3, it is obvious that the microwave-assisted protocol significantly cuts down the reaction time, and the higher yields obtained with respect to the thermal heating process reflect the nonthermal effects under microwave irradiation conditions.

Recognizing the advantages of our synthetic approach, we have observed that starting α,ω-diazidoalkane **1h**, easily prepared from the corresponding diol, is transformed into diaminoalkane **2h** (Table 1, entry 8). Unfortunately, we have observed that the monoselective reduction of diazido compound does not occur; as a consequence, our procedure cannot be used for the synthesis of azido amines.[43]

Having established what appeared to be the optimal conditions, we switched our attention to the fact that our organic transformation of azides can proceed very well without any special treatment of substrates, reagents, and solvents. Water

SCHEME 2. Proposed Mechanism for Transformation of Azides into Amines



(from $CeCl_3$•$7H_2O$) does not influence this reaction, and a very low yield of amines has been detected by GC when anhydrous cerium trichloride[44]has been employed in dry acetonitrile. Similar good yields, instead, have been observed when 1, 4, 7, and 10 equiv of water have been added into the dry reaction mixture. Further, the fact that our methodology is clean and the amines have been obtained in good yields without the observation of any side products such as aldimines and aldehydes, normally observed by acid-catalyzed treatment of azides,[44] excludes the existence of traces of HX, which might contaminate the reaction mixture.

For the role of NaI, contrary to the explanation proposed by Kamal et al. for $FeCl_3$−NaI combination,[13b] we believe that the activity of the $CeCl_3$•$7H_2O$/NaI system is not due to an halogen-exchange reaction. Recent studies by us and by others, in fact, have shown that hydrated CeI_3 or CeI_3−NaI combination provide a less efficient activity than $CeCl_3$•$7H_2O$/NaI.[20a,46] Thus, without conclusive data, the use of an excess of NaI, essential for this our reduction,[47] might indicate that our conditions the oxidation of iodide ion to iodine happens. We have found that when a mixture of azide **1a** (1 equiv) is treated only with NaI (5 equiv) and elemental iodine (1 equiv), the reaction is less efficient than treatment with our $CeCl_3$•$7H_2O$/NaI system. On the other hand, when to this reaction mixture $CeCl_3$•$7H_2O$ (1.5 equiv) has been added, the reduction to amine **2a** is accelerated, a demonstration that iodine is a weaker Lewis acid promoter than more commonly used Lewis acids such as $CeCl_3$. All of these results show that the combination of NaI and $CeCl_3$•$7H_2O$ is essential for this conversion, and although we could not forward an accurate mechanism, a reasonable explanation of our findings is tentatively proposed (Scheme 2).[48] Thus, although the mechanism of this reaction is still obscure, it can be rationalized assuming the formation of a cyclic iodonium intermediate of type **8**, which rapidly extrudes nitrogen to produce polyvalent iodine intermediate **9**.[49] This latter hydrolyzes to amine **2** by the water present in the reaction mixture. The first step involves the addition of a triiodide ion, obtained by the known reaction of iodine with iodide ion,[50] to an azide **1**.[4] The addition is promoted by the ability of rare earth derivatives to coordinate multiple bond.[51] On the basis of this

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(43) Lee, J. W.; Jun, S. I.; Kim, K. *Tetrahedron Lett.* **2001**, *42*, 2709−2711.

(44) Imamoto, T.; Takeda, N. *Org. Synth.* **1998**, *76*, 228−238.

(45) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325−327.

(46) (a) Bartoli, G.; Bosco, M.; Giuliani, A.; Marcantoni, E.; Palmieri, A.; Petrini, M.; Sambri, L. *J. Org. Chem.* **2004**, *69*, 1290−1297. (b) Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* **2002**, *4*, 4451−4453.

(47) The use of less than 5 equiv of NaI decreases not only the amount of the conversion but also the rate of the reaction.

(48) In order to avoid unnecessary complication of the formula **1** in Scheme 3, we have depicted only one of the two resonating structures of azido group: $R{-}N{=}N^{+}{=}N^{-} \leftrightarrow R{-}N^{-}{-}^{+}{\equiv}N$; see: *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience: London, 1971; p 4.

(49) Derivatives of polivalent iodine are highly unstable and can exist only as short lived reactive intermediate; see: Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997.

mechanism, the iodide ion is widely consumed during the process, thus justifying the usage of an excess of NaI, and furthermore, to support our proposed mechanism, the reaction has been carried out in the presence of 2,6-di-*tert*-butyl-4-methylphenol as a radical inhibitor.[52] The reaction produced the desired amine **2**, and then the reaction has not been accomplished through an electron-transfer pathway from iodide ion to the azide activated by Ce(III).[53]

3. Conclusion

In conclusion, regardless of the mechanistic details, the experimental simplicity of our $CeCl_3{\cdot}7H_2O$/NaI system, its low cost and easy accessibility, and the high chemoselectivity observed provide a convenient and practical method of converting the azides to primary amines. Our procedure represents an additional example where the activity of NaI is dramatically increased by the presence of a cerium(III) salt such as $CeCl_3{\cdot}7H_2O$. At the end of our investigations, it emerged that cerium(III) salt acts as Lewis acid promoter of azide reduction, and this aspect emphasizes once more the importance of this lanthanide derivative, characterized by low toxicity, ease of handling, low cost, and stability in the presence of moisture.[54] Since microwave-assisted organic synthesis is a rapidly expanding area of research because it often offers the opportunity to reduce reaction times and to increase product yield, this methodology has been applied with success to this reaction. The procedure with the use of microwave irradiation has described the advantages of this methodology over conventional technology. Finally, given that a variety of amines are of significant importance as building blocks for the synthesis of new pharmaceutical compounds,[55] further studies on the reaction mechanism and applications of this transformation are underway in our laboratories.

4. Experimental Section[56]

The amines **2a**−**i** and **2m**−**n** are all commercially available compounds, and their structures are consistent with their published physical data.

General Procedure for the $CeCl_3{\cdot}7H_2O$/NaI Reduction of Azides (2a). To a solution of benzylazide **1a** (1.0 mmol) in acetonitrile (10 mL) were added $CeCl_3{\cdot}7H_2O$ (1.5 mmol) and NaI (9.0 mmol), and the resulting mixture was stirred at reflux temperature for 24 h (no starting material remains as monitored by GC and TLC).[57] The reaction mixture was diluted with Et_2O and treated with 3 N HCl (pH = 2). The organic layer was separated, and the aqueous layer was washed with Et_2O. The acidic solution was then carefully basified with a solution of 3 N NaOH (pH = 11) and extracted with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, 5 mol % $Na_2S_2O_3$, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure provided the resulting crude product **2a** as an oil (65% yield) usually at >97% purity as judged by NMR, and then column chromatography was not necessary: IR (neat, cm^{-1}) 3400, 3310, 1610, 815; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (bs, 2H), 3.85 (s,3H), 7.18−7.37 (m, 5H), identical to commercially available compound; ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.3, 123.7, 127.3, 129.1, 144.4; EI-MS *m/z* 107 [M$^+$], 106 (100), 80, 77, 65, 51, 39. Anal. Calcd for C_7H_9CN: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.45; H, 8.43; N, 13.04.

General Procedure for Reduction of Azides in the presence $CeCl_3{\cdot}7H_2O$/NaI with Microwave Irradiation (2n). (The procedure was performed in a CEM Discover in PowerMax mode with the temperature monitored by a built-in infrared sensor.) A stirred mixture of azide **1n** (1.0 mmol), $CeCl_3{\cdot}7H_2O$ (1.5 mmol), and NaI (9.0mmol) in acetonitrile (10 mL) was subjected to microwave irradiation at 10 W for 20 min at 100 °C. After completion of the reaction as indicated by GC and TLC, the reaction mixture was cooled, and using the same workup as in the previous thermal general procedure, amine **2n** was isolated as an oil (96% yield): IR (neat, cm^{-1}) 3460, 3360, 1611, 1598, 1552, 1335, 795; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (bs, 2H), 4.02 (s, 2H), 7.49−7.52 (m, 1H), 7.66−7.69 (m, 1H), 8.06−8.11 (m, 1H), 8.19−8.22 (m, 1H), identical to commercially available compound; ^{13}C NMR (125 MHz, $CDCl_3$) δ 50.2, 119.5, 122.3, 131.1, 134.5, 138.4, 150.0; EI-MS *m/z* 152 [M$^+$], 136, 122 (100), 106, 77, 65, 51, 39. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.23; H, 5.23; N, 18.37.

Acknowledgment. This work was carried out under the framework of the National Projects “From the Free Molecules to Complexes and Nanoaggregates: Structure, Chirality, Reactivity and Theory” supported by the MIUR (PRIN 2006), Rome, and by the University of Camerino. We thank Pfizer Italia Ascoli Piceno Plant and Teuco Guzzini Montelupone for funding doctoral fellowships to M.P. and S.L., respectively. G.D.A. gratefully acknowledges Boehringer Ingelheim for doctoral fellowship. We are very grateful to Prof. Paolo Crotti (University of Pisa, Italy) for kindly donating the mixture of azides **3** and **4**.

Supporting Information Available: Detailed description of experimental procedures, characterization data for new compounds not reported previously, copies of NMR on structures determined. This material is available free of charge via the Internet at http://pubs.acs.org.

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(50) In this reaction, iodide ion is viewed as a Lewis base, and the iodine is a Lewis acid. Our solution appears yellow at the beginning then becomes brown for higher concentration of triiodide ion, and significant amount of triiodide has also been observed by mass spectral data.

(51) Bartoli, G.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Lanari, S.; Sambri, L. *Adv. Synth. Catal.* **2005**, *347*, 1673−1680.

(52) Janzen, E. G.; Wilcox, A. L.; Manoharant, V. *J. Org. Chem.* **1993**, *58*, 3597−3599.

(53) Hwu, J. R.; Jain, M. L.; Tsai, F.-Y.; Tsay, S.-C.; Balakumar, A.; Hakimelahi, G. H. *J. Org. Chem.* **2000**, *65*, 5077−5084.

(54) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302.

(55) Lawrence, S. A. *Amines: Synthesis, Properties, and Applications*; Cambridge University Press: Cambridge 2004.

(56) Presented in this Experimental Section is the general procedure for this transformation, complete experimental procedures, and spectral data for new compounds.

(57) For TLC detection of azide starting materials we have used Seebach staining solution, which is a mixture of molibdate phosphoric acid, cerium(IV) sulfate tetrahydrate, sulfuric acid, and water.