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Synthetic Methods

Direct, One-pot Sequential Reductive Alkylation of Lactams/Amides with Grignard and Organolithium Reagents through Lactam/Amide Activation**

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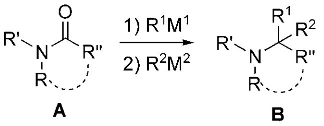
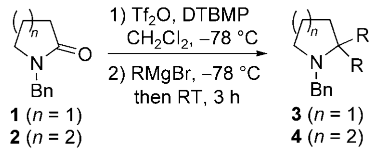
Simplicity is one of the major goals in current organic synthesis.[1] The development of versatile methods using simple starting materials[2] and multicomponent reactions leading to the formation of two or more carbon–carbon bonds in a one-pot process[3] are two powerful strategies directed at this goal. The transformation of lactams and amides into the corresponding *tert*-alkylamines by a one-pot reductive bisalkylation with different organometallic reagents is both a highly desirable and a challenging objective (Scheme 1). The merit of such a process is linked to the high stability of lactams/amides and the ready availability of both lactams/amides and Grignard/organolithium reagents. Moreover, *tert*-alkylamines are important target compounds in synthetic chemistry.[4] The research groups of Murai[5] and Renaud[6] have recently reported their synthesis of *tert*-alkylamines from thioamide derivatives. To develop a more convenient and less noxious general method, the direct use of readily available lactams and amides is highly desirable (Scheme 1). In this regard, de Meijere and co-workers recently reported an addition to formamides mediated by $Ti(OiPr)_4$/TMSCl, but their method is restricted to *N*,*N*-dialkylformamides.[7] Herein we report the first general and direct one-pot method for the conversion of lactams and amides into *tert*-alkylamines by the sequential addition of two organometallic reagents, which may be the same or different from one another.



Scheme 1. One-pot transformation of lactams/amides into the corresponding *tert*-alkylamines with cleavage of a C=O bond and formation of two C−C bonds.

To achieve the required one-pot reaction under milder conditions, triflic anhydride[8,9] was selected as an amide activator and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)[9d] as a base. When a CH_2Cl_2 solution of lactam **1** and DTBMP (1.2 equiv) was successively treated with 1.2 molar equivalents of Tf_2O (−78 °C, 45 min), and 3.0 molar equivalents of ethylmagnesium bromide in Et_2O (RT, 3 h; general procedure A), the desired 2,2-diethylpyrrolidine **3a** was obtained in 87 % yield (Table 1, entry 1). By using the same procedure, the reactions of lactam **1** with *n*-butyl, allyl, and benzyl Grignard reagents gave the corresponding pyrrolidines **3b–d** in 71–85 % yield (Table 1, entries 2–4). Similar results were obtained with lactam **2**, which provided the corresponding piperidines **4a–d** in good yield (Table 1, entries 5–8).

Table 1: Double addition of Grignard reagents to lactams activated by Tf_2O.



Entry	Substrate	RMgX	Product (yield[%])[a]
1	**1**	EtMgBr	**3a** (87)
2	**1**	*n*BuMgBr	**3b** (83)
3	**1**	allylMgBr	**3c** (85)
4	**1**	BnMgBr	**3d** (71)
5	**2**	EtMgBr	**4a** (74)
6	**2**	*n*BuMgBr	**4b** (70)
7	**2**	allylMgBr	**4c** (75)
8	**2**	BnMgBr	**4d** (60)

[a] Yield of isolated product. Bn = benzyl, Tf = trifluoromethanesulfonyl.

Encouraged by these results, the introduction of two different substituents was investigated. After successive treatment of a CH_2Cl_2 solution of lactam **1** and DTBMP (1.2 equiv) with 1.2 molar equivalents of Tf_2O at −78 °C for 45 minutes, 1.0 molar equivalent of ethylmagnesium bromide and 2.0 molar equivalents of *n*-butylmagnesium bromide, pyrrolidine **5a** bearing two different alkyl groups (Et, *n*Bu) was obtained in 75 % yield. A 9 % yield of pyrrolidine **3b** arising from the addition of two molecules of *n*-butylmagnesium bromide was also obtained (Table 2, entry 1). The one-pot reaction was then extended to other Grignard reagents and lactam **2**, and similar results were obtained (Table 2,

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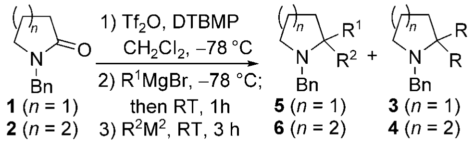
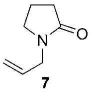
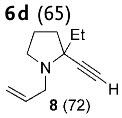
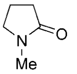
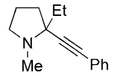
Table 2: Sequential addition of two organometallic reagents to lactams activated by Tf_2O.



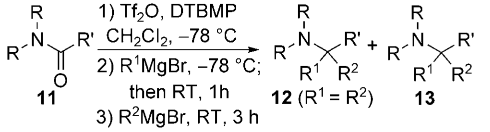
Entry	Substrate	R^1MgBr, R^2M^2	Product (yield[%])[a]
1	**1**	EtMgBr, *n*BuMgBr	**5a** (75), **3b** (9)
2	**1**	EtMgBr, allylMgBr	**5b** (74), **3c** (8)
3	**1**	EtMgBr, BnMgBr	**5c** (71), **3d** (8)
4	**2**	*n*BuMgBr, EtMgBr	**6a** (66), **4a** (6)
5	**2**	EtMgBr, allylMgBr	**6b** (68), **4c** (7)
6	**2**	EtMgBr, BnMgBr	**6c** (63), **4d**(4)
7	**1**	EtMgBr, *n*BuLi	**5a** (76), **3b** (9)
8	**2**	*n*BuMgBr, vinylMgBr	**6d** (65)
9	 **7**	EtMgBr, ≡—MgBr	 **8** (72)
10	 **9**	EtMgBr, Ph—≡—Li	 **10** (70)

[a] Yield of isolated product.

entries 2–6). Other varieties of organometallic reagent such as *n*-butyllithium and phenylethynyllithium were also effective (Table 2, entries 7 and 10). Notably, the reaction of sp^2- and sp-hybridized carbon nucleophiles led solely to the desired amines. Products arising from the addition of two molecules of the first Grignard reagent were not detected (Table 2, entries 8–10).

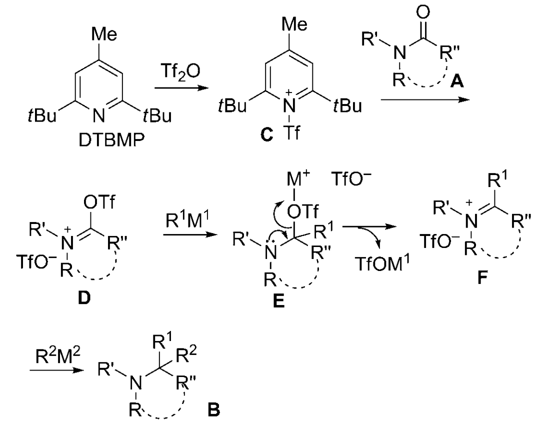
Similarly, the sequential addition of two of the same or different Grignard reagents to amides proceeded smoothly and gave the desired products in high yield (Table 3, entries 1–6).

Table 3: Sequential addition of two Grignard reagents to amides activated by Tf_2O.



Entry	Substrate	R^1MgBr, R^2MgBr	Product (yield[%])[a]
1	**11a**, R = Me, R′ = H	PhMgBr, PhMgBr	**12a** (93)
2	**11b**, R = Bn, R′ = Ph	BnMgBr, BnMgBr	**12b** (81)
3	**11c**, R = Bn, R′ = Me	EtMgBr, EtMgBr	**12c** (86)
4	**11c**	BnMgBr, BnMgBr	**12d** (90)
5	**11c**	*n*BuMgBr, EtMgBr	**13a** (78), **12c** (8)
6	**11c**	*n*BuMgBr, BnMgBr	**13b** (74), **12d** (7)

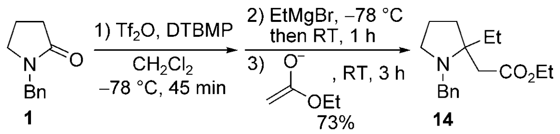
[a] Yield of isolated product.



Scheme 2. Proposed reaction mechanism.

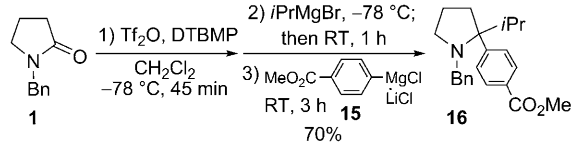
A plausible mechanism for the sequential addition of organometallic reagents to lactams and amides activated by Tf_2O is shown in Scheme 2. The DTBMP first reacts with triflic anhydride to generate the reactive pyridinium intermediate[10] **C**, which reacts with amide **A** to form highly electrophilic iminium triflate intermediate **D**. The latter reacts with one molecule of R^1M^1 to give N,O-acetal **E**. Then, elimination of $^-$OTf assisted by the lone pair of electrons on the nitrogen atom and metal cation leads to the formation of iminium ion **F**, which is trapped by a second molecule of nucleophile (R^2M^2) to give amine **B**.

To further reveal the scope of this approach, employment of functionalized nucleophiles other than allyl (Table 1, entries 3 and 7; Table 2, entries 2 and 5), vinyl (Table 2, entry 8), and alkynyl magnesium/lithium reagents (Table 2, entries 9 and 10) were investigated. We were aware that enolates are versatile nucleophiles, therefore we first tested the one-pot sequential introduction of ethyl and ethoxycarbonylmethyl groups. By using the general procedure B (see the Supporting Information for details), successive treatment of 2-pyrrolidinone **1** with triflic anhydride, ethylmagnesium bromide, and lithium enolate of ethyl acetate provided the desired pyrrolidine **14** in 73 % yield (Scheme 3). Next, we tried to use the functional aryl magnesium reagents developed by Knochel and co-workers.[10] These reagents are a novel class of versatile nucleophiles. Thus successive treatment of 2-pyrrolidinone **1** with triflic anhydride, isopropylmagnesium bromide, and Knochel's functional aryl magnesium reagent **15** (prepared in situ from methyl *p*-iodobenzoate)[10] furnished the expected pyrrolidine **16** in 70 % yield (Scheme 4).



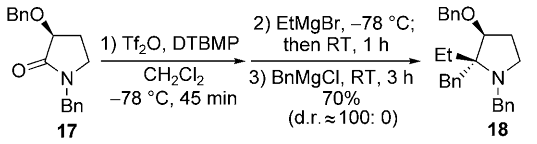
Scheme 3. Sequential reductive alkylation with an enolate.

To explore the use of this method for asymmetric synthesis, three-ring systems have been investigated. By using the general procedure B, successive treatment of (*S*)-3-benzyloxy-2-pyrrolidinone **17**[11] with triflic anhydride, ethylmagne-

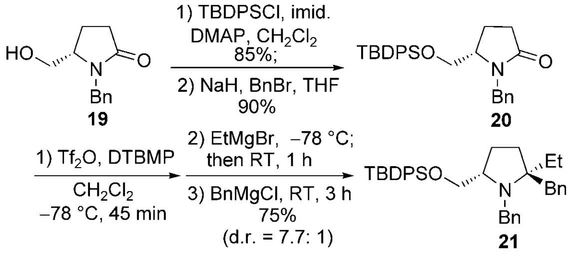


Scheme 4. Sequential reductive alkylation with a Knochel's reagent.

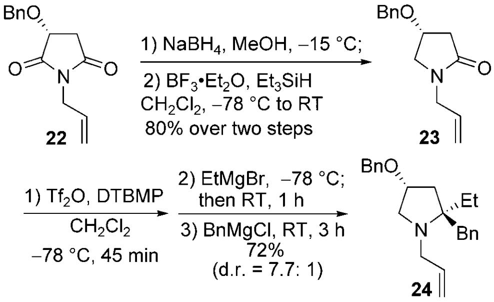
sium bromide, and benzylmagnesium chloride produced pyrrolidine **18** as the only diastereomer in 70% yield (Scheme 5). Compound **20** was easily available from the known **19** (derived from (*S*)-glutamic acid)[12] and its sequential ethylation and benzylation activated by Tf_2O proceeded with good 1,3-asymmetric induction, and yielded pyrrolidine **21** and its diastereomer with d.r. = 7.7:1 in a combined yield of 75% (Scheme 6). Similarly 2-pyrrolidinone **23** was available from (*S*)-malimide **22**,[13] and underwent sequential ethylation and benzylation activated by Tf_2O with good 1,3-asymmetric induction, and gave pyrrolidine **24** and its diastereomer with d.r. = 7.7:1 in a combined yield of 72% (Scheme 7).



Scheme 5. 1,2-Asymmetric induction in the sequential reductive alkylation of lactam **17**. Diastereomeric ratio was determined by HPLC analysis (Shim-pack VP-ODS) with a mobile phase of acetonitrile/water.



Scheme 6. 1,3-Asymmetric induction in the sequential reductive alkylation of lactam **20**. Diastereomeric ratio was determined by HPLC analysis (Shim-pack VP-ODS) with a mobile phase of acetonitrile/water. imid = imidazole, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 7. 1,3-Asymmetric induction in the sequential reductive alkylation of lactam **23**. Diastereomeric ratio was determined by HPLC analysis (Shim-pack VP-ODS) with a mobile phase of acetonitrile/water.

The newly formed quaternary stereocenters in pyrrolidines **18**, **21**, and **24** were confirmed by NOESY experiments. It was shown in all three cases that the second alkyl groups (benzyl group) are *trans* with respect to the substituents in the starting materials. These results are in agreement with the proposed mechanism shown in Scheme 2. Namely, to avoid steric hindrance the second Grignard reagent (benzylmagnesium chloride) approaches the intermediate cyclic iminium ion **F** from the direction opposite to the benzyloxy group at C3 (for **17**), the silyloxymethyl group at C5 (for **20**), or the benzyloxy group at C3 (for **23**).

In summary, by taking advantage of both the high electrophilicity of Tf_2O and excellent leaving group ability of ^{-}OTf, we have developed a highly efficient and general one-pot method for the synthesis of *tert*-alkylamines from lactams/amides. The advantages of this method are that: 1) this is a multicomponent reaction involving the one-pot formation of two C–C bonds, 2) both lactams and amides can be used as substrates, 3) two different Grignard reagents can be used in this one-pot process, 4) both Grignard and organolithium reagents can be used in this one-pot process, 5) for the second addition, either sp^3-, sp^2-, or sp-hybridized carbon nucleophiles, functionalized carbon nucleophiles such as enolates, and Knochel's functional aryl magnesium reagent can be used, 6) the sequential addition afforded excellent 1,2- and 1,3-asymmetric induction in substituted γ-lactams. The high stability of lactams/amides combined with the ready availability of both lactams/amides and Grignard/organolithium reagents make this a versatile method for the synthesis of various *tert*-alkylamines. Further work on the application of other kinds of nucleophile in this method is currently in progress and will be reported in due course.

Experimental Section

General procedure A for the double addition of Grignard Reagents to lactams/amides activated by Tf_2O: To a cooled (−78 °C) solution of lactam/amide (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.2 equiv) in CH_2Cl_2 (5 mL) was added Tf_2O (1.2 equiv) in a dropwise manner and stirred at −78 °C for 45 min. A solution of RMgBr (3.0 equiv) in Et_2O was added dropwise to the resultant mixture. Then the reaction mixture was warmed slowly to RT and stirred for 3 h. The reaction was quenched with a saturated ammonium chloride solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired amine.

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Keywords: amides · multicomponent reactions · sequential reductive alkylation · synthetic methods · *tert*-alkylamines

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