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# Magnesium Bistrifluoromethanesulfonimide as a New and Efficient Acylation Catalyst

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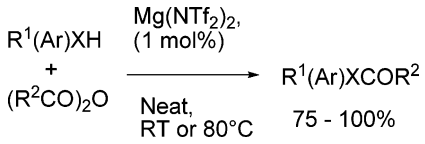


Magnesium bistrifluoromethanesulfonimide catalyzed the acetylation of phenols, alcohols, and thiols under solvent-free conditions at room temperature and in short times. Electron-deficient and sterically hindered phenols provided excellent yields. The catalyst was found to be general for acylation with other anhydrides, such as propionic, isobutyric, pivalic, chloroacetic, and benzoic anhydrides. The rate of acylation was influenced by the electronic and steric factors associated with the anhydride. The reaction with less electrophilic anhydrides (e.g., chloroacetic and benzoic anhydrides) required higher temperature (∼80 °C). Chemoselective acetylation, pivalation, and benzoylation took place with acid-sensitive alcohols without any competitive dehydration/rearrangement.

In the synthesis of multifunctional targets, one often needs to carry out a reaction at a particular functional group in the presence of other functional groups, such as phenol, alcohol, and thiol, that are sensitive to the desired chemical transformation. Thus, the protection of phenols, alcohols, and thiols is one of the most frequently employed reactions in organic synthesis and is normally achieved by acylation with anhydrides in the presence of suitable catalyst. Various organic (e.g., DMAP and $Bu_3P$) and inorganic (e.g., halides and triflates of transition and rare earth metals) catalysts have been employed for this purpose.[1] The recent efforts for the development of newer methods highlight the importance of heteroatom acylation.[2,3]

The reported methodologies suffer from one or more of the following disadvantages: (i) potential health hazard [DMAP is highly toxic (e.g., intravenous $LD_{50}$ in the rat = 56 mg/kg) and $Bu_3P$ is flammable (flash point = 37 °C), need to use halogenated solvents]; (ii) difficulty in handling ($Bu_3P$ undergoes aerial oxidation, and triflates are moisture sensitive); (iii) high cost of the catalysts (e.g., triflates); (iv) requirement of special efforts to prepare the catalysts [$Bi(OTf)_3$, Nafion-H, yttria-zirconia, $AlPW_{12}O_{40}$, and Mn(haacac)Cl]; (v) the lack of atom economy (use of excess of acetylating agents); (vi) stringent reaction conditions and the requirement of longer reaction times; and (vii) in many cases, the reported acylation methodologies are applicable to alcohols only and are not suitable for acid-sensitive substrates. Thus, there is a need for the development of a mild and cost-effective catalyst for the acylation reaction.

In continuation of our efforts for the development of newer and efficient methods for acylation,[4] we report that $Mg(NTf_2)_2$ is a new, efficient, and easily accessible acylation catalyst.

While designing the catalyst, we thought that a metal salt derived from a strong protic acid should be an ideal contender. The large negative $H_0$ value of −14.1 for TfOH[5] makes TfOH the strongest protic acid, and thus metal triflates have drawn the attention as acylation catalysts.[3] However, TfOH is often liberated from metal triflates during the triflate-catalyzed acylation reactions and may be the actual catalytic agent.[6] The in situ generation of TfOH might be the reason for the potential side reactions (e.g., dehydration, rearrangement, etc.) with acid-sensitive substrates. Thus, metal-triflate-catalyzed acylation reactions are often carried out at low temperatures (−8 to −60 °C) and in the presence of an excess of the acetylating agents. This has led us[4a−c] and others[2d,f,g] to develop acylation catalysts derived from $HClO_4$ as it is weaker than TfOH. However, the potential hazard associated with $HClO_4$ and metal perchlorates[7]

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(3) (a) $Cu(OTf)_2$: Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369−1374. (b) $In(OTf)_3$: Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743−1744. (c) $Bi(OTf)_3$: Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem*. **2001**, *66*, 8926−8934. (d) $Ce(OTf)_3$: Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Nardi, M.; Bartoli, G.; Romeo, R. *Tetrahedron Lett*. **2003**, *44*, 5621−5624. (e) LiOTf: Karimi, B.; Maleki, J. *J. Org. Chem*. **2003**, *68*, 4951−4954. (f) $Er(OTf)_3$: Procopio, A.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Russo, B.; Sindona, G. *Adv. Synth. Catal*. **2005**, *346*, 1465−1470.

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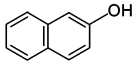
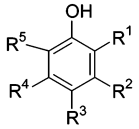
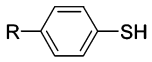
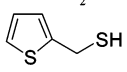
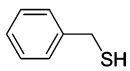
becomes detrimental for their use for large-scale preparation. Hence, we focused our attention to $HNTf_2$ as it is a weaker Brønsted acid than TfOH.[8] It has been observed that the ligand exchange does not take place with triflimides.[9] Therefore, the side reactions that are likely to occur as a result of in situ liberation of $HNTf_2$ will be avoided if a triflimide is used as a catalyst. The $^{29}Si$ chemical shift values in $TMSNTf_2$ and TMSOTf suggest that a metal triflimide should be a better Lewis acid catalyst compared to the corresponding triflate.[10] Thus, metal triflimides may be considered as safe substitutes for metal perchlorates.[11] The use of $Sc(NTf_2)_3$ as a catalyst for acetylation of alcohols and phenols has been reported.[12] However, it is not available commercially and involves a high cost for its preparation and therefore is not a good contender for general use. Moreover, the strong acidic property of $Sc(NTf_2)_3$ necessitates the use of solvent, a large excess of $Ac_2O$, and low temperature (−20 °C) for substrates that are likely to experience a side reaction (e.g., tertiary alcohol). To choose a suitable metal salt of $HNTf_2$, we considered the alkali and alkaline earth metal triflimides as the lower charge-size function of alkali and alkaline earth metal cations compared to that of the $Sc^{3+}$ ion ($Z^2/r$ values of $Li^+$, $Mg^{2+}$, and $Sc^{3+}$ ions are 1.35, 5.56, and 12.33 $e^2$ $m^{-10}$, respectively),[13] which makes the alkali and alkaline earth metal triflimides milder Lewis acids compared to $Sc(NTf_2)_3$. The commercial availability and cheaper prices of the alkali and alkaline earth metal triflimides make them better suited for catalytic use. The higher hydrolysis constant ($pK_h$) values of 13.82 and 11.42 for $Li^+$ and $Mg^{2+}$, respectively, compared to that of 4.6 for $Sc^{3+}$ make the alkali metal triflimides less susceptible to moisture (nonanhydrous conditions) compared to $Sc(NTf_2)_3$.[14] Thus, we used $LiNTf_2$ and $Mg(NTf_2)_2$ during the reaction of 2-naphthol (**1**), 4-nitrophenol (**2**), and 1-phenylethanol (**3**) as representative unactivated phenol, electron-deficient phenol, and secondary alcohol (acid-sensitive), respectively, with $Ac_2O$ under neat conditions at room temperature (Table 1). The corresponding acetates were formed in 92, 90, and 95% yields, respectively, in the presence of $Mg(NTf_2)_2$ compared to the yields of 75, 80, and 28%, respectively, obtained in the presence of $LiNTf_2$, and we established that $Mg(NTf_2)_2$ is the desired catalyst. To determine the crucial role of the counteranion in imparting catalytic property to $Mg^{2+}$, various magnesium salts were employed as catalysts for acetylation of **1**, **2**, and **3** (Table 1). Comparison of the results of entry 2 with those of entries 3−5 revealed the importance of the use of the magnesium salt of $HNTf_2$. The use of solvents, such as $MeNO_2$, MeCN, $Et_2O$, and DCM, was found to be detrimental to the catalytic efficiency of $Mg(NTf_2)_2$ as revealed by the formation of 2-acetoxynaphthalene in 22, 22, 17, and 22% yields after 1 h during the reaction of 2-hydroxynaphthalene with $Ac_2O$ (1.2 equiv) at room temperature.

**TABLE 1. Acylation of 1, 2, and 3 with $Ac_2O$ in the Presence of Different Lithium and Magnesium Salts[a]**

| | | | Yield (%)[c] | | |
|---|---|---|---|---|---|
| entry | catalyst (mol %)[b] | time (min) | **1** | **2** | **3** |
| 1 | $LiNTf_2$ (5) | 60 | 75 | 80 | 28 |
| 2 | $Mg(NTf_2)_2$ (1) | 30 | 92 | 90 | 95[d] |
| 3 | $MgCl_2$ (5) | 60 | 13 | 29 | nil |
| 4 | $MgBr_2$ (5) | 60 | 70 | 33 | 33 |
| 5 | $MgI_2$ (5) | 60 | 86 | 72 | 82 |

[a] The substrate (2.5 mmol) was treated with $Ac_2O$ (1.2 equiv) in the presence of the catalyst under neat conditions at room temperature. [b] Molar equiv of the catalyst used with respect to the substrate. [c] Isolated yield of the corresponding acetate. [d] The reaction was carried out for 15 min.

**TABLE 2. $Mg(NTf_2)_2$-Catalyzed Acylation of Phenols and Thiols[a]**

| entry | substrate | time (min) | yield (%)[b] |
|---|---|---|---|
| |  | | |
| 1 | R = 2-OH | 30 | 92[c] |
| 2 | R = 1-OH | 60 | 97 |
| |  | | |
| 3 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OMe$ | 15 | 90 |
| 4 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Br$ | 30 | 96 |
| 5 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Cl$ | 15 | 89 |
| 6 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = COMe$ | 30 | 85 |
| 7 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CO_2Et$ | 30 | 85 |
| 8 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = NO_2$ | 60 | 91 |
| 9 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CN$ | 30 | 82 |
| 10 | $R^1 = NO_2$; $R^2 = R^3 = R^4 = R^5 = H$ | 30 | 75 |
| 11 | $R^1 = OH$; $R^2 = R^3 = R^4 = R^5 = H$ | 15 | 86[d] |
| 12 | $R^1 = R^3 = R^4 = R^5 = H$; $R^2 = OH$ | 15 | 90[d] |
| 13 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OH$ | 15 | 98[d] |
| 14 | $R^1 = R^2 = OH$; $R^3 = R^4 = R^5 = H$ | 15 | 90[e] |
| |  | | |
| 15 | R = H | 30 | 95 |
| 16 | R = Me | 30 | 98 |
| 17 | R = OMe | 60 | 90 |
| 18 | $R = NO_2$ | 60 | 99 |
| 19 |  | 60 | 100 |
| 20 |  | 60 | 85 |

[a] The substrate (2.5 mmol) was treated with $Ac_2O$ (1.2 equiv per OH/SH) in the presence of $Mg(NTf_2)_2$ (1 mol %) under solvent-free conditions at room temperature (except for entry 10). [b] Isolated yield of the corresponding acylated products. [c] The reaction was carried out at 80 °C. [d] Isolated yield of the diacetate. [e] Isolated yield of the triacetate.

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(8) Foropoulos, J.; DesMarteau, D. D. *Inorg. Chem.* **1984**, *23*, 3720−3123.
(9) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Chem. Commun*. **2002**, 1564−1565.
(10) (a) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219−8226. (b) Vij, A.; Zheng, Y. Y.; Kirchmeier, R. L.; Shreeve, J. M. *Inorg. Chem.* **1994**, *33*, 3281−3288. (c) Olah, G. A.; Laali, K.; Farooq, O. *Organometallics* **1984**, *3*, 1337−1340.
(11) (a) Handy, S. T.; Grieco, P. A.; Mineur, C.; Ghosez, L. *Synlett* **1995**, 565−567. (b) Ghosez, L.; Mineur, C.; Tamion, R. *Tetrahedron Lett*. **1995**, *36*, 8977−8980.
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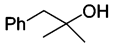
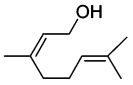
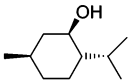
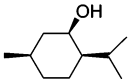
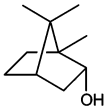
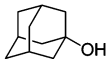
**TABLE 3. $Mg(NTf_2)_2$-Catalyzed Acylation of Alcohols[a]**

| entry | substrate | time (min) | yield (%)[b] |
|---|---|---|---|
| |  | | |
| 1 | $R^1$ = H; $R^2$ = Ph | 10 | 85 |
| 2 | $R^1$ = H; $R^2$ = $H_2$CPh | 10 | 85 |
| 3 | $R^1$ = Me; $R^2$ = Ph | 15 | 95 |
| 4 | $R^1$ = Et; $R^2$ = Ph | 60 | 97 |
| 5 | $R^1$ = COPh; $R^2$ = Ph | 60 | 94 |
| 6 | $R^1$ = H; $R^2$ = *trans*-PhCH=CH | 60 | 86 |
| 7 |  | 60 | 90 |
| 8 |  | 60 | 90 |
| 9 |  | 30 | 92 |
| 10 |  | 30 | 89 |
| 11 |  | 60 | 97 |
| 12 |  | 60 | 92 |
| 13 |  | 30 | 91 |

[a] The substrate (2.5 mmol) was treated with $Ac_2O$ (1.2 equiv) in the presence of $Mg(NTf_2)_2$ (1 mol %) under solvent-free conditions at room temperature. [b] Isolated yield of the corresponding acylated product.

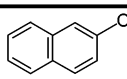
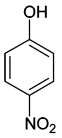
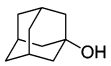
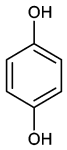
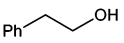
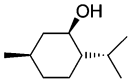
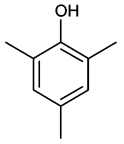
**TABLE 4. $Mg(NTf_2)_2$-Catalyzed Acylation of 1 with $(RCO)_2O$[a]**

| entry | R | equiv[b] | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | Me | 1 | 0.5 | 92 |
| 2 | Et | 1 | 1 | 100[d] |
| 3 | $^i$Pr | 1 | 1 | 75[e] |
| 4 | $^t$Bu | 1.5 | 0.5 | 88 |
| 5 | Ph | 1 | 1 | 92[f] |
| 6 | $ClCH_2$ | 1 | 1 | 70[f] |

[a] The substrate (2.5 mmol) was treated with the anhydride in the presence of $Mg(NTf_2)_2$ (1 mol %) under solvent-free conditions at room temperature (except for entries 4 and 5). [b] Molar equiv of the anhydride used with respect to the substrate. [c] Isolated yield of the corresponding acylated product. [d] A 99% yield was obtained in carrying out the reaction at 80 °C for 30 min. [e] An 86% yield was obtained in carrying out the reaction at 80 °C for 30 min. [f] The reaction was carried out at 80 °C.

To explore the generality and scope, structurally diverse phenols and thiols were subjected to acylation with $Ac_2O$ (1.2 equiv) at room temperature and under neat conditions in the presence of $Mg(NTf_2)_2$ (1 mol %) (Table 2). The catalyst was compatible with various functional groups, such as OMe, Br, Cl, COMe, $CO_2Me$, CN, and $NO_2$, that were likely to undergo complex formation with the catalyst and impede the acetylation (entries 3−10). Di- and trihydroxy aromatic compounds afforded the di- and triacetates, respectively, in excellent yields (entries 10−14). The reaction was influenced by the steric and electronic

**TABLE 5. $Mg(NTf_2)_2$-Catalyzed Benzoylation of Representative Phenols and Alcohols with $(PhCO)_2O$[a]**

| entry | substrate | time (h) | yield (%)[b] |
|---|---|---|---|
| 1 |  | 0.5 | 92[c] |
| 2 |  | 0.5 | 90 |
| 3 |  | 0.5 | 85 |
| 4 |  | 0.5 | 81[d] |
| 5 |  | 1 | 88 |
| 6 |  | 1 | 91[e] |
| 7 |  | 2 | 75[f] |

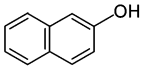
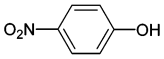
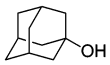
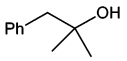
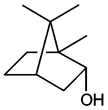
[a] The substrate (2.5 mmol) was treated with $(PhCO)_2O$ (1.2 equiv per OH group) in the presence of $Mg(NTf_2)_2$ (1 mol %) under solvent-free conditions at 80 °C (except for entry 7). [b] Isolated yield of the corresponding benzoylated product. [c] The benzoylated product was obtained in 88% yield after 1 h by carrying out the reaction at room temperature. [d] Isolated yield of the dibenzoylated product. [e] The benzoylated product was obtained in 78% yield after 2 h by carrying out the reaction at room temperature. [f] The reaction was carried out at room temperature.

factors associated with the substrates. The distinct difference in the rate of acylation of 2- and 1-hydroxynaphthalenes (entries 1 and 2) was due to the steric inhibition offered by the *peri*-hydrogen of 1-hydroxynaphthalene toward the approach of the electrophile. Excellent results were obtained with phenols that are less nucleophilic due to the presence of electron-withdrawing substituents, such as Br, Cl, COMe, $CO_2Me$, $NO_2$, and CN (entries 4−9). The requirement of heating the reaction mixture during the acylation of 2-nitrophenol (entry 10) was due to the steric hindrance of the $NO_2$ group at the *ortho* position of the phenolic OH group in addition to the electron-withdrawing effect in making 2-nitrophenol electron deficient.

The potential of $Mg(NTf_2)_2$ as a catalyst for acylation of various alcohols was investigated next, and excellent results were obtained when the reactions were carried out at room temperature with 1.2 equiv of $Ac_2O$ in the presence of 1 mol % of $Mg(NTf_2)_2$ (Table 3). Secondary and tertiary alcohols did not undergo any side reactions, such as dehydration or rearrangement (entries 3, 4, 7, 9−13). No rearrangement was observed for allylic (entry 8) and propargylic (entry 12) alcohols. These observations exemplified chemoselectivity. The mildness of the catalyst was tested with optically active substrates that were acetylated without any detrimental effect on the optical purity (entries 9−11) as determined by comparison of the optical rotation value of the products with that of authentic compounds.

To establish $Mg(NTf_2)_2$ as a general acylation catalyst, **1** was treated with various anhydrides (Table 4). Good to excellent

**TABLE 6. $Mg(NTf_2)_2$-Catalyzed Pivalation of Representative Phenols and Alcohols with $(^tBuCO)_2O$[a]**

| entry | substrate | time (h) | yield (%)[b] |
|---|---|---|---|
| 1 |  | 1 | 88 |
| 2 |  | 0.5 | 85 |
| 3 |  | 0.5 | 82 |
| 4 | $PhCH_2OH$ | 0.5 | 75 |
| 5 | *trans*-$PhCH{=}CHCH_2OH$ | 0.5 | 80 |
| 6 |  | 0.5 | 75 |
| 7 |  | 0.5 | 82 |

[a] The substrate (2.5 mmol) was treated with $(^tBuCO)_2O$ (1.5 equiv) in the presence of $Mg(NTf_2)_2$ (1 mol %) under solvent-free conditions at 80 °C (except for entry 1). [b] Isolated yield of the corresponding benzoylated product. [c] The reaction was carried out at room temperature.

yields were obtained at room temperature by reaction with propionic, isobutyric, and pivalic anhydrides. However, acylation with benzoic and chloroacetic anhydrides required heating at 80 °C as the phenyl group and the chlorine atom reduced the electrophilic character of the carbonyl carbon of benzoic and chloroacetic anhydrides, respectively.

As the combined effect of the electronic and steric factors of the phenyl group makes benzoic anhydride less susceptible to nucleophilic attack, benzoylation with benzoic anhydride is difficult to carry out. Thus, we felt it necessary to evaluate the catalytic effect of $Mg(NTf_2)_2$ for benzoylation of a few representative phenols and alcohols with benzoic anhydride (Table 5).

The excellent results obtained for the benzoylation reaction prompted us to carry out the pivalation of a few representative phenols and alcohols with pivalic anhydride (Table 6).

The following representative examples demonstrated the mildness/superiority of $Mg(NTf_2)_2$ compared to metal triflates. The $Bi(OTf)_3$ (3 mol %)-catalyzed pivalation of 3-phenyl-2-methyl-2-propanol (**4**) with $(^tBuCO)_2O$ (3 equiv) in DCM (3 mL/mmol) at room temperature failed to afford the desired product after 5 h,[4e] but 77% yield was obtained by the treatment of **4** with $(^tBuCO)_2O$ (1.5 equiv) after 30 min in the presence of $Mg(NTf_2)_2$ (1 mol %) under solvent-free conditions. No acylated product was obtained after 48 h by the treatment of cinnamyl alcohol (**5**) with $Ac_2O$ (1.5 equiv) in the presence of $Ce(OTf)_3$ (1 mol %).[4f] Acylation of **5** afforded 86% yield after 1 h when the reaction was carried out with 1.2 equiv of $Ac_2O$ in the presence of $Mg(NTf_2)_2$ (1 mol %). However, comparable yield was obtained after 15 h when **5** was treated with 5 equiv of $Ac_2O$ in the presence of LiOTf (20 mol %).[4g] The $Mg(NTf_2)_2$-catalyzed benzoylation of **1** and 2,4,6-trimethylphenol with $(PhCO)_2O$ (1.2 equiv) afforded 88 and 76% yields after 1 and 2 h, respectively, at room temperature under solvent-free conditions. Compared to these observations, 21% yield was obtained by the treatment of phenol with $(PhCO)_2O$ (1.5 equiv) in MeCN for 0.5 h in the presence of $Sc(NTf_2)_3$.[14] Benzoylation of menthol (**6**) with $(PhCO)_2O$ (1.5 equiv) in MeCN afforded 69% yield after 6 h in the presence of $Sc(NTf_2)_3$[14] compared to 78% yield obtained after 2 h at room temperature under solvent-free conditions by the treatment of **6** with $(PhCO)_2O$ (1.2 equiv) in the presence of $Mg(NTf_2)_2$.

In conclusion, we have found that $Mg(NTf_2)_2$ is a new and excellent catalyst for acylation of phenols, alcohols, and thiols at room temperature and under solvent-free conditions. The catalyst was general for acylation with a variety of anhydrides and was effective in benzoylation and pivalation of phenols and alcohols. The several unique properties of $Mg(NTf_2)_2$, such as stability, commercial availability, ease of preparation, minimal hygroscopic nature, and high Lewis acidity, make $Mg(NTf_2)_2$ useful for catalytic applications.[15]

## Experimental Section

**Typical Procedure for Acylation.** A mixture of **1** (360 mg, 2.5 mmol), $Ac_2O$ (0.24 mL, 3 mmol, 1.2 equiv), and $Mg(NTf_2)_2$ (14.6 mg, 0.025 mmol, 1 mol %) was stirred magnetically under neat conditions at room temperature for 15 min. The reaction mixture was diluted with $H_2O$ (10 mL) and extracted with $Et_2O$ (3 × 15 mL). The combined ethereal extracts were washed successively with 2% aqueous NaOH (15 mL) and saturated brine (15 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure to afford the product, which was in full agreement (mp, IR, NMR, MS) with an authentic sample of 2-acetoxynaphthalene. All the remaining reactions were carried out following this standard procedure, except that the reaction mixture was heated at 80 °C wherever applicable. On each occasion, the product obtained after the routine workup was of sufficient purity (spectral data) and did not require further purification.

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**Supporting Information Available:** Typical experimental procedure, spectral data of all compounds, and scanned spectra of unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2879−2882 and references therein.