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2-Nitro-thioglycosides: α- and β-Selective Generation and Their Potential as β-Selective Glycosyl Donors

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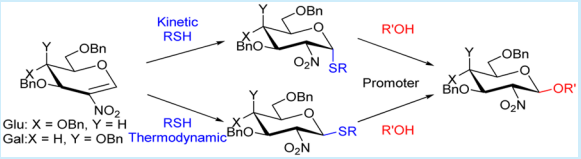
Supporting Information

ABSTRACT: Michael-type addition of thiolates to 2-nitro-D-glucal or to 2-nitro-D-galactal derivatives readily provides 2-deoxy-2-nitro-1-thioglycosides. Kinetic and thermodynamic reaction control permitted formation of either the α- or preferentially the β-anomers, respectively. Addition of achiral and chiral thiourea derivatives to the reaction mixture increased the reaction rate; the outcome is substrate-controlled. The 2-deoxy-2-nitro-1-thioglycosides are excellent glycosyl donors under arylsulfenyl chloride/silver triflate (ArSCl/AgOTf) activation, and they provide, anchimerically assisted by the nitro group, mostly β-glycosides.



Base-catalyzed 2-nitrogalactal concatenation with nucleophiles is a very useful tool for forming α-glycosidic bonds with L-serine or L-threonine.[1] This way, we synthesized all members of the mucin family.[1,2] This chemistry was successfully employed for the synthesis of various *O*-, *S*-, *P*-, and *C*-glycosides.[2,3] Also nucleosides could be readily obtained; thus, it was found that the base had a major influence on the α/β-selectivity.[4] This convenient and highly efficient glycosidation method could be also extended to 2-nitroglucal. However, anomeric stereocontrol in this base-catalyzed Michael-type addition to the nitroolefin moiety was more complex.[3d,5]

As thiol addition to 2-nitroglycals is particularly efficient, the derived 2-deoxy-2-nitro-1-thioglycosides are readily available.[6] These thioglycosides can also be used as glycosyl donors.[6b] Under NIS/TMSOTf activation in dichloromethane (DCM) at 0 °C or in propionitrile at −15 °C, respectively, with *O*-nucleophiles, preferentially β-glycosides were obtained. These studies were recently resumed, as we noticed that the base and time dependence of thiol additions to 2-nitroglycals could be used to generate either the α- or β-thioglycosides.

Bis-H-bond donors, such as achiral or chiral thioureas greatly effect Michael-type additions to nitroolefin moieties.[7,8] Hence, their influence on the reaction rate and α/β-selectivity of thiol additions to 2-nitroglycals was of interest.

For thioglycoside activation efficient reagents have been introduced in recent years.[9] Hence, the potential of 2-deoxy-2-nitro-thioglycosides as glycosyl donors and their usefulness for the important glycosamine glycosidation is now displayed.

In studies of the base and solvent dependence of thiophenol addition to the readily available 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal **1**,[3k] the use of *tert*-BuOK as the base and toluene as the solvent (see Scheme 1 and Table 1 in the Supporting Information), led to a mixture of the α-thioglucoside **2α** and the α-thiomannoside **3α**. An increase of the amount of base and the reaction time shifted the equilibrium in favor of the β-thioglucoside **2β**. Hünig's base and *N*-methylmorpholine furnished similar results; however, triethylamine led to clean formation of the α-thioglucoside **2α** which for stereoelectronic reasons is due to fast Michael addition from the α-side and following fast protonation from the β-side. The secondary amines diisopropylamine and piperidine gave product mixtures. In DCM as the solvent similar results were obtained: with triethylamine as the base after 30 min, **1** was completely transformed into **2α**; extending the reaction time to 24 h led to partial transformation into **3α**. As DCM is more polar than toluene, as expected, the reaction rate was slightly increased. 4-Pyrrolidinopyridine and DMAP led, depending on reaction time and base concentration, to an increase in the formation of **3α** and finally of **2β**; thus, steric effects override the anomeric effect. The reported exclusive formation of **2β** could not be confirmed.[3h] Also other solvents were studied, as for instance ether; however, no advantages were visible. Therefore, the optimization studies were performed in toluene as solvent with triethylamine as the base (Table 1).

The variation of the base concentration showed that 0.01 equiv of triethylamine led to complete formation of **2α** within 30 min (Table 1, entries 1, 2, and 6). Extension of the reaction time (entries 3−5) or increasing the triethylamine concentration gave in a slow reaction the α-thiomannoside **3α** and, in an even slower thermodynamically controlled reaction, the β-thioglucoside **2β** (entries 1−10) in up to ∼75% yield (entry 9). A very high base concentration and long reaction time (entry 10) led to slow degradation of **2α**, **2β**, and **3α** resulting in the formation of complex product mixtures.

Addition of thiourea **9** to the reaction mixture (entries 11−15), in order to raise the Michael-type properties of **1** via H-bonding to the nitro group, led to fast equilibration (compare entries 1 and 11, 4 and 13, 5 and 14, 9 and 15); however, the same results were obtained. Combination of the base and thiourea activation properties as in the chiral organocatalysts (*R*,*R*)-**10**[10]

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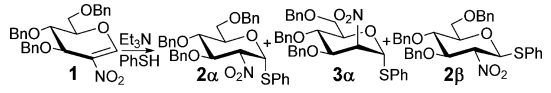
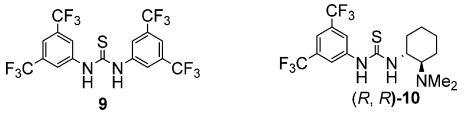
Table 1. Optimization of the Reaction Conditions with Triethylamine As Base and Toluene As Solvent



entry[a,b]	NEt_3(equiv)	time	additive	result[c]
1	0.005	30 min	none	**1**+2α (5:3)
2	0.01	30 min	none	**2α**
3	0.01	2 h	none	**2α**+3α (25:1)
4	0.01	10 h	none	**2α**+3α (6:1)
5	0.01	24 h	none	**2α**+3α (6:1)
6	0.1	30 min	none	**2α**
7	0.5	30 min	none	**2α**+3α+**2β** (10:1:2)
8	1.0	30 min	none	**2α**+3α+**2β** (10:2:5)
9	1.0	24 h	none	**2α**+3α+**2β** (3:2:16)
10	15.0	24 h	none	**2α**+3α+**2β** (1:1:5)
11	0.005	30 min	**9**	**1**+2α (1:3)
12	0.01	30 min	**9**	**2α**
13	0.01	12 h	**9**	**2α**+3α+**2β** (1:1:1)
14	0.01	24 h	**9**	**2α**+3α+**2β** (3:2:6)
15	1.0	24 h	**9**	**2α**+3α+**2β** (1:1:6)
16	none	30 min	(*R*,*R*)-**10**	**2α**+3α (12:1)
17	none	30 min	(*S*,*S*)-**10**	**2α**+3α (7:1)

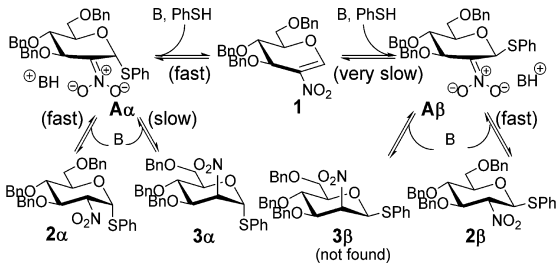
[a]Reactions 1−10 were carried out with 1.0 equiv of **1** and 2.0 equiv of PhSH at rt. [b]Reactions 11−17 were carried out by adding 0.3 equiv of thiourea **9** or 0.05 equiv of (*R*,*R*)-**10** and (*S*,*S*)-**10**, respectively. [c]Yields were 90%−100%; product ratio was determined by NMR.



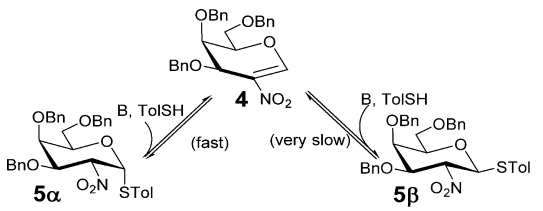
and (*S*,*S*)-**10**[11] showed only a slight rate difference, with (*S*,*S*)-**10** being the more efficient catalyst (entries 16, 17). Site selectivity in favor of α- or β-thiolate addition with (*R*,*R*)-**10** and (*S*,*S*)-**10**, respectively, was not observed. Hence, different from conformationally nonstrained nitro-olefins, thiolate addition to the conformationally constrained 2-nitroglycal is essentially controlled by the structure of the substrate and not by the asymmetric induction of the chiral thiourea catalyst.

In order to confirm the base catalyzed equilibration between **2*α***, **3*α***, and **2*β*** (Schemes 1, 2), **2*α*** was treated with triethylamine

Scheme 1. Base Catalyzed Thiophenol Addition to 2-Nitroglucal 1



Scheme 2. Thiophenol Addition to 2-Nitrogalactal 4



in toluene which led after 3 h to ~25% of starting material **1** (Table 2, entry 1). Upon addition of thiophenol, **2*α*** was retained,

Table 2. Stability of 2*α* and 2*β* in the Presence of Trethylamine As Base in Toluene As Solvent at Room Temperature[a]

entry	2	NEt_3(equiv)	PhSH	time	result[b]
1	**2α**	0.01	none	3 h	**1**+2α (1:3)
2	**2α**	0.01	2.0 equiv	18 h	**2α**
3	**2α**	1.0	2.0 equiv	30 min	**2α**+3α+**2β** (1:1:1)
4	**2α**	1.0	2.0 equiv	24 h	**2α**+3α+**2β** (1:1:6)
5	**2β**	1.0	none	24 h	**1**+**2α**+3α+**2β** (1:2:1:19)
6	**2β**	1.0	2.0 equiv	24 h	**2α**+3α+**2β** (3:2:18)

[a]All reactions were carried out with 1.0 equiv of **2**. [b]Yields were 90%−100%; product ratio was obtained by NMR.

as readdition of thiophenol was faster than elimination to **1**; therefore, also no **3*α*** (and **3*β***) was formed (entry 2). However, with more base, after 30 min, appreciable amounts of **3*α*** and **2*β*** were formed (entry 3) and after 18 h an ~1:1:6 ratio of **2*α***, **3*α***, and **2*β*** was obtained (entry 4). Practically the same results were found for **2*β***: no addition of thiophenol to the reaction mixture led to equilibration with **1**, **2*α***, and **3*α*** (entry 5), whereas addition of thiophenol suppressed the formation of **1** (entry 6). Under all equilibrating conditions the same amount of **2*β*** (~70−75%) was found. These results confirm the reaction course in Scheme 1 with nitronates **A*α*** and **A*β*** that lead via **1** to **2*α***, **3*α***, and **2*β***. Protonation of **A*β*** from the α-side is for stereoelectronic and thermodynamic reasons disfavored; hence, **3*β*** is not found.

Isolation of **2*β*** was performed by chromatography on silica gel of equilibrated reaction mixtures (Table 1, entry 9). As **2*α*** decomposes under these conditions, **2*β*** could be readily obtained. Pure **2*α*** was obtained by crystallization from solutions that contained only **2*α*** (Table 1, entries 2, 6). Hence, chromatography of a mixture of **2*α*** and **3*α*** led to pure **3*α***. The structures of these compounds were unequivocally assigned with the help of NMR data (Table 3). The ^{1}H NMR data clearly

Table 3. Selected NMR Data of Compounds 2*α*, *β*, 3*α*, 5*α*, *β*

	2α[a]	**2β**[a]	**3α**[a]	**5α**[b]	**5β**[b]
1-H ($J_{1,2}$)	5.78 (6.0)	4.84 (10.0)	5.77 (1.8)	5.94 (6.0)	5.20 (10.1)
2-H ($J_{2,3}$)	4.84 (10.8)	4.42 (10.0)	5.04 (4.8)	5.21 (11.1)	4.64 (10.2)
3-H ($J_{3,4}$)	4.36 (10.2)	4.18 (10.0)	4.05 (7.6)	4.43-4.61[c] (3.0)	4.38 (2.6)
4-H ($J_{4,5}$)	3.73 (9.6)	3.51-3.59	4.26 (9.6)	4.33 (0)	4.23 (0)
5-H	4.35- (4.0)	3.51-3.59[c]	4.28- (4.5)	4.53- (5.0)	4.10 (6.2)
($J_{5,6}$)($J_{5,6'}$)	4.38[c] (2.0)		4.31[c] (1.4)	4.56[c] (7.0)	(6.2)
6-H ($J_{6,6'}$)	3.76 (11.0)	3.66-3.73[c]	3.73 (11.0)	3.63 (10.0)	3.57-3.64[c]
6'-H	3.62		3.64	3.56	
C-1($J_{c\text{-}1,1\text{-}H}$)	85.64	82.92	83.97 (176)	84.36	81.83

[a]Solvent: $CDCl_3$. [b]Solvent: DMSO-d_6. [c]The NMR peaks overlap.

show that the compounds are preferentially in the $^4C_1$-conformation ($J_{2,3} \approx J_{3,4} \approx 10$ Hz for **2*α*** and **2*β*** and $J_{3,4} = 7.6$ Hz, $J_{4,5} = 9.6$ Hz for **3*α***). The $J_{1,2}$ values confirmed the assigned structures, and the ^{13}C NMR shift of *C*-1 of **3*α*** ($\delta = 83.97$) and the coupling constant of $J_{C\text{-}1,\ 1\text{-}H}$ 176 Hz is in accordance with the expected value.[12] Instead of the β-anomer **2*β***, the α-anomer **2*α*** was employed in the previously described glycosidation reactions that led, as correctly assigned, mainly to β-glycosides.[6b]

Thiophenol addition to 2-nitrogalactal **4**[1b] (Scheme 2) furnished similar results as those found for **1**. The α-anomer **5*α*** was obtained in a very fast triethylamine catalyzed reaction. A longer reaction time led to the formation of **5*β*** that finally became the main product. As equilibration was faster in this case, for stereoelectronic reasons neither the α- nor the β-*talo*-product was found. Hence, protonation of the *C*-2 carbanion

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intermediate at the α-side is by far slower than protonation at the β-side. As **5α** is more stable than **2α**, separation of **5α** and **5β** by silica gel chromatography was possible. The structural assignments are based on NMR data (Table 3). As the ^{1}H NMR data of **5α** and **5β** were previously collected from $CDCl_3$ solutions, where the proton signals partly overlap, the anomeric assignments were ambiguous. Solutions of **5α** and **5β** in DMSO-d_6 led to quite well separated ^{1}H NMR shifts, and also the X-ray analysis of **5β** confirmed the C_1-configuration (Figure 1, CCDC no. 1043491). Thus, the structures could be unequivocally assigned.

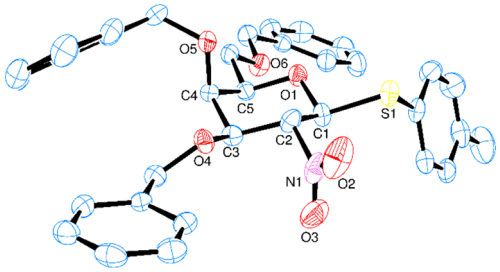
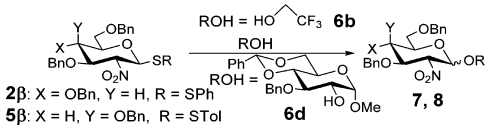


Figure 1. X-ray diffraction analysis of compound **5β** (Ortep plot at 50% probability ellipsoids).

Improvements in glycosidation methodology are still in demand.[13] Hence, glycosyl donors with a nitro group in the 2-position could provide a versatile alternative for the synthesis of glycosamine glycosides, as the nitro group can be readily reduced to the amino group.[1c] Thus, this approach is of importance, for instance, for the synthesis of glycopeptide *O*- and *N*-glycans and of glycosaminoglycans, respectively.

Previous glycosidation attempts with 2-nitro-1-thioglycosides **2α** and **5α** as glycosyl donors (not the β-anomers **2β** and **5β** but the α-anomers were employed; see above) were performed with NIS/TMSOTf as the promoter in DCM at 0 °C.[6b] The present studies with **2β** as the donor and **6d** as the acceptor under varying reaction conditions show (see Table 4, entries 1−5) that ArSCl/AgOTf as the promoter system, in DCM as the solvent at −60 °C, leads to much better results in terms of product yield and anomeric selectivity. Thus, from **2β** and **6d** the β-disaccharide **7dβ** could be stereoselectively obtained in high yield (entries 4, 5). Diethyl ether as solvent did neither support the reaction nor lead to preferential α-glycoside formation (entries 6, 7), and THF as solvent led to a dramatic decrease in yield, as THF was decomposed by the promoter system (entries 8−10). Hence, the nitro group provides strong anchimeric assistance in these glycosidations. A direct neighboring group participation of the 2-nitro group at the anomeric center is for energetic reasons not expected.[14] A nitro group mediated stabilization of the ^{3}H$_4$-conformer of the glycosyl cation together with a strong electronic shielding of incoming nucleophiles on the α-side favor β-anomeric attack. The β-directing effect of corresponding 2-fluoro substituted glycosyl donors was also explained by the preference for the ^{3}H$_4$-conformer.[15] These effects cannot be overcome by the ether solvent effect; the results in THF as the solvent are not conclusive due to the unknown influence of the solvent decomposition products on the anomeric selectivity. However, H-bond formation of the acceptor to the donor nitro group could overcome the shielding effect and thus favor α-product formation. Hence, trifluoroethanol (**6b**) that is prone to H-bond formation[16] was selected as the acceptor and, indeed, appreciable amounts of the α-products (**7bα**, **8bα**) were formed (entries 11−13). Thus, via increased H-bonding a strong dual-directing effect of the nitro group can be envisaged.[17,18]

Table 4. Optimization of the Glycosidation Conditions[a]



entry	donor	acceptor	promotor	solvent	result
1	2β	6d	NIS/TMSOTf[b]	DCM	no reaction
2	2β	6d	NIS/TMSOTf[b]	Et_2O	no reaction
3	2β	6d	NIS/TMSOTf[b,c]	DCM/THF (1:1)	no product
4	2β	6d	*p*-TolSCl/AgOTf[d]	DCM	**7d**β (87%)
5	2β	6d	*p*-$O_2NC_6H_4SCl$/AgOTf[e]	DCM	**7d**β (85%)
6	2β	6d	″	DCM/Et_2O (1:1)	**7d**β (85%)
7	2β	6d	″	Et_2O	**7d**β (80%)
8	2β	6d	″	DCM/THF (10:1)	**7d**α/β (42%, 1:2)
9	2β	6d	″	DCM/THF (5:1)	**7d**α/β (13%, 1:1)
10	2β	6d	″	THF	**7d**α/β (trace)
11	2β	6b	″	DCM	**7b**α/β (81%, 1:4)
12	5β	6b	″	DCM	**8b**α/β (83%, 3:4)
13	5β	6b[f]	″	DCM	**8b**α/β (87%, 1:1)

[a]Reactions were carried out at −60 °C for 5 h except as otherwise noted. [b]NIS (2.0 equiv), TMSOTf (0.1 equiv) for 1 h. [c]Reaction temperature 0 °C. [d]*p*-TolSCl (1.1 equiv), AgOTf (3.0 equiv). [e]*p*-$O_2NC_6H_5SCl$ (1.2 equiv), AgOTf (3.0 equiv) [f]Preactivation.

With this activation protocol for the glycosyl donors **2α**, **2β**, **5α**, and **5β** in hand, we studied the glycosidation of various acceptors (Table 5). The reactions with isopropanol show (entries 1, 2 and 8, 9) that, independent of the anomeric configuration of the donor, exclusively the β-products **7aβ**[6b] and **8aβ**,[6b] respectively, were obtained. Hence, we used for the following reactions the β-thioglycoside donors **2β** and **5β**. Reaction with 6-*O*-, 2-*O*-, 3-*O*-, and 4-*O*-unprotected glucosides **6c**−**6f** as acceptors furnished the β-products **7cβ**[3h] and unknown **7dβ**, **7eβ**, and **7fβ** in very good yields (entries 3−6). Also less reactive 2,3,4-tri-*O*-benzoyl protected galactoside **6g** gave with **2β** exclusively the β-disaccharide **7gβ** (entry 7). Similarly, with the preactivation protocol,[9a,19] from **5β** as the donor and **6c** and **6e** as acceptors, almost exclusively the β-linked disaccharides **8cβ**[1b] and **8eβ** were generated (entries 10, 11).With the present procedures, the thiogalactoside acceptor **6h** could also be glycosidated yielding practically exclusively β-linked disaccharide **8hβ**, that is available for further chain extension with the same promoter system (entry 12).[9a] Not unexpected for galactosyl donors, some minor amounts of the α-linked glycosides were detected that could be readily separated by chromatography. It is noteworthy that β-1,4-linked disaccharides **7eβ** and **8eβ** could not be obtained by direct Michael-type addition of the sterically demanding acceptor **6e** to 2-nitro-glycals.[1b,3h]

In conclusion, kinetic and thermodynamic reaction control of thiolate addition to 2-nitroglycals permits the selective synthesis of either α- or β-2-deoxy-2-nitro-1-thiogluco- and galatopyranosides, respectively. The reaction rate is increased by the addition of bis-H-bonding thioureas as the catalyst; with chiral derivatives no influence on the α/β ratio was observed. The substrate inherent strong stereoelectronic effect, favoring fast thiolate addition from the α-side, overrides the anomeric diastereoselection control by a chiral thiourea.

The aryl 2-deoxy-2-nitro-thioglycosides obtained were efficient glycosyl donors under arylsulfenyl chloride/silver triflate activation. Moreover, due to anchimeric assistance by the nitro group, they afford mainly the β-products. As the nitro group can be readily transformed into the amino group, a competitive alternative to the acylamino group assisted glycosidation of glucosamine and galactosamine derivatives is available.

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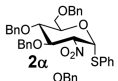
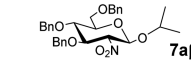
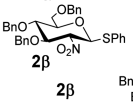
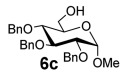
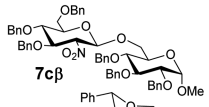
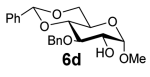
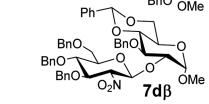
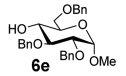
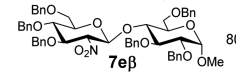
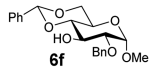
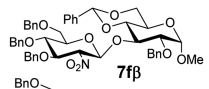
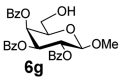
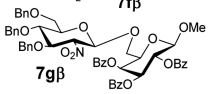
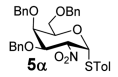
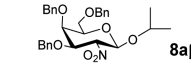
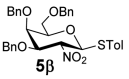
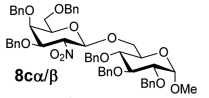
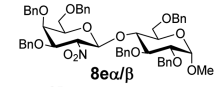
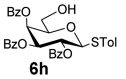
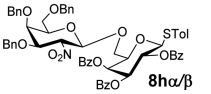
Table 5. Glycosidation Results with Glycosyl Donor 2*α*, 2*β*, 5*α*, 5*β* with Acceptors 6a, 6c−6f[a]

entry	donor	acceptor	product	yield
1	 **2α**	 **6a**	 **7aβ**	70% (β)
2	 **2β**	**6a**	**7aβ**	93% (β)
3	**2β**	 **6c**	 **7cβ**	95% (β)
4	**2β**	 **6d**	 **7dβ**	85% (β)
5[b]	**2β**	 **6e**	 **7eβ**	80% (β)
6	**2β**	 **6f**	 **7fβ**	82% (β)
7	**2β**	 **6g**	 **7gβ**	85% (β)
8	 **5α**	**6a**	 **8aβ**	87% (β)
9	 **5β**	**6a**	**8aβ**	90% (β)
10[c]	**5β**	**6c**	 **8cα/β**	87% (β:α>20:1)
11[c]	**5β**	**6e**	 **8eα/β**	75% (β:α>10:1)
12[c]	**5β**	 **6h**	 **8hα/β**	93% (β:α>20:1)

[a]The reactions were performed in DCM at −60 °C with 1.2 equiv of donor, 1.0 equiv of acceptor and *p*-$O_2NC_6H_5SCl$ (1.2 equiv)/AgOTf (3.0 equiv) as promoter for 5 h. [b]1.5 equiv of **2b**; with 1.0 equiv of **2b** only 66% of **7e*β*** was obtained. [c]Preactivation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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