EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200239

C–C Coupling of Acyclic Nitronates with Silyl Ketene Acetals under Silyl Triflate Catalysis: Reactivity Umpolung of Aliphatic Nitro Compounds

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Dedicated to Professor Dr. Dieter Seebach on the occasion of his 75th birthday

Keywords: Umpolung / C–C coupling / Nitro compounds / Hydrogenation / Amino acids

TBSOTf-promoted C–C coupling of alkyl and trialkylsilyl nitronates with silyl ketene acetals yields functionalized nitroso acetals. This conversion may serve as a new simple procedure to reverse the conventional reactivity of aliphatic nitro compounds. Preliminary results on the hydrogenation of nitroso acetals into amino acids derivatives, as well as TFA-catalyzed transformations of nitroso acetals, are examined to prove the possible utility of this umpolung procedure.

Introduction

Reactivity umpolung of organic compounds is commonly understood as an interchange of their usual alternating donor and acceptor reactivity patterns. Such inversion of conventional reactivity of functional groups obviously extends the application of the corresponding type of organic compounds in targeted organic synthesis. In this regard, reversal of polarity of readily available aliphatic nitro compounds (AN), which are widely employed as α-nucleophiles, appears to be of high interest for expanding organic synthesis methodology.[1] In this paper, we report on a new efficient way to solve this challenging task. To make the idea of our design most clear, a brief survey of state-of-the-art methods for umpolung precedes the Results and Discussion section.

Prof. D. Seebach, in his classic review on reactivity reversal,[2] discussed conversion of AN into the respective carbonyl compounds (known for more than a century as the Nef reaction)[3] as the key step in the umpolung procedure.[4] However, this approach has the serious disadvantage of losing a nitrogen atom in the substrate, whose presence in the final structure is often highly preferable. At the same time, change of polarity of the α-carbon atom of AN **1** might be achieved with retention of the nitrogen atom according to a fairly simple and effective approach based on the peculiarity of the AN structure (Scheme 1).

When treated with bases, AN **1** reversibly form ambident anions **A**, which smoothly interact successively with various π-electrophiles **E** and a proton to yield corresponding adducts **3**. This is the classic reactivity of AN that becomes apparent in Henry, Michael, and Mannich reactions.[1] On the other hand, *aci*-forms **2**, which exist in equilibrium with AN **1**, can react with Brønsted acids reversibly to give resonance stabilized cations **B**.[3b,6] The latter can be formally regarded as bis-protonated anions **A**. The C–C bond-forming reactions of cations **B** with π-nucleophiles NuH afford corresponding nitroso compounds **4** or oxime isomers **4′**. If the nitro functionality is desirable again, it could be created by final oxidation of **4** or **4′** to $RR'C(NO_2)Nu$ nitro compounds.

In contrast to the well-studied reactivity of highly nucleophilic anions **A**,[7] there are only a few reports on the C–C bond-forming reactions of cations **B**. Until recently, the only example was the C–C coupling of primary AN **1** with benzene and its electron-rich derivatives (Nu = Ar).[8] This was discovered and developed independently by French and Japanese groups about 20 years ago, and the reaction runs under highly acidic conditions to yield the oximes **4′**. Cations **B** were found to be weak electrophiles[8a] requiring additional protonation to be involved in the C–C coupling, which brings about the necessity of using strong acids. Despite some improvements in this approach,[9] any of its variants requires strongly acidic conditions, which significantly restricts the set of suitable nucleophiles for C–C coupling.[10,11]

To avoid this inevitable restriction, we now propose substantial modification (Scheme 2) of the above approach by replacing both OH protons in cations **B** (Scheme 1) with alkyl and/or trialkylsilyl moieties (cations **C**, Scheme 2).

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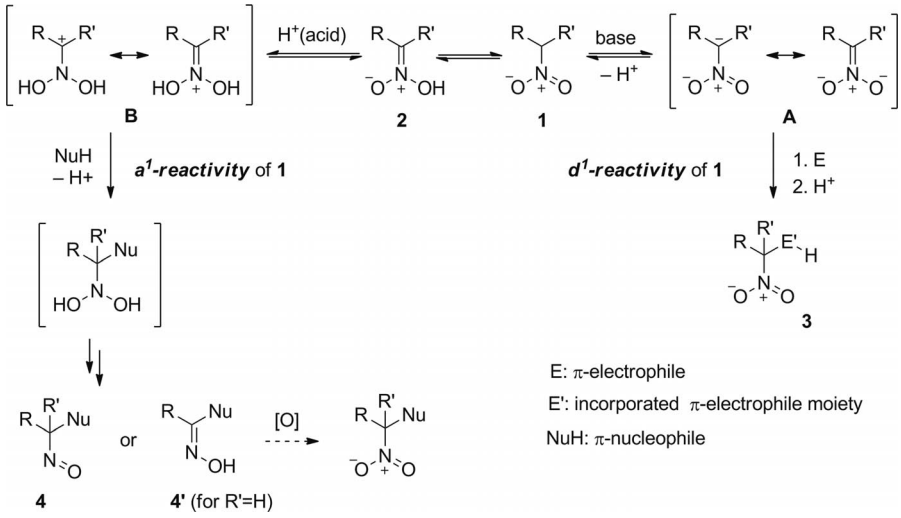
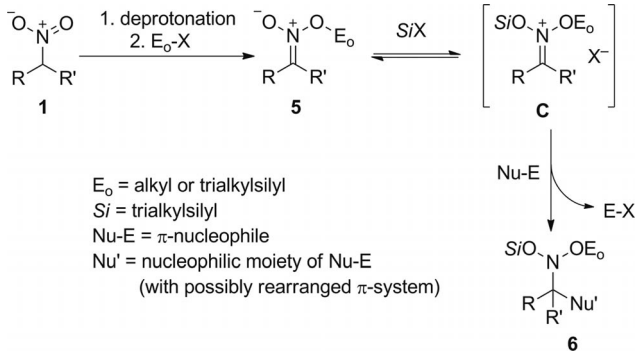
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200239.



Scheme 1. Reactivity umpolung of AN.[5]

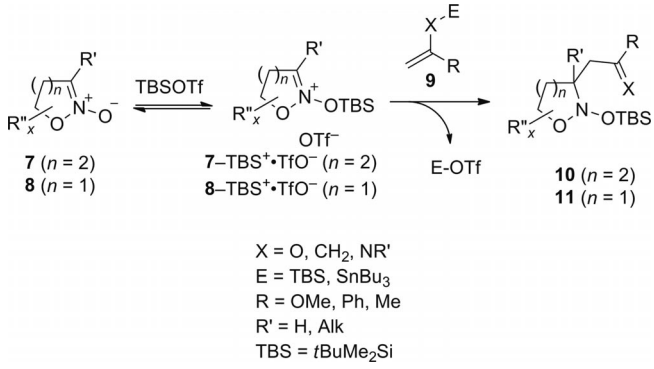
This allows one to transfer resulting intermediates **C** from protic to aprotic solvents to facilitate their reactivity change. Such modification of the reactive intermediate can be easily effected via available nitronates **5**, which can be easily obtained from AN **1**. The reversible silylation of **5** with the appropriate silyl Lewis acid *Si*X is expected to afford cations **C**, which will couple with π-nucleophile Nu–E to yield target nitroso acetals **6**.[12]



Scheme 2. Our approach to reactivity umpolung of AN **1**.[5a,12]

The expected efficiency of such a modification is supported by successful C–C coupling of six-membered cyclic nitronates **7** (n = 2) with a rather diverse collection of π-nucleophiles **9**,[12a] and also the successful C–C coupling of five-membered cyclic nitronates **8** (n = 1) with silyl ketene acetal **9a** (X = O, E = TBS, R = OMe)[12c] (Scheme 3). These transformations were shown truly to proceed through bis(oxy)iminium cation intermediates **7**-TBS$^+$ and **8**-TBS$^+$, respectively. It was also proved that acyclic silyl and alkyl nitronates generate similar cations under close conditions.[12b]

Thus, we have all the prerequisites for the proposed reactivity umpolung of AN **1** via corresponding nitronates **5** (Scheme 2) to be successful. In continuation of our previous studies, the present work systematically explores the C–C



Scheme 3. C–C coupling of cyclic nitronates with π-nucleophiles **9**.[12]

coupling between acyclic nitronates **5** and silyl ketene acetals **9** (X = O, E = $SiAlk_3$, R = OAlk), which proved to be most effective in the C–C coupling reactions with cyclic nitronates **7** and **8**[12] and, therefore, can be considered as π-nucleophiles of choice.[13]

Results and Discussion

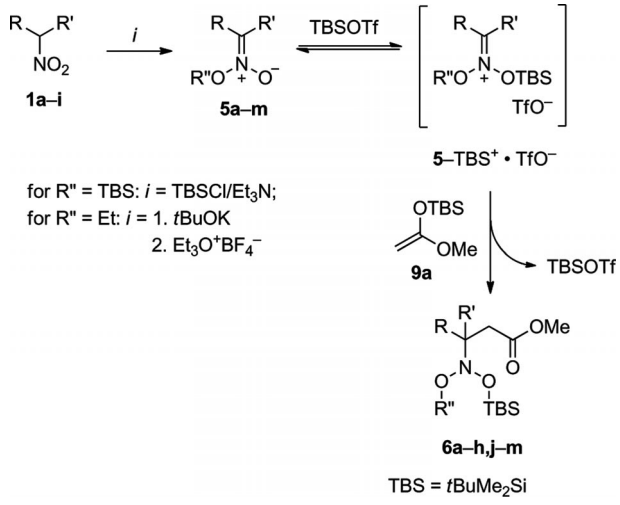
C–C Coupling of Nitronates 5 with Silyl Ketene Acetals 9

Silyl nitronates **5a–d** and **5i** (Scheme 4, Table 1) were prepared by standard silylation procedures from the appropriate AN **1a–d** or **1f**.[14] Alkyl nitronates **5e–h** and **5j–m** (Scheme 4, Table 1) were generated from isolated potassium salts of the corresponding AN **1b–i** by treatment with $Et_3O^+BF_4^-$ in CH_2Cl_2 according to a known method[15] and used in situ because of their thermal instability. Readily available silyl ketene acetal **9a** was exploited as a model π-nucleophile. The main results for the C–C coupling of nitronates **5** with **9a** (Scheme 4) are summarized in Table 1.

Table 1. Addition of silyl ketene acetal **9a** to silyl and alkyl nitronates **5a**–**m**.

Entry	AN **1**, Nitronate **5**	R	R′	R′′	TBSOTf [equiv.]	*T* [°C]	Time [h]	Product **6**	Yield of **6** [%][a]
1	**1a**, **5a**	H	Me	TBS	0.20	–94	0.75	**6a**	88
2	**1b**, **5b**	H	Et	TBS	0.20	–94	1.0	**6b**	82
3	**1c**, **5c**	H	$PhCH_2$	TBS	0.10	–94	2.0	**6c**	90
4	**1d**, **5d**	H	$MeO_2CCH_2CH_2$	TBS	0.10	–94	1.0	**6d**	92
5	**1b**, **5e**	H	Et	Et	0.10	–78	1.5	**6e**	70
6	**1c**, **5f**	H	$PhCH_2$	Et	0.10	–78	18	**6f**	78
7	**1d**, **5g**	H	$MeO_2CCH_2CH_2$	Et	0.10	–78	15	**6g**	87
8	**1e**, **5h**	H	$MeCOCH_2CH_2$	Et	0.10	–78	18	**6h**	56
9	**1f**, **5i**	Me	Me	TBS	0.20	–78	18	–	–[b]
10	**1f**, **5i**	Me	Me	TBS	0.20	–30	18	–	–[c]
11	**1f**, **5j**	Me	Me	Et	0.20	–78	1.0	**6j**	70
12	**1g**, **5k**	Me	$PhCH_2$	Et	0.20	–78	18	**6k**	18
13	**1h**, **5l**		$–(CH_2)_4–$	Et	0.20	–78	2.0	**6l**	51
14	**1i**, **5m**		$–(CH_2)_5–$	Et	0.20	–78	1.0	**6m**	72

[a] Isolated yield. [b] No target product, initial nitronate **5i** was recovered in nearly quantitative yield after workup. [c] No target product, complex mixture of intractable products was obtained.



Scheme 4. C–C coupling of silyl and alkyl nitronates **5a**–**m** with ketene acetal **9a**.

This umpolung procedure was found to be applicable to a wide range of AN **1a**–**i**. Importantly, mild conditions during the reaction mixture workup are crucial for preparation of pure nitroso acetals **6** in good yields. Quenching with saturated aqueous sodium hydrogen carbonate solution, which was used earlier in the processes run with nitronates **7**,[12a] results in decreased yields of nitroso acetals **6** and their contamination with difficult-to-remove impurities. This can be avoided by addition of methanol and triethylamine to the reaction mixture prior to aqueous workup, as it was done previously with nitronates **8**.[12c] Certain precautions should be also taken in the purification of nitroso acetals **6**. Whereas adducts **6a**–**d** can be isolated by using conventional column chromatography, purification of adducts **6e**–**m** requires chromatography on triethylamine-treated silica gel. We attribute this dissimilarity to the fact that nitroso acetals **6** are very sensitive to Brønsted acids (for more detail, see section "Transformations of Nitroso Acetals **6**").

As can be seen from Table 1, both silyl and alkyl nitronates derived from primary AN **1a**–**e** (Table 1, Entries 1–8) smoothly react with silyl ketene acetal **9a** to afford desired nitroso acetals **6a**–**h** in good to excellent yields. With silyl nitronates, the yields obtained are typically higher than those for the corresponding alkyl nitronates. The situation, however, is drastically changed with a switch to nitronates **5i**–**m** derived from secondary AN **1f**–**i**. In particular, silyl nitronate **5i** derived from 2-nitropropane is completely unreactive toward ketene acetal **9a** (Table 1, Entries 9 and 10 and footnotes), although ethyl analogue **5j** affords corresponding adduct **6j** in a good yield (Table 1, Entry 11). Ethyl nitronates **5k**–**m** derived from other typical secondary AN **1f**–**i** react with **9a** in a similar fashion to give corresponding adducts **6k**–**m** in low to good yields (Table 1, Entries 11–14).

A priori, the absence of C–C coupling between silyl nitronate **5i** derived from secondary AN **1f** and π-nucleophile **9a** can be due to thermodynamic as well as kinetic factors. Thermodynamic causes could consist of an insufficient equilibrium concentration of ionic intermediate **5i**-$TBS^+ \cdot OTf^-$ or the thermodynamically unfavorable reaction of **5** with **9** as a whole in the case of silyl nitronates derived from secondary AN **1**. The first reason can be ruled out, as treatment of nitronate **5i** with 1.5–2 equiv. of TBSOTf in the temperature range from –60 to –10 °C results in complete formation of corresponding cation **5i**-$TBS^+ \cdot TfO^-$.[16] The second reason seems to be very unlikely, because ethyl nitronates derived from secondary AN (Table 1, entries 11–14), as well as cyclic nitronates with a substituent at the C-3 atom, react with **9a** smoothly.[12a,12b] The nature of the oxygen substituent of nitronate **5** also has a negligible (if any) influence on the thermodynamics of **5**+**9** coupling, as both ethyl and silyl nitronates derived from primary AN **1** react with **9a** in a similar fashion (cf. Table 1, Entries 2 and 5). Therefore, there is no reason to expect drastic changes in the thermodynamics of the reaction **5**+**9** for the respective silyl derivatives of secondary AN **1**. Apparently, the lack of reactivity of cation **5i**-TBS^+ toward **9a** is due to

Table 2. C–C coupling of AN **1** with silyl ketene acetal **9a**.

Entry	AN **1**	R	Base	*T* [°C]	Time [h]	Product **6**	Yield of **6** [%][a]
1	**1b**	Et	DBU	–94	1.0	**6b**	65
2	**1c**	$PhCH_2$	DBU	–94	0.75	**6c**	93
3	**1c**	$PhCH_2$	Et_3N	–25	18.0	–	0[b]
4	**1d**	$MeO_2C(CH_2)_2$	DBU	–94	0.75	**6d**	87
5	**1j**	H	DBU	–94	1.0	**6n**	82
6	**1k**	4-MeO-C_6H_4	Et_3N	–25	18	**6o**	88

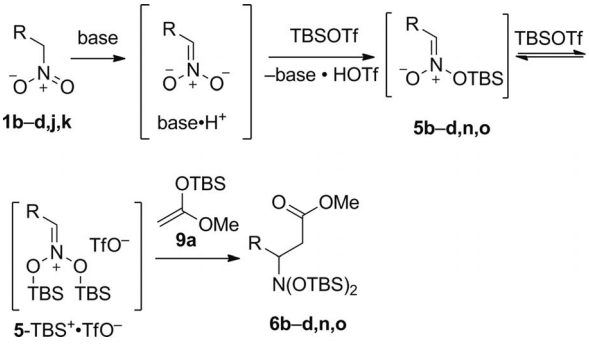
[a] Isolated yield. [b] No product of C–C coupling was detected by TLC.

kinetic factors, most likely due to steric hindrance arising from the presence of two bulky TBSO substituents in the reactive species.[17]

Thus, the successful C–C coupling between nitronates **5** derived from secondary AN **1** and π-nucleophiles **9** requires the use of alkyl derivatives only, whereas in the case of primary AN **1**, the more stable and readily available silyl nitronates are preferred.

It is noteworthy that with primary AN **1**, the method can be performed in a one-pot fashion, combining the generation of appropriate silyl nitronate **5** and its C–C coupling with π-nucleophile **9**. Specifically, consecutive treatment of primary AN **1** with 1 equiv. of DBU taken as a base and 1.1 equiv. of TBSOTf in the presence of silyl ketene acetal **9a** furnishes the corresponding adducts **6** in good to excellent yields (Scheme 5, Table 2). The yields obtained here compare well with those for the corresponding products **6** obtained from isolated silyl nitronates **5** (cf. Tables 1 and 2). If the parent AN **1** has no protons in the β-position, triethylamine may be used instead of DBU (cf. Table 2, Entries 3 and 6).

Along with convenience and simplicity, the procedure illustrated in Scheme 5 offers some additional advantages



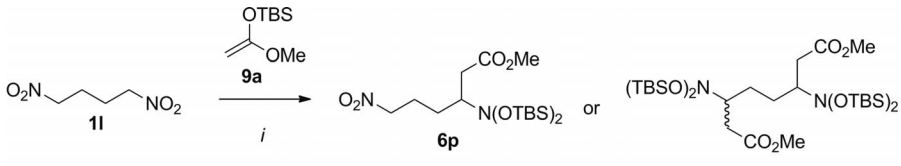
Scheme 5. One-pot procedure for C–C coupling of primary AN **1** with π-nucleophile **9a**.

compared to the initially used procedure for the synthesis of nitroso acetals **6** (Scheme 4). In particular, it allows the employment of AN **1** that produce non-isolable silyl nitronates **5** (for example, nitromethane;[18] Table 2, Entry 5, adduct **6n**) in the C–C coupling with π-nucleophiles. Another plus is the ability to vary the number of reacting $–CH_2NO_2$ centers in the C–C coupling reactions of polynitro compounds. This can be demonstrated with 1,4-dinitrobutane (**1l**). Depending on the ratio of reactants, the **1l** + **9a** one-step procedure may lead to monoadduct **6p** (86%) or to bis-coupling product **6q** (58%) with minor formation of an easily removable admixture of **6p** (20%, Scheme 6).

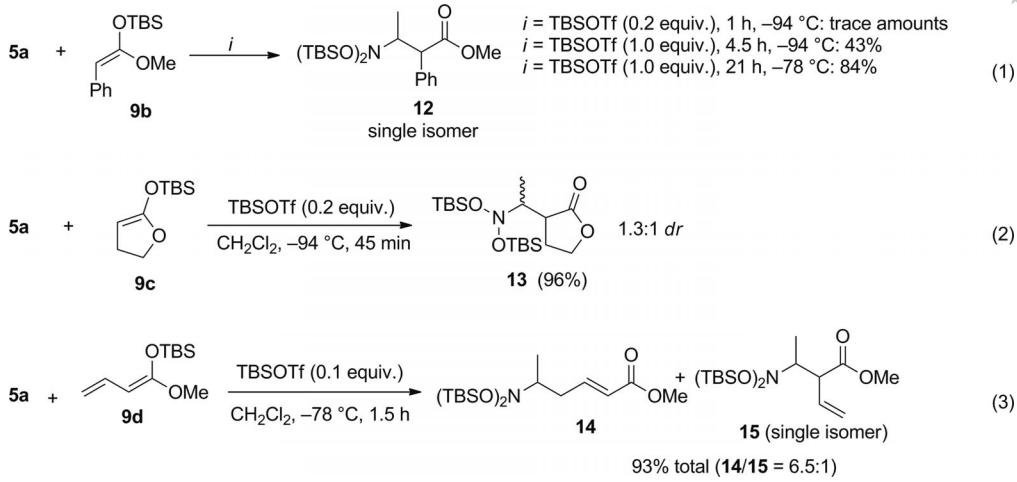
The scope and limitations of the above C–C coupling reaction with regard to the nature of silyl ketene acetals **9** were studied briefly by using model nitronate **5a** (Scheme 7).

Substituted silyl ketene acetal **9b** reacted with **5a** to afford target nitroso acetal **12** diastereoselectively in high yield [Scheme 7, Eq. (1)]. In this case, however, the reaction required a rather long time and an increased amount of TBSOTf to go to completion. Cyclic silyl ketene acetal **9c** reacted with nitronate **5a** under the same conditions that were used for unsubstituted π-nucleophile **9a** to afford adduct **13** in excellent overall yield but with low diastereoselectivity [1.3:1 *dr*; Scheme 7, Eq. (2)]. With ambident silyl ketene acetal **9d**, the addition preferably occurred at the less sterically hindered terminal nucleophilic center to give adduct (*E*)-**14** along with the formation of an insignificant amount of alternative adduct **15** as a single isomer of unassigned configuration. The total yield of **14** + **15** adducts was fairly high [Scheme 7, Eq. (3)].

As shown in our preliminary experiments, the range of π-nucleophiles active toward nitronates **5** under conditions of electrophilic catalysis is not confined to silyl ketene acetals. However, the use of less-reactive nucleophiles requires much more effort to optimize the synthesis procedure; the



Scheme 6. Selectivity in coupling of 1,4-dinitrobutane (**1l**) with silyl ketene acetal **9a**.



Scheme 7. C–C coupling of nitronate **5a** with silyl ketene acetals **9b**–**d**.

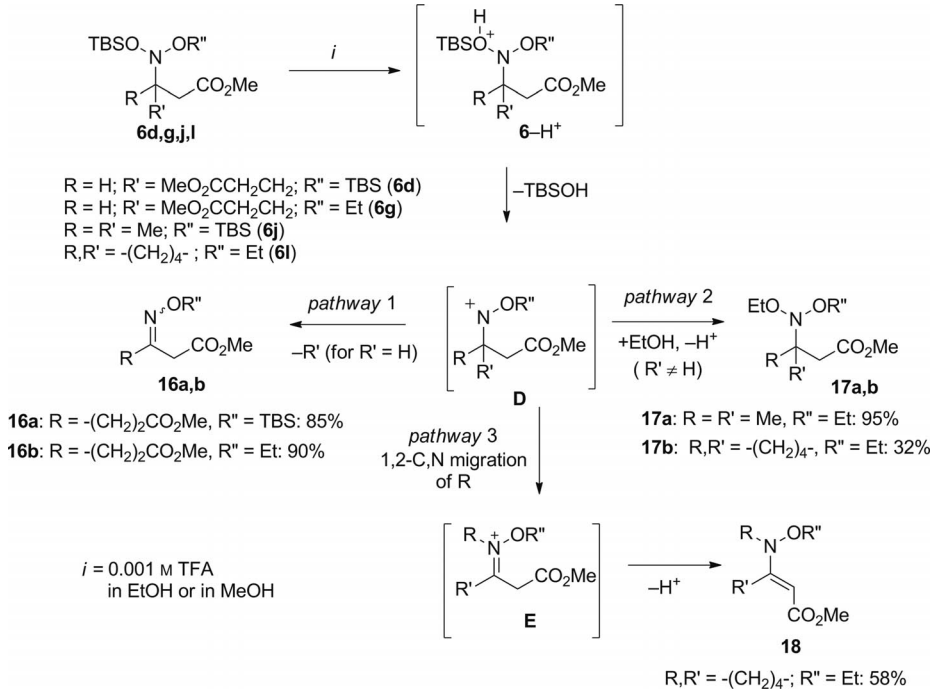
results of these studies will be reported in our next publications.

The structures of nitroso acetals **6a**–**q** and **12**–**15** were unequivocally confirmed by NMR spectroscopy (^{1}H, ^{13}C, and ^{29}Si nuclei), and elemental analysis was used to assess product purity. Due to the well-known slow nitrogen inversion in nitroso acetals,[19] the nitrogen atom of the N(OEt)(OTBS) moiety forms a stereocenter in adducts **6e**–**h** and **6j**–**m**; in addition, the TBSO groups of the N(OTBS)$_2$ moiety are diastereotopic in adducts **6a**–**d**, **6o**–**q**, and **12**–**15**, which is clearly observable in their NMR spectra.

Transformations of Nitroso Acetals 6

From the aforesaid, it is evident that AN **1** are convenient precursors for nitroso acetals **6**. In contrast to the well-known chemistry of acetals, studies of the chemistry of nitroso acetals is rather fragmented (the main reviews on nitroso acetals are given in ref.[19]). Here we report some reactions of nitroso acetals **6** that may be helpful to understand their properties somewhat better. However, this study is made in an illustrative manner only.

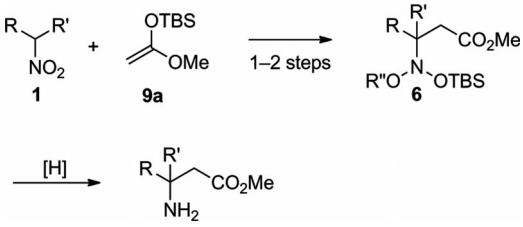
The acid sensitivity of nitroso acetals is well known.[19a] In full keeping with this, even very dilute TFA solutions in MeOH or EtOH cause the conversion of **6d**, **6g**, **6j**, and **6l** into products **16**–**18**, whose formation is likely to occur via nitrenium cation intermediates **D** (Scheme 8). If one of the R and R′ radicals in these cations is a proton, they are stabilized through the elimination of the latter (possibly through initial 1,2-C,N hydride shift) to form oximes **16a** and **16b** (Scheme 8, pathway 1). If nitroso acetals **6** are de-



Scheme 8. Acid-catalyzed transformations of nitroso acetals **6**.

rived from secondary AN **1**, that is R = R′ ≠ H, cations **D** are stabilized by alternative pathways, that is, either through addition of the solvent (EtOH) followed by deprotonation (products **17a** and **17b**; Scheme 8, pathway 2), or by 1,2-C,N shift of radical R with generation of cations **E** followed by elimination of the flexible proton from the carbon atom attached to the CO_2Me moiety (product **18**; Scheme 8, pathway 3). Noticeably, nitroso acetals **6d** and **6j** containing the N(OEt)(OTBS) moiety underwent exclusive elimination of the more sterically hindered TBSO group to form **16b** and **18**, respectively.

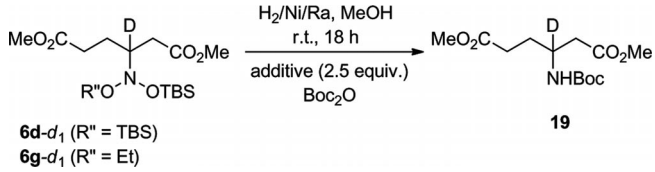
Among the reactions of nitroso acetals **6**, the selective reduction of the O–N–O fragment into the amino function, commonly effected by hydrogenation over Raney nickel, seems to be of the highest synthetic value.[19,20] In this context, the reduction of adducts **6** can be considered as a final step in the convenient synthetic route to unnatural β-amino acids utilizing available AN **1** as precursors (Scheme 9).



Scheme 9. A new strategy for the synthesis of unnatural β-amino acids from AN **1**.

If R ≠ R′, the **1**+**9** coupling results in adducts **6** with an asymmetric center at the carbon atom attached to the nitroso acetal nitrogen atom. When using primary AN **1** (R′ = H), this asymmetric center may be lost in the course of the reduction of the corresponding nitroso acetals **6** due to the ease of formation of oxime derivatives **16** (Scheme 8), whose reduction would ultimately lead to the same product as the direct reduction of **6**. To probe the behavior of the asymmetric center during the reduction of the nitroso acetal fragment, we performed Raney nickel catalyzed hydrogenation of deuterium-labeled nitroso acetals **6d**-d_1 and **6g**-d_1 (Scheme 10, Table 3).

The data of Scheme 10 and Table 3 present experimental evidence that the stereoselective hydrogenation of nitroso acetals **6** is realizable. Of note, hydrogenation product **19** can be formed with complete retention of the deuterium label. Surprisingly, deuterium retention and, probably, the



Scheme 10. Hydrogenation of nitrosoacetals **6d**-d_1 and **6g**-d_1 on Ni/Ra.

mechanism of hydrogenation depend on the nature of the oxygen substituents in the nitroso acetal moiety.[21] Specifically, successful hydrogenation of more sterically hindered $N(OTBS)_2$ group requires the presence of KF or KHF_2, which provides essentially complete retention of the deuterium label and an excellent yield of target amino derivative **19** (Table 3, Entries 2 and 3). At the same time, the N(OEt)(OTBS) moiety is smoothly hydrogenated without any additives, yet with an 80% loss of the deuterium label (Table 3, Entry 4). In the presence of KHF_2, hydrogenation also proceeds with a considerable (although lesser) loss of the deuterium label and affords product **19** in good yield, whereas the use of KF, on the contrary, results in almost complete retention of the deuterium label but a low yield of **19** (Table 3, Entries 5 and 6). A partial loss of deuterium in the hydrogenation of **6g**-d_1 (Table 3, Entries 4 and 6) implies a complicated mechanism for this reaction. The above hydrogenation is likely to follow two (or more) competitive pathways with one involving C–D bond cleavage and another retaining it unchanged. Such a result is of particular interest and warrants further investigation, as the hydrogenation of the nitroso acetal moiety is commonly considered to proceed while keeping the adjacent carbon stereocenter intact.[19b,20]

Conclusions

The conversion of AN **1** into the corresponding silyl or alkyl nitronates **5** followed by their C–C coupling with silyl ketene acetals **9** (π-nucleophiles) under conditions of electrophilic catalysis with TBSOTf to yield functionalized nitroso acetals **6** was realized and proposed as a new general strategy for reactivity umpolung of AN **1**. Tentative interpretation of the results on the catalytic hydrogenation of nitroso acetals **6** and their interaction with dilute alcohol solutions of TFA are suggested. Nitroso acetals **6** were

Table 3. Hydrogenation of labeled adducts **6d**-d_1 and **6g**-d_1.

Entry	Adduct (% isotopic purity)[a]	Additive (2.5 equiv.)	Yield of **19** [%][b]	Isotopic purity of **19**[a] [%]	Deuterium retention in **19** [%]
1	**6d**-d_1, R″ = TBS (88)	none	n.r.[c]	–	–
2	**6d**-d_1, R″ = TBS (88)	KF	83	87	99
3	**6d**-d_1, R″ = TBS (88)	KHF_2	95	84	95
4	**6g**-d_1, R″ = Et (84)	none	85	15	18
5	**6g**-d_1, R″ = Et (84)	KF	35	81	96
6	**6g**-d_1, R″ = Et (84)	KHF_2	81	44	52

[a] Determined by NMR spectroscopy. [b] Hydrogenation of nonlabeled compounds **6d** and **6g** under tested conditions leads to nonlabeled aminoester **19** in essentially the same yields. [c] No reaction product was determined by TLC.

shown to be convenient precursors of unnatural β-amino acids. Alcoholysis of nitroso acetals **6** bearing the N(OEt)-(OTBS) moiety with C1–C2 alcohols under acid catalysis proceeds with selective N–OTBS bond cleavage.

Experimental Section

General Remarks: 1D and 2D NMR spectra were recorded at room temperature in $CDCl_3$, unless otherwise stated. The chemical shifts (^1H, ^{13}C, and ^{29}Si) are given in ppm (δ scale) relative to the solvent residual signals.[22] All 1D and 2D NMR experiments were performed by using standard techniques and Bruker NMR software. The ratios of the stereoisomers were derived from the relative integral intensities of the characteristic signals in the ^1H NMR spectra. Elemental analyses were performed by the Analytical Laboratory of the N. D. Zelinsky Institute of Organic Chemistry. Melting points were determined with a Kofler apparatus. Reactions with TBSOTf were performed under an atmosphere of dry Ar. CH_2Cl_2 was distilled prior to use from CaH_2. Triethylamine was distilled from KOH under an atmosphere of Ar. Ethyl acetate and hexane for column chromatography and extractions were distilled without additional agents. Merck silica gel 60 (0.040–0.063 mm) was used for column chromatography. For the successful isolation of some products, silica gel was deactivated with triethylamine.[23] Aluminum TLC plates with silica gel QF 254 (Merck) were used for analytical thin-layer chromatography; the eluents used for analytical TLC are specified in parentheses after the R_f values. Visualization for analytical TLC: UV (254 nm) and treatment with 4-$MeOC_6H_4$-CHO (AnCHO), phosphomolybdic acid (PMA), or ninhydrin (NHN) solutions followed by heating. "Brine" refers to saturated aqueous solution of sodium chloride.

Conventional procedures were applied for the synthesis and isolation of silyl nitronates **5a**–**d** and **5i**[14] and silyl ketene acetals **9a**,[24] **9b**,[25] **9c**,[26] and **9d**.[27] For isolation of potassium nitronates, a known procedure[15] was applied with a minor modification: solution of KO*t*Bu in THF was used instead of methanolic NaOH. Labeled adducts **6d** and **6g** were obtained from methyl γ,γ-dideutero-γ-nitropentanoate by the same procedure as for respective nonlabeled compounds.

General Procedures

Procedure A

C–C Coupling of Isolated Silyl Nitronates 5a–d with Silyl Ketene Acetals 9: To a stirred solution of silyl nitronate **5a**–**d** (1.0 equiv.) and silyl ketene acetal **9** (1.10 equiv.) in CH_2Cl_2 (2.0–3.0 mL/mmol of **5**) at –94 °C was added TBSOTf (0.1–1.0 equiv.), and the reaction mixture was stirred at –94 °C for the indicated time. The mixture was then quenched at –94 °C by the successive addition of Et_3N (2 equiv. per equiv. of TBSOTf) and methanol (1.5 equiv. per equiv. of TBSOTf). After additional stirring at –94 °C for 5 min, hexane (4 mL per mmol of nitronate **5**) and water (2 mL per mmol of nitronate **5**) were added, and the reaction mixture was warmed to room temperature. The aqueous layer was separated and washed with hexane (2 × 5 mL per mmol of nitronate **5**), and the combined organic layers were washed with brine (one-third of the combined organic layers volume) and dried with anhydrous sodium sulfate. After evaporation of the solvents, the crude products were purified by gradient column chromatography (ethyl acetate/hexane, from 1:30 to 1:5 by volume).

Procedure B

C–C Coupling of AN 1 (via Silyl Nitronates 5) with Silyl Ketene Acetal 9a: To a stirred solution of AN **1** (1.0 equiv.) and silyl ketene acetal **9a** (1.1 equiv.) in CH_2Cl_2 (2.5–3.3 mL/mmol of **1**) at 0 °C was added DBU (1.0 equiv.), and the reaction mixture was stirred for an additional 10 min. Then, the reaction mixture was cooled to –94 °C, and TBSOTf (1.10 equiv.) was added with stirring. The reaction mixture was stirred at –94 °C for 45–80 min. (In preparation of adduct **6s** from AN **1m**, a twofold amount of other reagents was used; for details, see Scheme 5, Table 2 and the respective text in the Supporting Information), quenched at –94 °C by the successive addition of Et_3N (0.25 equiv.) and methanol (0.15 equiv.). Further operations are the same as in Procedure A.

Procedure C

C–C Coupling of AN 1 (via Silyl Nitronates 5) with Silyl Ketene Acetal 9a: To a stirred solution of AN **1** (1.0 equiv.), triethylamine (1.5 equiv.), and silyl ketene acetal **9a** (1.1 equiv.) in CH_2Cl_2 (3.0 mL/mmol of **1**) at –50 °C was added TBSOTf (1.20 equiv.), and the reaction mixture was kept at –25 °C (freezer) for 18 h, cooled to –50 °C, and methanol (1.5 equiv.) was added with stirring. Further operations are the same as in Procedure A.

Procedure D

C–C Coupling of Alkyl Nitronates 5 with Silyl Ketene Acetal 9a: To a stirred solution of $Et_3O^+BF_4^-$ (1.0 equiv.) in CH_2Cl_2 (2 mL/mmol of **1**) was added the potassium salt of AN **1** (1.03 equiv.) at –78 °C, and the resulting slurry was stirred at –78 °C for 45–150 min (see the Supporting Information for details; for the K salt of AN **1e**, the reverse order of addition was applied.) Then, silyl ketene acetal **9a** (1.1 equiv.) and TBSOTf (0.1–0.2 equiv.) were added successively at –78 °C with stirring. The resulting mixture was kept at –78 °C for 1–18 h, quenched at –94 °C by the successive addition of Et_3N (0.4 equiv.) and methanol (0.3 equiv.). Further operations are the same as in Procedure A, except silica gel deactivated with triethylamine was used for column chromatography.

Procedure E

TFA-Catalyzed Transformations of Nitroso Acetals 6d, 6g, 6j, and 6l (Scheme 8): To a stirred solution of nitroso acetal **6** (0.60 mmol) in the indicated alcohol (EtOH or MeOH, 2.9 mL) was added a freshly prepared solution (0.10 mL) of TFA (23 μL, 34 mg, 0.30 mmol) in the same alcohol (10.0 mL) at room temperature to achieve a 0.20 M solution of adduct in 0.0010 M alcoholic solution of TFA. The resulting reaction mixture was stirred for 16 h (for **6i** and **6m**) or 3 d (for **6d** and **6g**). Then, Et_3N (4.0 μL, 2.9 mg, 29 μmol, 9.6 equiv. to TFA) was added with stirring. The reaction mixture was concentrated, and the residue was purified by short-path distillation or column chromatography to afford target products **16**–**18**.

Procedure F

Hydrogenation of Nitroso Acetals 6d-d_1 and 6g-d_1 (Scheme 10, Table 3): Adduct **6d** or **6g** (0.4 mmol) was hydrogenated over Raney nickel in MeOH (≈200 mg, 2.0 mL) under an atmosphere of hydrogen (25 bar) at room temperature with stirring in the presence of Boc_2O (0.15 mL, 0.15 g, 0.7 mmol) and, in some cases, with indicated promoter (Table 3). After 18 h, the catalyst was filtered off, washed twice with methanol (≈4 mL), and the combined filtrates were concentrated. The residue was treated with ethyl acetate (5 mL), the inorganic precipitate was filtered off, and the filtrate was evaporated. Crude products were purified by gradient column chromatography (ethyl acetate/hexane, from 1:3 to 1:1 by volume).

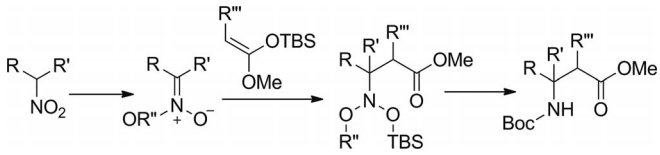
Supporting Information (see footnote on the first page of this article): Detailed experimental procedures for the synthesis of nitroso acetals **6**, **12**–**15**, and **17**; compounds **16**, **18**, and **19**; and their characterization, including NMR spectra.

Acknowledgments

This work was performed with the financial support of the Russian Foundation for Basic Research (Grants 12-03-00278-a, 05-03-08175, and 03-03-04001), Deutsche Forschungsgemeinschaft (MA 673/19), and the Federal program "Scientific and Educational Personnel of Innovative Russia" (Project 02.740.11.0258).

[1] For synthesis and reactivity of AN, see: N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.
[2] D. Seebach, *Angew. Chem.* **1979**, *91*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239–258.
[3] a) For a recent review on the Nef reaction, see: R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047; b) for the mechanism of the Nef reaction, see: N. Kornblum, R. A. Brown, *J. Am. Chem. Soc.* **1965**, *87*, 1742–1747.
[4] It is noteworthy that the Nef reaction as a tool for reactivity inversion initially was considered with acyl synthon umpolung through alkylation of AN followed by the Nef reaction. This consideration reveals AN as equivalents of the acyl anion synthon; see, for example, the review: H. W. Pinnick, *Org. React.* **1990**, *38*, 655–792. To the best of our knowledge, the Nef reaction as a route for umpolung of AN themselves was considered for the first time in the paper: J. E. McMurry, J. Melton, *J. Org. Chem.* **1973**, *38*, 4367–4373.
[5] a) S. L. Ioffe in *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis* (Ed.: H. Feuer), John Wiley & Sons, Inc., Hoboken, **2007**, p. 626; b) M. Takamoto, H. Kurouchi, Yu. Otani, T. Ohwada, *Synthesis* **2009**, 4129–4136.
[6] Unlike the tautomerization between keto and enol forms, tautomerization between nitro and *aci* forms *is not* acid catalyzed in dilute aqueous acids. Moreover, it is even somewhat inhibited under acidic conditions due to the lowered activity of water, which acts as a base in tautomerization via the nitronate anion, see J. T. Edward, P. H. Tremaine, *Can. J. Chem.* **1971**, *49*, 3493–3501. It should be noted, however, that previously reported examples of protic acid-assisted AN umpolung according to Scheme 1(see ref.[5b,8,9]) were realized in non-basic solvents (such as dichloromethane or trifluoroacetic acid) or without solvent at all, and under these conditions acid catalysis for **1** to **2** tautomerization is plausible. Furthermore, *aci*-nitro forms may be generated from isolated nitronate salts by the action of acid, as kinetic protonation of anion **A** takes place at the oxygen atom.
[7] For the estimation of the nucleophilicity of anions **A** see: T. Bug, T. Lemek, H. Mayr, *J. Org. Chem.* **2004**, *69*, 7565–7576.
[8] a) T. Ohwada, N. Yamagata, K. Shudo, *J. Am. Chem. Soc.* **1991**, *113*, 1364–1373; b) C. Berrier, R. Brahmi, H. Carreyre, J.-M. Coustard, J.-C. Jacquesy, *Tetrahedron Lett.* **1989**, *30*, 5763–5766; c) J.-M. Coustard, J.-C. Jacquesy, B. Violeau, *Tetrahedron Lett.* **1991**, *32*, 3075–3078; d) J.-M. Coustard, J.-C. Jacquesy, B. Violeau, *Tetrahedron Lett.* **1992**, *33*, 8085–8086.
[9] Among the most recent improvements of the originally proposed procedure (see ref.[8]) are the modified procedure for treating **B** with arenes (see ref.[5b]), as well as an alternative method to activate cations **B** on the basis of the replacement of both their O–H protons by more electronegative polyphosphoric acid residues $\{[MeCH=N(OPPA)_2]^+\}$, see A. V. Aksenov, N. A. Aksenov, O. N. Nadein, I. V. Aksenova, *Synlett* **2010**, 2628–2630.
[10] It cannot be excluded that the active species in the above-discussed C–C coupling reactions is the N-hydroxynitrilium ion $[R–C{\equiv}NOH]^+$ formed after dehydration of cations **B** rather than cations **B** themselves. Anyhow, that was the conclusion of French researchers (see ref.[8c,8d]). This is additionally supported by the fact that, as yet, the C–C coupling with π-nucleophiles was realized successfully with cations **B** derived only from primary AN.
[11] Only fragmentary literature data can be interpreted as examples of interaction of various nitronates with nucleophiles. For reactions of nitronates with organometallic compounds, see: a) S. L. Ioffe, O. P. Shitov, I. E. Chlenov, A. A. Medvedeva, V. A. Tartakovsky, S. S. Novikov, *Russ. Chem. Bull. Div. Chem. Sci.* **1967**, 2522–2526 (in Russian); S. L. Ioffe, O. P. Shitov, I. E. Chlenov, A. A. Medvedeva, V. A. Tartakovsky, S. S. Novikov, *Russ. Chem. Bull. Div. Chem. Sci.* **1967**, 2399–2402 (in English) b) T. Fujisawa, Yo. Kurita, T. Sato, *Chem. Lett.* **1983**, 1537–1540; c) E. W. Colvin, A. D. Robertson, D. Seebach, A. K. Beck, *J. Chem. Soc., Chem. Commun.* **1981**, 952–953; d) W. M. David, S. M. Kerwin, *J. Am. Chem. Soc.* **1997**, *119*, 1464–1465; with isonitriles: e) P. Dumestre, L. El Kaim, A. Gregoire, *Chem. Commun.* **1999**, 775–776; f) P. Dumestre, L. El Kaim, *Tetrahedron Lett.* **1999**, *40*, 7985–7986.
[12] a) V. O. Smirnov, S. L. Ioffe, A. A. Tishkov, Yu. A. Khomutova, I. D. Nesterov, M. Yu. Antipin, W. A. Smit, V. A. Tartakovsky, *J. Org. Chem.* **2004**, *69*, 8485–8488; b) Yu. A. Khomutova, V. O. Smirnov, H. Mayr, S. L. Ioffe, *J. Org. Chem.* **2007**, *72*, 9134–9140; c) V. O. Smirnov, A. S. Sidorenkov, Yu. A. Khomutova, S. L. Ioffe, V. A. Tartakovsky, *Eur. J. Org. Chem.* **2009**, 3066–3074.
[13] For the general reactivity scale, see: H. Mayr, B. Kemp, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77.
[14] For the silylation of AN, see ref.[5a] (pp. 469–484) and literature therein.
[15] N. Kornblum, R. A. Brown, *J. Am. Chem. Soc.* **1964**, *86*, 2681–2687.
[16] Yu. A. Khomutova, A. A. Mikhaylov, S. L. Ioffe, unpublished data.
[17] The replacement of the C-3 proton by the Me group in six-membered cyclic nitronates **7** also resulted in a sharp decrease in the rate of C–C coupling with π-nucleophiles (see ref.[12b]). In the near future, we plan to thoroughly investigate the C–C coupling mechanism of acyclic nitronates **5** with π-nucleophiles by using experimental and computational methods.
[18] J. F. Klebe, *J. Am. Chem. Soc.* **1964**, *86*, 3399–3400.
[19] For reviews on nitroso acetals, see: a) V. F. Rudchenko, *Chem. Rev.* **1993**, *93*, 725–739; b) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137–166.
[20] The reduction of bicyclic nitroso acetals into amines is discussed in: a) S. E. Denmark, A. Thorarensen, *J. Org. Chem.* **1994**, *59*, 5672–5680; b) S. E. Denmark, V. Guagnano, J. Vaugeois, *Can. J. Chem.* **2001**, *79*, 1606–1616.
[21] It should be emphasized that although retention of the deuterium label in the reductive process points on the retained configuration of a stereocenter at the carbon atom attached to the nitroso acetal nitrogen atom, its loss does not mean the loss of configuration of this stereocenter.
[22] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512–7515.
[23] J. A. Marshall, C. A. Sehon, *Organic Syntheses*, Wiley, New York, **2004**, Collect. Vol. 10, 599; J. A. Marshall, C. A. Sehon, *Org. Synth.* **1999**, *76*, 263.
[24] Y. Kita, J. Segawa, J. Haruta, H. Yasuda, Y. Tamura, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1099–1104.
[25] H. Emde, D. Domsch, H. Feger, U. Frick, A. Goetz, H. H. Hergott, K. Hofmann, W. Kober, K. Kraegeloh, T. Oesterle, W. Steppan, W. West, G. Simchen, *Synthesis* **1982**, 1–26.
[26] C. H. Heathcock, S. K. Davidsen, K. T. Hug, L. A. Flippin, *J. Org. Chem.* **1986**, *51*, 3027–3037.
[27] R. V. Hoffman, H. O. Kim, *J. Org. Chem.* **1991**, *56*, 1014–1019.

Received: February 28, 2012
Published Online: ■



A very simple approach for umpolung of the conventional reactivity of nitroalkanes through their activation by silylation offers a convenient and efficient strategy for their C–C coupling with π-nucleophiles. Both primary (8 examples) and secondary (4 examples) nitroalkanes may be involved in coupling with silyl ketene acetals (4 examples) to provide a concise route to substituted β-amino acids.

Keywords: Umpolung / C–C coupling / Nitro compounds / Hydrogenation / Amino acids

