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Aromatic Allylation via Diazotization: Variation of the Allylic Moiety and a Short Route to a Benzazepine Derivative

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A continued study of the recently discovered diazotizative allylation (DiazAll) reaction of aniline derivatives is reported. Several allyl reagents, commonly used in radical allylation reactions, were evaluated, and some of these reagents resulted in allylation when used in the DiazAll reaction. The best result was obtained with allyl bromide. Substituted allylic bromides gave the corresponding allyl aromatic compounds in poor to excellent yields. In comparison with an established method for aromatic allylation, the DiazAll reaction performed well and was superior when a more complex allylic bromide was used. Finally, a new allylation−bromocyclization reaction was demonstrated and used in the synthesis of a known inhibitor of phenylethanolamine *N*-methyltransferase (PNMT), an enzyme involved in the biosynthesis of adrenaline.

Introduction

Free-radical allylations provide some of the mildest methods for the introduction of an allyl functionality in organic compounds, although most of the reported applications involve alkyl radicals.[1−3] Recently, we reported a novel method for the synthesis of allyl aromatic compounds via diazotization of arylamines with *tert*-butyl nitrite in acetonitrile and allyl bromide.[4,5] For simplicity, we call the reaction DiazAll (diazotizative allylation). It was found that a large number of different substituents were tolerated due to the mild reaction conditions. A convenient experimental procedure avoiding metal-containing reagents and catalysts together with a demonstrated insensitivity toward moisture, air, type of solvent, and short reaction times made it useful for multigram synthesis. The mechanism probably involves a phenyl radical intermediate attacking allyl bromide as seen in Scheme 1. In our previous paper, we investigated structural changes in the aromatic moiety. We now continue our study of the scope and limitation of the DiazAll reaction and focus on the structural variation of the allylic moiety. 3,5-Dinitroaniline was chosen as a standard starting material because of the possibility to use the corresponding allylated products in the synthesis of iodinated X-ray contrast agents.[6] When other aniline derivatives are used, it is possible to access biologically relevant substances, which will be demonstrated in this paper.

Results and Discussion

The experimental procedure of the DiazAll reaction is very convenient and robust in comparison with most other aromatic allylation reactions that usually require sensitive reagents. However, dry reaction conditions and inert atmosphere were employed in the present study, but as reported previously, the reactions could be performed without these precautions and still give almost as good yields. The arylamine (solid) was added in portions to an acetonitrile solution of *tert*-butyl nitrite and the appropriate allylic component during approximately 20 min, if otherwise not stated, at a temperature ensuring a gentle formation of nitrogen gas. **WARNING! A too rapid addition of the arylamine to the reaction mixture may result in an uncontrolled evolution of heat and gas.** A reaction time of 60 min was employed although in several cases complete conversion was achieved already ca. 5−10 min after the final addition of the arylamines.

A number of different allylating reagents have been reported in radical allylation reactions, the most common reagents being allyltributyltin.[1,3] However, the potential toxicity of organotin compounds and the difficulties in removal of tin byproducts have turned the focus toward the development of alternative reagents such as sulfides, sulfoxides, sulfones, silanes, and halides.[3] In the ongoing study of the DiazAll reaction, we were interested to see which of these functionalities were best suited under the present reaction conditions.

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SCHEME 1. Suggested Mechanism of the DiazAll Reaction

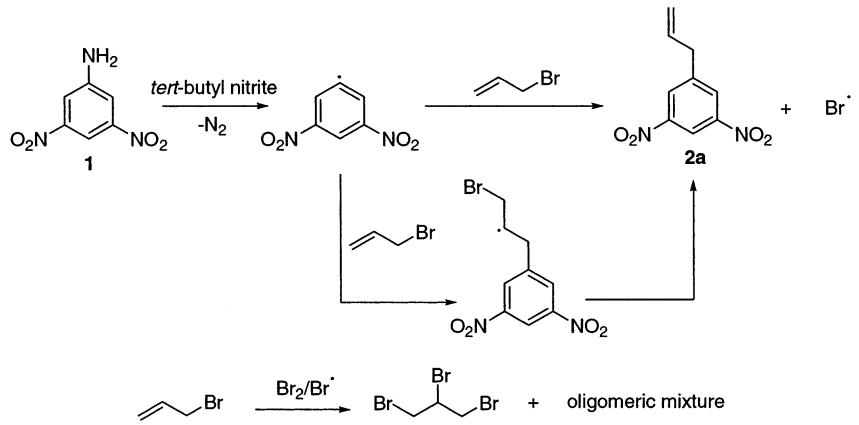
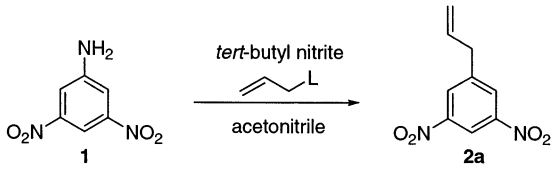


TABLE 1. Investigation of Different Leaving Groups in the DiazAll Reaction with 3,5-Dinitroaniline[a]



L	yield (%)	L	yield (%)
Br[b]	74	SMe	28
I[c]	18	S(allyl)	34
SO_2Ph	51	SPh	61
SO_2CF_3	29	$SiMe_3$	25

[a] A general procedure (internal standard) was used as described in the Experimental Section. [b] Selectivity: allyl-3,5-dinitrobenzene/3,5-dinitrobromobenzene = 25:1.[4] [c] Selectivity: allyl-3,5-dinitrobenzene/3,5-dinitroiodobenzene = 1:4.3.

As seen in Table 1, allyl bromide gave the highest yield of the allylated product, although both allyl phenyl sulfide and allyl phenyl sulfone gave fair yields. Allyl trifluoromethyl sulfones[7] and allyltrimethylsilane[3] have been reported to give high yields in allylation of alkyl radicals. However, using these reagents in this DiazAll reaction gave only poor yields of **2a**. Moreover, in accordance with an earlier paper,[8] using allyl iodide in the radical allylation reaction mainly resulted in iodination and only 18% of **2a**. This is probably due to a too homolytically weak carbon−iodide bond which favors halogen abstraction over addition to the double bond. On the other hand, the use of allyl chloride did not result in any allylation due to a too strong carbon−chlorine bond toward homolytical cleavage. Surprisingly, allyltributyltin did not give the allylated product despite numerous reports of successful radical allylations using this reagent.[3,9] Only the starting material **1** was recovered at the end of the experiments, although temperature, concentration, and type of solvent were varied. Similarly, allyltris(trimethylsilyl)silane, allyltriisopropylsilane, allyltriphenyltin, and allyldiphenylphosphine were nonproductive. A large excess of the allylic reagents is used the DiazAll reaction. Hence, one plausible reason for the failure could be that the highly nonpolar character of these reagents may influence the polarity of the reaction mixture thus preventing the initial, presumably, ionic reaction between **1** and *tert*-butyl nitrite.

Since allyl bromide gave the best yield, we continued to study the effects of structural variation in the allylic moiety using allylic bromides as preferred reagents. Thus, a number of different substituted allyl aromatic compounds were synthesized in poor to excellent yields (see Table 2). The resulting allyl derivatives and, in particular, vinylic, allylic, and homoallylic bromides and allyl acetates are obvious starting materials for the synthesis of more complex organic molecules. In ionic reactions involving highly reactive reagents there is often a need for protection of sensitive functional groups. However, in radical reactions, this can be avoided both because O−H and N−H bonds are resistant toward homolytical cleavage and the absence of the typical nucleophilic behavior of anionic species. This was exemplified by the one-step synthesis of acrylic acid **2f** (Table 2) without the need for protection of the carboxylic acid moiety. Previously reported methods of the synthesis of 2-benzylacrylic acid derivatives involves at least two synthetic steps.[10,11] This type of compounds are important in the synthesis of pseudopeptides of pharmacological interest, e.g., inhibitors of neutral endopeptidase (NEP), tumor necrosis factor (TNF), metalloprotease (MMP), and angiotensin-converting enzymes (ACE).[12−15]

The yields dropped significantly when allyl bromides with internal double bonds were used (Table 2, **2h** and **2i**). In these cases, the amount of the byproduct 3,5-dinitrobromobenzene increased as well. There seems to be ambiguous conclusions concerning the sensitivity of

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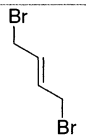
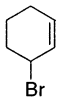
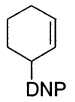
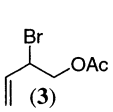
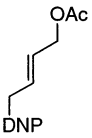
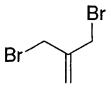
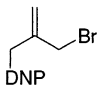
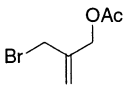
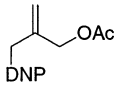
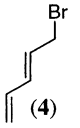
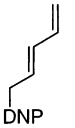
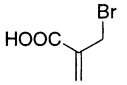
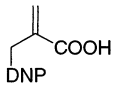
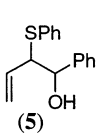
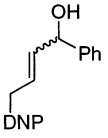
TABLE 2. Results of the Allylation of 3,5-Dinitroaniline on a 3 mmol Scale (DNP = 3,5-Dinitrophenyl)

Allylbromide	Product	Temp(°C)[a]	Yield(%)[b]	Allylbromide	Product	Temp(°C)[a]	Yield(%)[b]
		11-13/23	81(**2a**)[c]			20-22/22	28(**2h**)
		38-42/24	75(**2b**)			13-16/23	28(**2i**)
		11-15/22	93(**2c**)			40-45/26	43[e](**2j**)
		40-42/40	71(**2d**)			22-26/23	23(**2k**)
		20-22/22	75(**2e**)[d]			15-20/20	0
		15-20/22	60(**2f**)			25-30/40	0
		42-45/44	58(**2g**)				

[a] Temperature during the addition of 3,5-dinitroaniline/temperature after the addition. [b] Isolated yields if otherwise not stated. [c] See ref 4. [d] 2.0 mmol scale. [e] 1.0 mmol scale. The yield was determined by ^{1}H NMR spectroscopy using toluene as internal standard. 7% of the corresponding cis isomer of **2j** was also formed. The isolated yield of **2j** was 35%.

radical reactions toward sterical hindrance. For instance, Keck et al. found that crotyltributyltin/(t-BuO)$_2$ did not give the expected allylation of an alkyl bromide but instead resulted in reductive dehalogenation.[1] However, Ryu et al. later demonstrated a successful allylation using this particular reagent, although the yields were somewhat lower compared to allyltributyltin.[16] Also Fuchs et al. failed to use sterically hindered allylic triflones for allylic substitution of C−H positions.[7] The examples shown (Table 2, **2h** and **2i**) are, to our knowledge, the first cases of allylation of phenyl radicals using sterically hindered allyl derivatives.

We also wanted to use 1-substituted allyl bromides in the DiazAll reaction. However, they are often difficult to synthesize due to the rapid isomerization to the more stable 3-substituted allylic bromides as demonstrated by the equilibrium at room temperature between 3-bromobutene and crotyl bromide favoring the latter (15:85).[17] Fortunately, it was possible to synthesize isomerically pure allylic bromide **3** from butadiene monoxide.[18,19] Using **3** in the DiazAll reaction together with 1 equiv of pyridine gave 43% of **2j** according to ^{1}H NMR analysis (Table 2). The yield of **2j** dropped significantly if pyridine was excluded.[20] Compared to the nonsubstituted or 2-substituted allylic bromides a larger amount of 3,5-dinitrobromobenzene was formed when **3** was employed as the allylic component. Aryl radical attack on the bromine atom of **3** would possibly be aided by anchimeric

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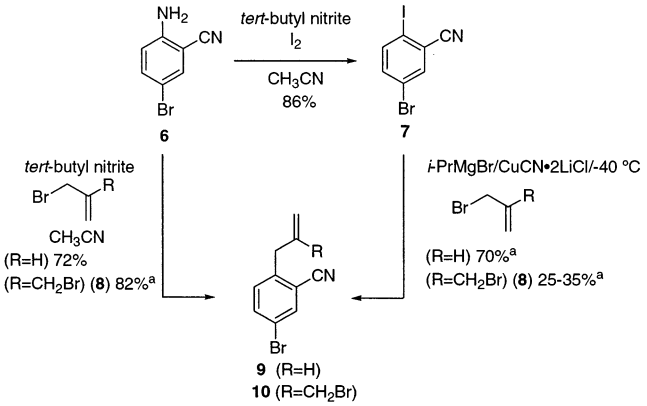
(20) Using **3** in the DiazAll reaction gave according to ^{1}H NMR analysis not only the expected products **2j**, the corresponding cis isomer of **2j**, and 3,5-dinitrobromobenzene but also 3,5-dinitro-1-(1-acetoxymethyl-2-propenyl)benzene in considerable amounts (ratio 1:0.15:1:1). We also noted that all of **3** had isomerized to 4-bromobut-2-enyl acetate during the reaction. However, by adding 1 equiv of pyridine to the reaction mixture before the addition of **1**, the ratio was changed in favor of **2j** (ratio 2:0.3:1:0.3). The ratio between **2j** and the corresponding cis isomer of **2j** was the same in both procedures. Apparently, the added pyridine suppresses the rearrangement of **3** to 4-bromo-but-2-enyl acetate, which was confirmed by ^{1}H NMR analysis of the crude product.

SCHEME 2. Comparison between the DiazAll Reaction and the Halide−Magnesium Exchange Reaction



[a] The yields were determined by ^{1}H NMR spectroscopy using toluene as internal standard.

assistance from the acetoxy group, thus decreasing the carbon−bromine bond strength.

Alkyl radicals have been reported to react with triphenylprop-2-ynylstannane to give terminal allens.[21] In a similar fashion, propargyl bromide was used in the DiazAll reaction, which gave allene **2k**, although the yield was low (Table 2).

Some olefins could not be used in the DiazAll reaction (Table 2). The dienyl bromide **4**, which was synthesized from penta-1,4-dien-3-ol using PBr_3,[22] did not give the expected product. This is in contrast to the tributyltin analogue of **4**, which was reported to react with alkyl radicals to give the dienyl products.[23−25] One could speculate that even if the diene is formed in the DiazAll reaction this type of compounds are often quite reactive and could continue to react with the bromine/bromine radical formed in the reaction.

Unfortunately, sulfide **5** gave a large number of reaction products which were not further analyzed. This was somewhat unexpected since allyl phenyl sulfide was successfully used in the DiazAll reaction as seen in Table 1.

In a related project, we needed **10** in gram quantities (Scheme 2). Several methods were considered, but we decided to use the halide−magnesium exchange reaction, which has proven to give good to excellent yields of allyl aromatic compounds.[26]

The starting material **7** was synthesized utilizing a modification of the method reported by Friedman et al.; we replaced CCl_4 with acetonitrile or some other water miscible solvent.[27]

However, the result of the magnesium exchange reaction was disappointing. Even though 5 equiv of **8** was used, the yield of **10** never exceeded 35% even when a number of parameters were varied (temperature, amount of CuCN, concentration, and the use of slow addition of the in situ generated arylmagnesium species to **8**). The product was always accompanied by the symmetrical bisarylated byproduct and other unidentified compounds. When allyl bromide itself was used, the result was comparable to those reported in the literature for similar systems. We therefore decided to investigate the possibility of using the DiazAll reaction in the synthesis of **10**. In contrast to the previous method, the yield in fact increased somewhat when **8** was employed compared to the case in which allyl bromide was used (from 72% to 82%). Although 10 equiv of **8** was added, five of these could be recovered and reused. Comparing these two methods clearly shows the potential of the DiazAll reaction especially when using more complex allyl bromides, and the good results may even justify the need of an excess of the allylic bromides.

The cyano group of aromatic nitriles is an interesting handle for further derivatization, e.g., to generate heterocycles such as tetrazoles. This motivated the synthesis of the tricylic fused tetrazole **13** belonging to a group of compounds which have shown affinity for GABA-receptors (Scheme 3).[28] The tetrazole **11** was conveniently synthesized in 84% yield from the corresponding commercially available anthranilonitrile.[29,30] We could imagine that after an initial allylation of **11** with **8** the product **12** would be ready for cyclization, which might take place either in situ or in a separate synthetic step. The allylation took place indeed, but the final result was not the expected compounds **12** or **13** but **15b**. As indicated in Scheme 3, **14b** could react with bromine in a reaction that resembles a bromolactonisation. We have earlier suggested that bromine is formed during the DiazAll reaction and the bromocyclization further supports this hypothesis.[4] The preliminary result with **8** was confirmed with metallyl bromide and allyl bromide which gave 15% of **15c** and 22% of **15a**, respectively (Scheme 3). Also the anthranilic acid **16** gave the isocoumarin **17** in 39% yield (Scheme 4). To obtain complete conversion of the arylamine, it was sometimes necessary to add more than 2 equiv of *tert*-butyl nitrite to the reaction mixture. Although the yields are poor, the allylation−bromocyclization constitutes a tandem reaction, which gives access to useful substances from commercially available reagents in a one-pot procedure. For instance, there is now a possibility to synthesize **19** in merely three steps, where previously seven steps were required (Scheme 4).[31] The benzoazepine **19** is a potent inhibitor of phenylethanolamine *N*-methyltransferase (PNMT), an enzyme involved in the biosynthesis of adrenaline.[32] Moreover, with the new tandem reaction it is possible to access new analogues of **19**, which could be difficult to synthesize with the previously published methodology. Compound

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(30) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910−914.
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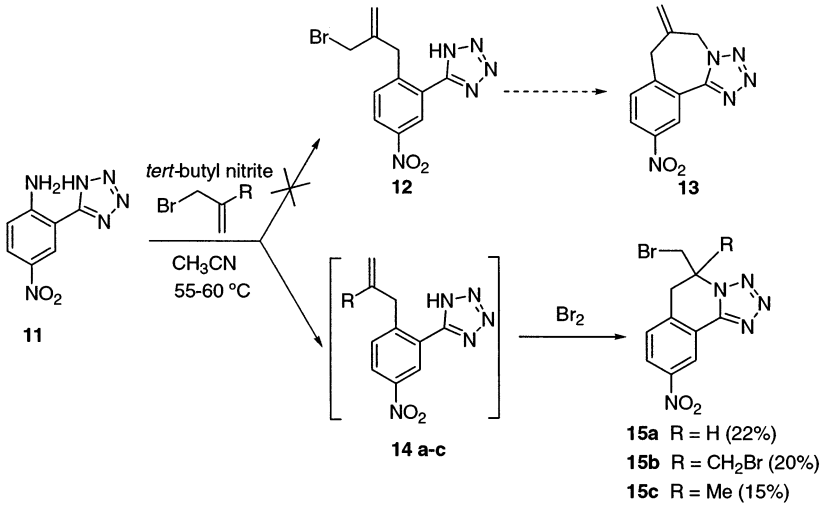
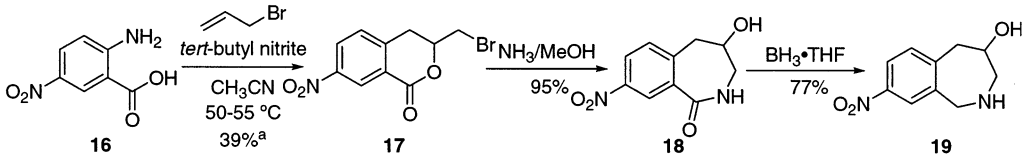
SCHEME 3. A New Allylation−Bromocyclization Reaction



SCHEME 4. A three-step synthesis of 19 and 16



[a] The yield was determined by ^{1}H-NMR spectroscopy using toluene as internal standard.

19 has also been utilized as starting material in the synthesis of substances which inhibit the neuronal isoform of nitric oxide synthase and thereby may be useful in the treatment of a number of diseases or conditions, e.g., stroke (hypoxia), ischaemia, and pain.[33]

In conclusion, allyl bromide was found the be the reagent of choice in the DiazAll reaction although both allyl phenyl sulfide and allyl phenyl sulfone gave acceptable yields. More surprising was the failure of allyltributyltin, which is otherwise extensively used in radical allylation reactions. Several functionalities, which could cause problems in other methods, were tolerated. Some of the compounds generated, e.g., the aromatic allyl bromide, allyl acetates, and vinyl bromide, would be useful starting materials for further transformations into more complex molecules. Even when sterically hindered allyl bromides were employed in the DiazAll reaction the allylated products could be isolated, although the yields were poor. These results confirm the observation made in our previous study that steric hindrance is badly tolerated. In comparison with an established method for the synthesis of allylated aromatic compounds, the DiazAll reaction performed well and was even superior when a more complex allylic bromide was used, both regarding the yield but also because of the more convenient experimental procedure. Finally, a new tandem allylation−bromolactonization reaction was demonstrated, and one of the products was used in the synthesis of a known inhibitor of PNMT.

The DiazAll reaction is a useful complement to existing methodology to introduce an allyl functionality into an aromatic system. The major strength of the reaction is the convenient experimental procedure, the tolerance of functionalities, and the possibility to access allyl aromatic compounds directly from commercially available arylamines, circumventing aryl halides or arylboronic acids, common starting materials in other allylation reactions. The DiazAll reaction is under continuous development in our laboratories.

Experimental Section

General Methods. HPLC analyses were performed on a HiChrom column (Kromasil 100-5C18, 150 × 4.6 mm); eluent: CH_3CN (HPLC grade)/H_2O (0.1% TFA); flow rate 1 mL/min. Preparative HPLC was performed with a HiChrom column (Kromasil 100-10C18, 250 × 20 mm); eluent: CH_3CN (HPLC grade)/H_2O; flow rate 20 mL/min. NMR spectra were recorded on a 400 MHz instrument using $CDCl_3$, DMSO-d_6 or acetone-d_6 as internal standard. Elemental analyses were made by A. Kolbe, Mikroanalytisches Laboratorium, Germany. Chromatographic separations were performed on Matrex Amicon normal-phase silica gel 60 (0.035−0.070 mm). Thin-layer chromatography was performed on Merck precoated TLC plates with silica gel 60 F-254, 0.25 mm. After eluation, the TLC plates were visualized with UV light and sprayed with a solution of $KMnO_4$ (10 g), K_2CO_3 (50 g), NaOH (20 mL, 5%), and H_2O (900 mL) followed by heating. Chemicals were reagent grade except for 2,3-dibromopropene, which was of technical grade (80% purity). All reagents were used as received if not otherwise noted. Propargyl bromide (97% purity), 3-bromocyclohexene, 3-bromo-2-methylpropene, and allyl bromide were distilled, and 5-nitroanthranilic acid (95% purity) was recrystallized from MeOH prior to use. *i*-PrMgBr was freshly prepared from 2-bromopropane and magnesium. 3-Bromo-2-bromomethylpropene,[34] 3-bromo-2-acetoxymethyl-

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propene,[35] 2-bromo-but-3-enyl acetate,[18,19] 3-bromo-2-phenylpropene,[36] 5-bromo-penta-1,3-diene,[22] 1-phenyl-2-phenylsulfanylbut-3-en-1-ol,[37] 3-trifluoromethanesulfonylpropene,[38] and allyltris(trimethylsilyl)silane[39] were synthesized according to literature procedures. Solvents were of p.a. quality except for the acetonitrile used in analytical and preparative HPLC, which was of HPLC grade. The acetonitrile used in the reactions was stored over molecular sieves (4 Å).

General Procedure for the Allylation. The arylamine (3.0 mmol) was added during 20 min to a solution of *tert*-butyl nitrite (535 μL, 4.5 mmol) and the appropriate allylic reagent (45.0 mmol) in dry CH_3CN (3.0 mL if not otherwise stated) under an argon atmosphere while maintaining the specified temperature. At the end of the addition of the arylamine, extra *tert*-butyl nitrite (180 μL, 1.5 mmol) was added. The reaction mixture was then stirred at the specified temperature for 1 h. Acetonitrile, *tert*-butyl nitrite, and the remaining allylic reagent (depending on the boiling point) were distilled off at reduced pressure (10 mmHg).

With Internal Standard. 3,5-Dinitroaniline (92 mg, 0.5 mmol) was added to a solution of *tert*-butyl nitrite (119 μL, 1.0 mmol) and the allylic reagent (see Table 1) in CH_3CN (0.5 mL) during 10 min while maintaining the temperature of the reaction mixture between 11.5 and 14 °C. The reaction mixture was then stirred at 22 °C for 1 h followed by addition of 2-nitrobenzyl alcohol (50 mg, 0.33 mmol) as an internal standard. The yield and product distribution were determined by HPLC using a calibration curve.[40]

3,5-Dinitro-1-(2-methyl-2-propenyl)benzene (2b). The reaction was performed according to the general procedure. Column chromatography (heptane−EtOAc 23:2) gave 670 mg of a pale yellow oil, which crystallized upon standing overnight in the refrigerator. Recrystallization (heptane−EtOAc 49:1) gave 500 mg (75%) of the title compound as pale yellow crystals: mp 46−47 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92, (t, 1H, J = 2.1 Hz), 8.41, (d, 2H, J = 2.1 Hz), 5.01, (s, 1H), 4.83, (s, 1H), 3.56, (s, 2H), 1.74, (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 144.8, 142.5, 129.5, 117.4, 115.3, 44.4, 22.4. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.19; H, 4.66; N, 12.48.

3,5-Dinitro-1-(2-bromo-2-propenyl)benzene (2c). The reaction was performed according to the general procedure. The remaining allyl bromide was removed by distillation at reduced pressure. Column chromatography (heptane−EtOAc 10:1) gave 800 mg (93%) of the title compound as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.98, (t, 1H, J = 2.1 Hz), 8.47, (d, 2H, J = 2.1 Hz), 5.89, (m, 1H), 5.71, (d, 1H, J = 2.1 Hz), 4.00, (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.05, 142.1, 129.6, 129.3, 121.4, 118.2, 47.3. Anal. Calcd for $C_9H_7BrN_2O_4$: C, 37.66; H, 2.46; N, 9.76. Found: C, 37.75; H, 2.38; N, 9.78.

3,5-Dinitro-1-(2-bromomethyl-2-propenyl)benzene (2d). The reaction was performed according to the general procedure. The remaining allyl bromide was removed by distillation at reduced pressure (0.7 mmHg, 30 °C, 5.3 g, 55% recovery). Column chromatography (heptane−EtOAc 9:1) followed by crystallization (heptane−EtOAc 9:1) gave 645 mg (71%) of the title compound as pale yellow crystals: mp 73−74 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96, (t, 1H, J = 2.1 Hz), 8.45, (d, 2H, J = 2.1 Hz), 5.44, (s, 1H), 5.03, (s, 1H), 3.93, (s, 2H), 3.81, (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.1, 143.4, 142.8, 129.7, 119.5, 117.9, 39.9, 35.5. Anal. Calcd for $C_{10}H_9BrN_2O_4$: C, 39.89; H, 3.01; N, 9.30. Found: C, 39.83; H, 2.93; N, 9.18.

3,5-Dinitro-1-(2-acetoxymethyl-2-propenyl)benzene (2e). The reaction was performed according to the general procedure on a 2.0 mmol scale. The remaining allyl bromide was removed by distillation at reduced pressure. Column chromatography (heptane−EtOAc 5:1) followed by crystallization (heptane−ether 2:1) gave 420 mg (75%) of the title compound as yellow crystals: mp 48−49 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91, (t, 1H, J = 2.1 Hz), 8.41, (d, 2H, J = 2.1 Hz), 5.33, (s, 1H), 5.05, (s, 1H), 4.51, (s, 2H), 3.64, (s, 2H), 2.06, (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 149.0, 143.4, 141.0, 129.5, 117.7, 117.4, 66.1, 39.6, 21.0. Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.52; H, 4.26; N, 9.92.

2-(3,5-Dinitrobenzyl)acrylic Acid (2f). The reaction was performed according to the general procedure except that three times the amount of CH_3CN was used as solvent. The remaining crystalline residue was washed with heptane (5 × 50 mL) to remove nonreacted 2-(bromomethyl)acrylic acid (2-(bromomethyl)acrylic acid crystallized from the combined heptane phases). Column chromatography (heptane−EtOAc−MeOH−HOAc 5:4:1:0.04) of the remaining crude product followed by crystallization from toluene gave 450 mg (60%) of the title compound as large yellow needles: mp 149−151 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.72, (br s, 1H), 8.69, (t, 1H, J = 2.0 Hz), 8.50, (br d, 2H, J = 1.7 Hz), 6.22, (br s, 1H), 5.84, (br s, 1H), 3.86, (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.2, 147.8, 144.0, 138.7, 129.1, 127.8, 116.5, 36.4. Anal. Calcd for $C_{10}H_8N_2O_6$: C, 47.63; H, 3.20; N, 11.11. Found: C, 47.74; H, 3.16; N, 10.97.

3,5-Dinitro-1-(2-phenyl-2-propenyl)benzene (2g). The reaction was performed according to the general procedure except that twice the amount of CH_3CN was used as solvent. The remaining allyl bromide was removed by distillation at reduced pressure (0.3 mmHg, 50−55 °C, 5.9 g, 66% recovery). Column chromatography (heptane−EtOAc 49:1 to 23:2) followed by crystallization (heptane−EtOAc 49:1) gave 495 mg (58%) of the title compound as pale yellow crystals: mp 130−131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87, (t, 1H, J = 2.1 Hz), 8.42, (d, 2H, J = 2.1 Hz), 7.42−7.39, (m, 2H), 7.35−7.25, (m, 3H), 5.65, (s, 1H), 5.22, (d, 1H, J = 0.8 Hz), 4.09, (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.9, 144.9, 144.6, 139.3, 129.4, 129.2, 128.7, 126.5, 126.5, 117.5, 117.3, 41.7. Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.23; H, 4.24; N, 9.76.

3,5-Dinitro-1-(1-bromomethyl-2-propenyl)benzene (2h). The reaction was performed according to the general procedure except that three times the amount of CH_3CN was used as solvent. Column chromatography (heptane−EtOAc 9:1) gave 250 mg (28%) of the title compound as pale yellow crystals: mp 59−60 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.98, (t, 1H, J = 2.1 Hz), 8.41, (dd, 2H, J = 2.1, 0.5 Hz), 6.08−5.98, (ddd, 1H, J = 17.2, 10.4, 7.3 Hz), 5.39, (ddd, 1H, J = 10.4, 1.0, 0.7 Hz), 5.28, (ddd, 1H, J = 17.2, 1.3, 0.7), 4.01, (br q, 1H, J = 7.2 Hz), 3.81−3.76, (dd, 1H, J = 10.5, 5.5 Hz), 3.70−3.65, (dd, 1H, J = 10.4, 8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.1, 146.0, 136.4, 128.7, 120.0, 118.2, 51.2, 35.0. Anal. Calcd for $C_{10}H_9BrN_2O_4$: C, 39.89; H, 3.01; N, 9.30. Found: C, 40.03; H, 2.95; N, 9.25.

3-(3,5-Dinitrophenyl)cyclohexene (2i). The reaction was performed according to the general procedure. The remaining allyl bromide was removed by distillation at reduced pressure. Column chromatography (cyclohexane−*t*-BuOMe 15:1) followed by crystallization (heptane−EtOAc 49:1) gave 210 mg (28%) of the title compound as pale yellow crystals: mp 90−91 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90, (t, 1H, J = 2.1 Hz), 8.43, (d, 2H, J = 2.1 Hz), 6.13−6.08, (m, 1H), 5.73−5.69, (m, 1H), 3.68, (m, 1H), 2.20−2.12, (m, 3H), 1.75−1.57, (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.71, 149,0 131.9, 128.5, 127.2, 117.2, 41.9, 32.7, 25.1, 20.9. Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.14; H, 4.96; N, 11.36.

***trans*-4-(3,5-Dinitrophenyl)but-2-enyl Acetate (2j).** The reaction was performed according to the general procedure on a 1.0 mmol scale. Pyridine (79 μL, 1 mmol) was added to the reaction mixture before the addition of 3,5-dinitroaniline. The

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remaining allyl bromide was removed by distillation at reduced pressure. The yield of **2j** was determined to be 43% according to ^{1}H NMR spectroscopy using toluene as internal standard. The toluene was then removed by distillation at reduced pressure. Flash chromatography (heptane−EtOAc 4:1) followed by crystallization (heptane−EtOAc 4:1) of the remaining yellow oil gave 100 mg (35%) of the title compound as pale yellow crystals: mp 57−58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91, (t, 1H, J = 2.1 Hz), 8.38, (d, 2H, J = 2.1 Hz), 5.96−5.87, (dtt, 1H, J = 15.4, 6.7, 1.3 Hz), 5.80−5.72, (dtt, 1H, J = 15.4, 6.0, 1.4 Hz), 4.60, (dd, 2H, J = 6.0, 1.1 Hz), 3.64, (d, 2H, J = 6.7 Hz), 2.08, (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 148.8, 144.3, 130.6, 129.0, 128.8, 117.3, 64.3, 38.2, 21.1. Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.49; H, 4.37; N, 9.98.

1-Allenyl-3,5-dinitrobenzene (2k). The reaction was performed according to the general procedure. Column chromatography (heptane−EtOAc 23:2) followed by crystallization (heptane−EtOAc 23:2) gave 145 mg (23%) of the title compound as pale yellow crystals: mp 122−124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85, (t, 1H, J = 2.1 Hz), 8.44, (d, 2H, J = 2.1 Hz), 6.34, (t, 1H, J = 6.7 Hz), 5.43, (d, 2H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.3, 149.3, 139.3, 126.5, 117.0, 92.4, 81.9. Anal. Calcd for $C_9H_6N_2O_4$: C, 52.43; H, 2.93; N, 13.59. Found: C, 52.46; H, 2.85; N, 13.49.

5-Bromo-2-iodobenzonitrile (7). 2-Amino-5-bromobenzonitrile (296 mg, 1.5 mmol) was added during 10 min to *tert*-butyl nitrite (0.36 mL, 2.3 mmol) and iodine (1.1 g, 4.5 mmol) in dry CH_3CN (2 mL) under argon atmosphere while maintaining the temperature between 30 and 35 °C. Stirring was continued for 60 min at 23 °C. Subsequent addition of saturated aqueous Na_2SO_3 (20 mL) gave a precipitate which was collected by filtration. Recrystallization from heptane gave 397 mg (86%) of the title compound as off-white crystals: mp 123−124 °C (lit.[41] mp 113−114 °C[42]).

2-Allyl-5-bromobenzonitrile (9). The reaction was performed according to the general procedure using **10** (590 mg, 3.0 mmol) as starting material. The temperature during the addition was 30−35 °C, and the temperature after the addition was kept at 26 °C. Column chromatography (heptane−EtOAc 49:1) gave 524 mg of **13** as a clear oil containing 8% of 2,5-dibromobenzonitrile. This corresponds to a 72% yield of **13**. An analytically pure sample was obtained by preparative HPLC (CH_3CN-H_2O 65:35): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74, (d, 1H, J = 2.1 Hz), 7.64, (dd, 1H, J = 8.4, 2.1 Hz), 7.22, (dd, 1H, J = 8.4, 0.5 Hz), 5,96−5.86, (m, 1H), 5.19−5.09, (m, 2H), 3.56, (dt, 2H, J = 6.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.0, 136.2, 135.3, 134.4, 131.5, 120.2, 118.1, 116.6, 114.5, 38.2. Anal. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.06; H, 3.62; N, 6.38.

5-Bromo-2-(2-bromomethyl-2-propenyl)benzonitrile (10). The reaction was performed according to the general procedure starting from **10** (99 mg, 0.50 mmol) and using 10 equiv of 3-bromo-2-bromomethylpropene in CH_3CN (1 mL). The addition temperature and the temperature after addition were 30−35 and 24 °C, respectively. The remaining allylic bromide was removed by distillation at reduced pressure (0.7 mmHg, 30 °C). The yield of the title compound was determined to be 82% according to ^{1}H NMR analysis using toluene as internal standard. The toluene was then removed by distillation at reduced pressure. Flash chromatography (heptane−EtOAc 95:5) followed by recrystallization (heptane−diethyl ether 10:1) provided the title compound (100 mg, 62%, R_f = 0.31)[43] as white crystals: mp 45−46 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78, (d, 1H, J = 2.1 Hz), 7.68, (dd, 1H, J = 8.3, 2.1 Hz), 7.29, (d, 1H, J = 8.3 Hz), 5.34, (br s, 1H), 4.91, (br s, 1H), 3.92, (s, 2H), 3.73, (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.4, 141.3, 136.3, 135.7, 132.2, 120.9, 118.6, 116.5, 115.2, 38.1, 35.7; HRMS (FAB+) calcd for $C_{11}H_{10}Br_2N$ [(M + H)$^+$] 313.9181, found 313.9174. Anal. Calcd for $C_{11}H_9Br_2N$: C, 41.94; H, 2.88; N, 4.45. Found: C, 42.04; H, 2.90; N, 4.37.

9-Nitro-5-bromomethyl-5,6-dihydrotetrazolo[5,1-*a*]isoquinoline (15a). The reaction was performed according to the general procedure using **11** (103 mg, 0.50 mmol) as starting material and 10 equiv of allyl bromide in dry CH_3CN (1 mL). Column chromatography (heptane−EtOAc 1:1) gave 34 mg (22%) of the title compound as pale yellow crystals (90−95% purity according to HPLC and ^{1}H NMR analyses). An analytically pure sample was prepared by preparative HPLC (CH_3CN-H_2O 60:40): mp 143−144 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.77, (dd, 1H, J = 2.4, 0.4 Hz), 8.42, (dd, 1H, J = 8.5, 2.4 Hz), 7.89, (br d, 1H, J = 8.0 Hz), 5.51, (m, 1H), 4.22, (dd, 1H, J = 11.4, 5.2 Hz), 4.13, (dd, 11.4, 4.2 Hz), 3.97−3.88, (ddt, 1H, J = 17.3, 6.6, 0.5 Hz), 3.80−3.72, (dd, 1H, J = 17.3, 6.9 Hz); ^{13}C NMR (acetone-d_6, 100 MHz) δ 150.7, 148.5, 142.0, 131.5, 127.1, 123.3, 120.5, 55.8, 33.9, 33.2. Anal. Calcd for $C_{10}H_8BrN_5O_2$: C, 38.73; H, 2.60; N, 22.58. Found: C, 38.88; H, 2.53; N, 22.48.

9-Nitro-5,5-bis(bromomethyl)-5,6-dihydrotetrazolo[5,1-*a*]isoquinoline (15b). The reaction was performed according to the general procedure using **11** (103 mg, 0.50 mmol) as starting material and 10 equiv of 3-bromo-2-bromomethylpropene in dry CH_3CN (1 mL). Column chromatography (heptane−EtOAc 1:1) gave 41 mg (20%) of the title compound as pale yellow crystals (90−95% purity according to HPLC and ^{1}H NMR analyses). An analytically pure sample was prepared by preparative HPLC (CH_3CN-H_2O 65:35): mp 179−180 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.79, (dd, 1H, J = 2.4, 0.5 Hz), 8.43, (dd, 1H, J = 8.5, 2.4 Hz), 7.91, (br d, 1H, J = 8.5, 0.5 Hz), 4.34, (d, 2H, J = 11.4 Hz), 4.25, (d, 11.4 Hz), 4.03, (br s, 2H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 150.8, 148.7, 141.2, 131.7, 127.5, 122.6, 120.8, 63.8, 37.6, 36.7. Anal. Calcd for $C_{11}H_9Br_2N_5O_2$: C, 32.78; H, 2.25; N, 17.38. Found: C, 32.89; H, 2.18; N, 17.26.

9-Nitro-5-bromomethyl-5-methyl-5,6-dihydrotetrazolo-[5,1-*a*]isoquinoline (15c). The reaction was performed according to the general procedure using **11** (103 mg, 0.50 mmol) as starting material and 10 equiv of methallyl bromide in dry CH_3CN (1 mL). Column chromatography (heptane−EtOAc 1:1) gave 25 mg (15%) of the title compound as pale yellow crystals (90% purity according to HPLC and ^{1}H NMR analyses). An analytically pure sample was prepared by preparative HPLC (CH_3CN-H_2O 60:40): mp 121−123 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.78, (dd, 1H, J = 2.4, 0.4 Hz), 8.43, (dd, 1H, J = 8.4, 2.4 Hz), 7.88, (dd, 1H, J = 8.4, 0.4 Hz), 4.10, (d, 1H, J = 11.3 Hz), 4.01, (d, 11.3 Hz), 3.90, (d, 1H, J = 17.2 Hz), 3.75, (d, 1H, J = 17.2 Hz), 2.03,(s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 150.2, 148.6, 141.7, 131.6, 127.2, 123.2, 120.6, 61.7, 39.7, 39.1, 24.7. Anal. Calcd for $C_{11}H_{10}BrN_5O_2$: C, 40.76; H, 3.11; N, 21.61. Found: C, 40.89; H, 3.12; N, 21.46.

3-Bromomethyl-7-nitro-2,3-dihydroisocoumarin (17). The reaction was performed according to the general procedure using **16** (910 mg, 5.0 mmol) as starting material and 10 equiv of allyl bromide in dry CH_3CN (10 mL). The yield of **17** was determined to be 39% according to ^{1}H NMR using toluene as internal standard. The toluene was then removed by distillation at reduced pressure. Column chromatography (heptane−EtOAc 3:1) followed by crystallization (heptane−EtOAc 3:1) gave 460 mg (32%) of the title compound as pale yellow crystals: mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.95, (d, 1H, J = 2.4 Hz), 8.42, (dd, 1H, J = 8.4, 2.4 Hz), 7.53, (d, 1H, J = 8.4 Hz), 4.80, (m, 1H), 3.72, (dd, 1H, J = 11.0, 4.3 Hz), 3.63, (dd, 1H, J = 11.0, 6.8 Hz), 3.31, (d, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3, 148.1, 144.5, 129.4, 128.5,

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(42) Melting point of the crude product. NMR data can be found in the Supporting Information.

(43) As seen in the Experimental Section, a large difference was detected between the yield using internal standard and the isolated yield. This is probably due to deterioration of the product during column chromatography.

126.2, 125.8, 76.6, 32.1, 31.8. Anal. Calcd for $C_{10}H_8BrNO_4$: C, 41.98; H, 2.82; N, 4.90. Found: C, 42.08; H, 2.86; N, 4.79.

4-Hydroxy-8-nitro-2,3,4,5-tetrahydrobenzo[*c*]azepin-1-one (18). Isocoumarin **17** (145 mg, 0.5 mmol), dissolved in dry MeOH (5 mL), was added dropwise to dry MeOH (10 mL) saturated with NH_3(g) during 15 min at 0 °C. The pale yellow solution was then stirred for 30 min at 0 °C and 51 h at 23−25 °C. Removal of the MeOH−NH_3 at reduced pressure gave a yellow residue that was partly dissolved again in MeOH (20 mL) and NH_4OH (2 mL, 25%). Silica was added to the mixture, and the volatile material was removed at reduced pressure. Column chromatography ($CHCl_3$−MeOH−NH_4OH (25%) 9:1:0.1) of the yellow residue followed by rinsing the obtained pale yellow solid with heptane−EtOAc (1:1) gave 105 mg (95%) of the title compound as a white solid: mp 228−229 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.40, (m, 1H), 8.25, (m, 2H), 7.55, (m, 1H), 5.21, (d, 1H, J = 4.2 Hz), 4.18, (m, 1H), 3.12−3.00, (m, 2H), 2.81−2.68, (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.4, 146.6, 143.9, 137.0, 131.3, 124.9, 123.1, 71.2, 46.0.[44] Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.89; H, 4.68; N, 12.55.

4-Hydroxy-8-nitro-2,3,4,5-tetrahydro-1*H*-benzo[*c*]-azepine (19). Solid **18** was added in portions to BH_3·THF (1 mL, 1 M) in THF (5 mL) at 0 °C under argon atmosphere. The clear solution was refluxed under argon for 24 h and then cooled in an ice bath. Careful addition of methanol destroyed the remaining borane, and the volatile material in the reaction mixture was removed at reduced pressure. The remaining pale yellow oil was dissolved in MeOH, and then HCl (3 mL, 6 M) was added to this solution. The solution was refluxed for 2 h, and the MeOH was removed at reduced pressure. The remaining aqueous phase was made basic (pH >10) with NaOH (2 M) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over anhydrous potassium carbonate. Removal of CH_2Cl_2 at reduced pressure gave 46 mg of **19** as a yellow solid that was dissolved in acetone. Subsequent addition of diethyl ether precipitated 40 mg (77%) of the title compound as a pale yellow solid: mp 150−151 °C (lit.[31] 147−149 °C).

(44) One of the signals in the ^{13}C-spectrum of **18** is coinciding with the solvent signals (DMSO-d_6). NMR data (CD_3OD) of **18** can be found in the Supporting Information.

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Supporting Information Available: The synthesis of **9** and **10** using the magnesium exchange reaction and the synthesis of **11**. NMR data for **18** in CD_3OD and **7** in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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