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Stereoselective reactions of nitro compounds in the synthesis of natural compound analogs and active pharmaceutical ingredients

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Abbreviations: AIBN, azobisisobutyronitrile; AZADO, 2-azaadamantane-*N*-oxyl; 9-BBN, 9-borabicyclo[3.3.1]nonane; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; BINOL, 1,1′-bi-2-naphthol; Boc, *tert*-butoxycarbonyl; Bop, (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate; BOX, bis(oxazoline); BroP, bromo tris(dimethylamino) phosphonium hexafluorophosphate; BSA, *N*,*O*-bis(trimethylsilyl)acetamide; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CDI, *N*,*N*′-carbonyldiimidazole; CNS, central nervous system; Cp, cyclopentyl; Cy, cyclohexyl; *m*CPBA, *m*-chloroperoxybenzoic acid; CPME, cyclopentyl methyl ether; CTAB, hexadecyltrimethylammonium bromide; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DCE, dichloroethane; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; *de*, diastereomeric excess; DEAD, diethyl azodicarboxylate; DIBAL(DIBAL-H), diisobutylaluminium hydride; DIPCl, diisopinocamphenyl chloroborane; DIPEA, *N*,*N*-diisopropylethylamine; DMA, *N*,*N*′-dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMDO, dimethyldioxirane; DMP, Dess–Martin periodinane; DPM, diphenylmethyl; *dr*, diastereomeric ratio; E, electrophile; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; *ee*, enantiomeric excess; *er*, enantiomeric ratio; GABA, gamma-aminobutyric acid; Gly, glycine; HMDS, hexamethyldisilazane; HOAT, 1-hydroxy-7-azabenzotriazole; IBX, *o*-iodoxybenzoic acid; INOC, intramolecular nitrile oxide—olefin cycloaddition; IPA, isopropyl alcohol; ISOC, intramolecular silyl nitronate-olefin cycloaddition; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; Leu, leucine; LHMDS, lithium hexamethyldisilazide; MAHT, malonic acid half thioester; MAPh, Methylaluminum Bis(2,6-diphenylphenoxide); MMPP, magnesium monoperoxyphthalate; MOM, methoxymethyl; MS, molecular sieves; Ms(Mes), mesyl; MTBE(TBME), methyl *tert*-butyl ether; MW, microwave; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NMDA, *N*-methyl-D-aspartate; NMM, *N*-methylmorpholine; NMO, *N*-Methylmorpholine *N*-oxide; NMP, *N*-methylpyrrolidinone; Nu, nucleophile; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; PEG, polyethylene glycol; PEI, polyethyleneimine; PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; PPTs, pyridinium *p*-toluenesulfonate; PS, polystyrene; PTSA, *p*-toluenesulfonic acid; Py, pyridine; RCM, ring-closing metathesis; Red-Al, sodium bis(2-methoxyethoxy)aluminumhydride; rt, room temperature; SG, silica gel; TBAB, tetrabutylammonium bromide; TBAF, tetrabutylammonium fluoride; TBDMS(TBS), *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TC, thiophenecarboxylate; TES, triethylsilyl; Tf, triflate; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMEDA, tetramethylethylenediamine; TMG, 1,1,3,3-tetramethylguanidine; TMS, trimethylsilyl; TMP, 2,2,6,6-tetramethylpiperidine; Tol, tolyl; Tr, trityl; Ts(Tos), tosyl; Val, valine.

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1. Introduction

Nitroalkanes and nitroalkenes have been always considered as convenient and readily available intermediates in organic synthesis, including total synthesis of natural products.[1] The versatile reactivity of nitro compounds in carbon–carbon and carbon–heteroatom bond forming reactions together with an amazing transformability of the nitro-group to a number of other functional groups makes them reagents of choice for organic chemists.

Over the last 15 years, there has been a considerable growth of interest to the chemistry of non-aromatic nitro compounds which has resulted in the development of numerous useful synthetic applications.[2,3] This may be attributed to an excellent compatibility of the nitro compounds with novel asymmetric strategies, in particular, organocatalysis, which have emerged in the early 2000th.[4,5] Catalytic asymmetric transformations of nitroalkanes and nitroolefins is a rapidly growing area of research. Many highly efficient catalytic enantioselective C–C-bond forming reactions utilizing nitro compounds have been recently developed, including organocatalytic or transition metal-catalyzed asymmetric Michael addition, nitro-Michael addition, Henry, aza-Henry, cascade, and some other reactions. Moreover, reduction of enantiomerically and/or diastereomerically enriched nitro compounds obtained by these methods provides an expedient access to various bioactive amine scaffolds, which are presently of high demand by pharmaceutical industry and R&D.[6–9]

Medicinal chemistry is now an important area of nitro compounds application. In particular, nitroalkanes and nitroalkenes are considered as indispensable building blocks for concise synthesis of medically relevant molecules. Scale-up and semi-industrial processes utilizing nitro compounds as key precursors of various pharmaceutical ingredients are widely reported in research papers and patents. At this point, a systematization of the growing data on nitro compounds application to target-oriented synthesis is obviously needed. The present review is focused on the stereoselective transformations of nitro compounds and their derivatives, which have been employed at the key stereocontrolling steps in the synthesis of natural products and pharmaceutical ingredients. In this review, all modern stereoselective and asymmetric strategies employing nitro compounds (organocatalytic, transition metal catalyzed and chiral auxiliary-based methods), which have proven to be useful in the synthesis of clinically applied or being in various phases of clinical (preclinical) trials bioactive molecules, are summarized. It mostly covers literature after year 2000, though some earlier reported classical strategies utilizing nitro compounds in total synthesis are also included. (Some useful applications of nitroalkanes and nitroalkenes are outlined in recent reviews on organocatalysis[2–5,10,11] and reactions of nitro compounds.[4,6,7,12–15] However, these reviews mostly deal with the methodological and mechanistic aspects of these transformations.)

The content of the review is classified by types of starting compounds, including nitroalkanes, nitroolefins, and nitroalkane derivatives (nitrile oxides, nitronates, and bis(oxy)enamines). With in each class of compounds, the data are arranged according to reaction type (Michael, Henry, aza-Henry, Mannich, cascade reactions, etc.) and further sub-divided in accordance with methodologies used (non-catalytic methodologies, metal catalysis, organocatalysis). As a number of bioactive molecules produced by alternative synthetic approaches are considered in different chapters (sections) of the review, for the readership convenience, most important of them are listed in the alphabetic order in Table 1 which contains references and links with corresponding sections and schemes. Structural formulas of organocatalysts and ligands used in stereoselective transformation of nitro compounds are summarized in Figs. 1–4.

2. Reactions of nitroalkanes

Nitroalkanes are classical α-C-nucleophilic syntons. Due to the high electronwithdrawing character of the nitro-group, they are easily deprotonated to form nitronate-anions, which smoothly react with carbon- and heteroatom-based electrophiles.[1] In presence of bases, nitroalkanes readily react with electron-deficient alkenes (Michael reaction), carbonyl compounds (Henry or nitroaldol reaction) and imines (aza-Henry or nitro-Mannich reaction), and may serve as di-nucleophiles in cascade electrophilic addition reactions (reviews and monographs:[1,3b,8,12]). In reactions of prochiral nitroalkanes with electrophiles at least one new stereogenic center is formed. In this way, diastereo- and/or enantiomerically pure adducts can be accessed by using electrophiles or nitro compounds bearing chiral auxiliary groups or performing the reactions in the presence of chiral metal complexes or organocatalysts. These stereoselective reactions have found numerous applications in total synthesis of natural products as well as various pharmaceutically relevant molecules.

2.1. Addition to electron-deficient olefins

The conjugate addition of nitroalkanes to electron-deficient olefins, primarily to α,β-unsaturated carbonyl compounds, is an important class of C–C bond forming reactions.[1] The products of these reactions are useful intermediates for a variety of natural and non-natural pharmaceutically valuable compounds. In particular, γ-nitrocarbonyl compounds resulting from the nitro-