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Preparation of chiral key intermediates of morpholine based neurokinin receptor antagonists by asymmetric allylic alkylation

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ABSTRACT

The preparation of optically active morpholine-2-aryl-2-allyl derivative from morpholine-2-aryl-3-ones is reported. The optically active tetrasubstituted stereocenter is introduced during a palladium promoted asymmetric allylic alkylation. The resulting compounds are useful intermediates in the synthesis and development of potent NK antagonists.

1. Introduction

The neurokinins (also known as tachykinins) constitute a neurotransmettor peptide family covering substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), which share the common carboxy-terminal sequence Phe-X-Gly-Leu-Met-NH_2. They are widely spread in the central and peripheral nervous systems.[1] Relying on the affinity of natural neurokinins, three distinct 7-transmembrane G protein-coupled receptor types have been identified: NK1 (SP-preferring), NK2 (NKA-preferring), NK3 (NKB-preferring).[2] The numerous forms of mammalian neurokinin assume a large number of biological activities, including muscle contraction and relaxation, vasodilatation, secretion, activation of the immune system, pain transmission, and neurogenic inflammation. Thus, antagonists of these NK receptors have attracted a great deal of interest as potent therapeutic agents.[3] Some specific morpholine based derivatives exhibit such properties and optically active SSR240600, SSR144190, and SSR241586 have been described to be active against depression, emesis, irritable bowel syndrome, schizophrenia, and urinary trouble (Fig. 1).[4] To implement the tetrasubstituted stereogenic centre of optically active 2,2′-disubstituted morpholines, which are valuable intermediates in the multistep sequences to access such potent antagonists,[5] a few elegant approaches have been developed. Nishi et al. have applied the Sharpless asymmetric dihydroxylation reaction (AD) to prepare homochiral diols (Scheme 1A).[6] A subsequent recrystallization in the presence of D-(−)-tartaric acid afforded an optically pure 2-aryl-

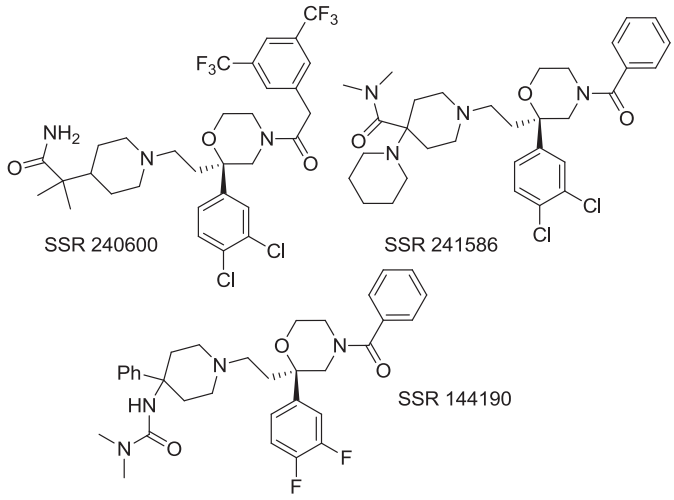

Fig. 1. Examples of morpholine based NK antagonists.

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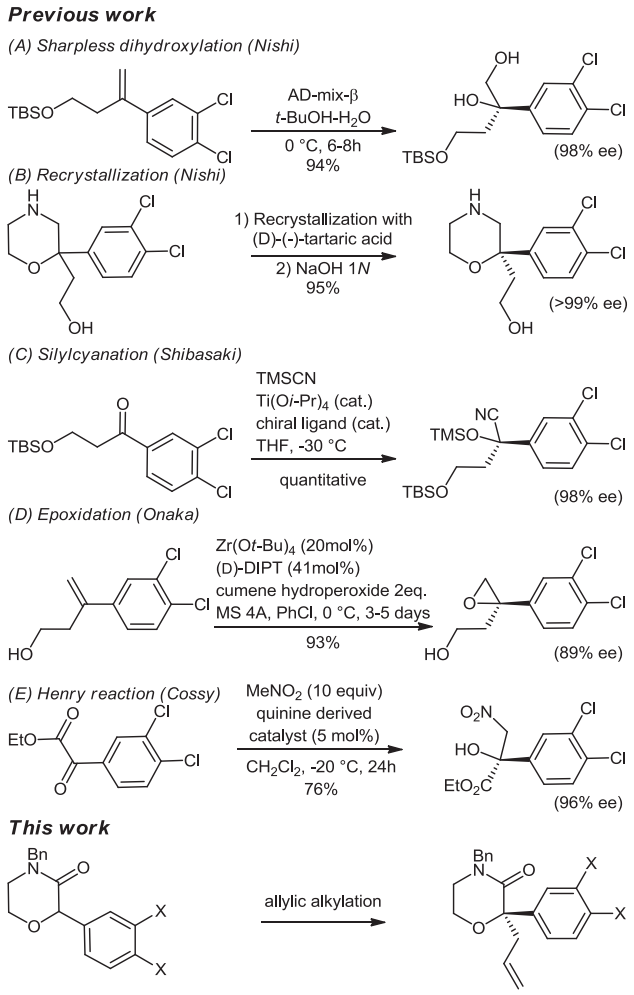
2-ethanol-morpholine intermediate (Scheme 1B).[7] Later on, Shibasaki disclosed an efficient trimethylsilylcyanation reaction to convert a keto silylether into the corresponding cyano disilylether (Scheme 1C).[8]



Scheme 1. Different routes to access the benzylic stereocenter of arylmorpholine precursors.

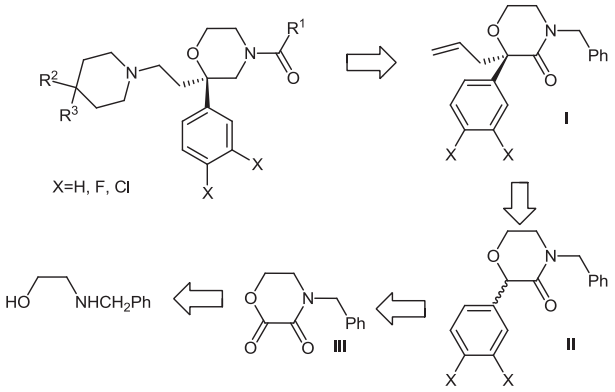
In the mean time, Onaka described an enantioselective epoxidation reaction of a homoallylic alcohol (Scheme 1D).[9] Finally, Cossy recently reported a powerful approach to convert an α-ketoester into a β-nitro alcohol through an organo-catalysed Henry reaction (Scheme 1E).[10]

For several years, our laboratory has been interested in the application of asymmetric allylic alkylation to prepare quaternary stereocenters.[11,12] We applied this methodology to the preparation of morpholines and piperidines exhibiting tetrasubstituted stereocenters.[13] Herein, we report our development of the asymmetric allylic alkylation to access chiral key 2,2′-substituted morpholinone intermediates (Scheme 1).

2. Results and discussion

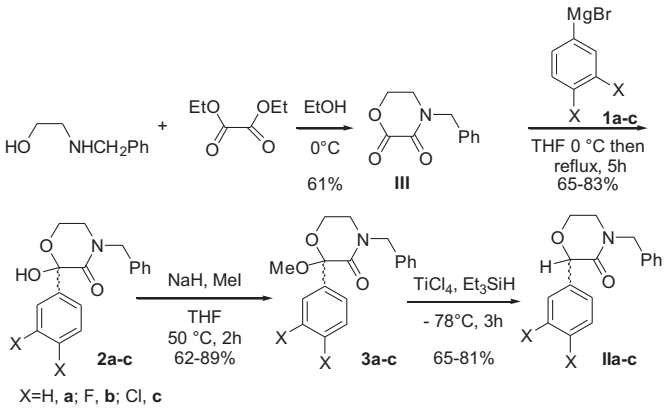
The synthesis of chiral intermediates **I** (R=H, F, Cl) was meant from asymmetric allylation of **II**. This morpholinone could be obtained easily from morpholinedione **III** prepared from 2-(benzylamino)ethanol (Scheme 2). We focused thus on the preparation of optically active **I**.

The three substrates **IIa**–**c** needed for the asymmetric allylic alkylation reactions were prepared easily in a few steps (Scheme 3).



Scheme 2. Retrosynthetic analysis for 2,2′ disubstituted morpholines.

Morpholinedione **III** was readily prepared from 2-(benzylamino) ethanol.[14] Thus, the reaction of commercially available 2-(benzylamino)ethanol (1 equiv) and diethyloxalate (1 equiv) led to dione compound **III** in 61% yield after purification. The subsequent reaction of **III** with the corresponding freshly prepared arylmagnesium bromides **1a**–**c** (1.1 equiv) afforded the cyclic hemiketals **2a**–**c** in 65–83% yield. Then, compounds **2a**–**c** were allowed to react with methyl iodide (1.5 equiv) in the presence of NaH (1.5 equiv).[15] After workup, the cyclic ketals **3a**–**c** were isolated in 62–89% yield.



Scheme 3. Synthesis of morpholinones.

Next, a Lewis acid promoted silane reduction of ketals **3a**–**c** furnished morpholinones **IIa**–**c**. Thus, ketals **3a**–**c** were reacted with Et_3SiH (3 equiv) in the presence of $TiCl_4$ (6 equiv) in dichloromethane providing compounds **IIa**–**c** in 65–81% yield (Scheme 3).[15] The preparation of **IIa**–**c** could also be achieved in a one step procedure from **2a**–**c** under similar conditions (3 h, −78 °C, 69–73%).

In order to find the most appropriate conditions for the palladium catalysed allylic alkylation of **II**, we first carried out experiments to screen different bases in the presence of the diphosphine ligand DPPB (1,4-bis(diphenylphosphino)butane) and allylpalladium chloride dimer as the precatalyst (Scheme 4 and Table 1). Among the various bases tried, the best catalytic conditions were found by using a combination of *n*-BuLi and TMEDA (entry 7, 9, 16) in conjunction with the palladium complex.

Hence, the combined use of THF and a bidentate ligand like TMEDA proved to be crucial breaking down *n*-BuLi aggregates to form monomers and dimers and thereby increasing significantly their basicity.[16] Afterwards, asymmetric allylic alkylation reactions of **IIa**–**c** were then studied in the presence of BINAP or one of the Trost ligands and allylpalladium chloride dimer (Fig. 2 and Table 2).