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Diastereofacial Solid Phase Synthesis and Self-Promoted Cleavage of a [2.2.1] Bicyclic Diversity Scaffold

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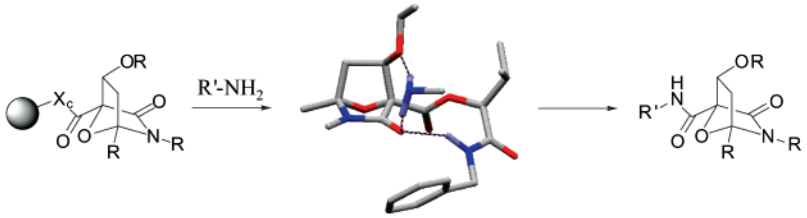
ABSTRACT



We have previously described a diastereofacially selective 1,3-dipolar cycloaddition reaction of isomünchnones with vinyl ethers. While adapting this methodology for solid phase synthesis, we discovered a chemoselective and self-promoted linker aminolysis that provides liberated product in high purity, at a significantly enhanced rate. Herein we describe the implementation of a chiral auxiliary as a solid-phase linker, the detailed investigation of its unique aminolysis, and the utility of this cleavage within a chemical diversity format.

In our previous Letter we described the development of a chiral auxiliary for facial selectivity in a 1,3-dipolar cycloaddition reaction of isomünchnones with vinyl ethers, for the construction of [2.2.1] bicyclic molecules.[1] Examples of both the synthesis[2] and use[3] of these molecules as a scaffold for chemical diversity have also been described. In this Letter, we report the adaptation of this chiral auxiliary to the solid phase synthesis of this diversity scaffold. In addition, we describe a unique self-catalyzed and rate-accelerated aminolysis that undergoes a self-promoted, selective cleavage from the resin, yielding a single product.

The development of diversely functionalized probes for the discovery and understanding of basic biological pathways has exploded in the past few years.[4] The synthetic generality of cycloaddition chemistry, the facility of polymer-supported synthesis for chemical diversity,[5] and the adaptation of the 1,3-dipolar cycloaddition reaction to resin-based synthesis[6] have prompted our interest in porting the 1,3-dipolar cycloaddition of isomünchnones with vinyl ethers to the solid phase. A rhodium-catalyzed isomünchnone cycloaddition−cycloreversion with alkyne dipolarophiles has recently been reported, by us[7] and others,[8] to proceed quite efficiently on solid phase. It remained to be evaluated, however, whether the diastereo-[2] and enantiofacial[1] selectivity of the vinyl ethers would also transfer to solid phase reaction conditions.

A solid phase asymmetric linker, structurally analogous to the most successful solution phase auxiliary design,[1] was constructed starting with the benzhydrylamine (BHA) resin.[9]

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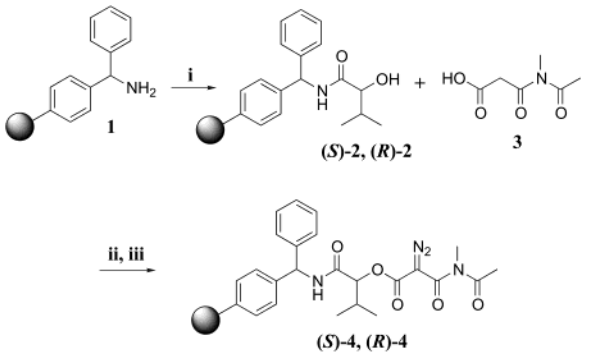
Linking to the solid support via the *para* position of the aromatic ring ensured little influence of the extra asymmetric center on the facial selectivity, while preserving its convergent assembly.[1] Coupling of the BHA resin with both enantiomers of α-hydroxyvaline furnished the immobilized auxiliaries (*S*)-**2** and (*R*)-**2** (Scheme 1), as evident by a

Scheme 1. Synthesis of Chiral Linkers (*S*)- and (*R*)-**4**[a]



[a] (i) D- or L-hydroxyvaline, BOP, HOBt; (ii) DIC, DMAP; (iii) MsN_3, Et_3N.

negative ninhydrin test and strong amide I band ($\nu_{C=O}$ = 1654 cm^{-1}) in the FTIR spectrum. These, in turn, were functionalized with *N*-acylmalonamic acid **3** and subjected to diazotransfer, providing diazoimide resins (*S*)-**4** and (*R*)-**4**. Characteristic diazo (ν_{diazo} = 2139 cm^{-1}) stretch in the FTIR spectra was employed to monitor the course of the reaction.

Rh(II)-catalyzed nitrogen extrusion, followed by cycloaddition in the presence of vinyl ethers, completed the solid phase assembly. The high solubility and high turnover ratio (>3000)[2] of the $Rh_2(pfbm)_4$ catalyst enabled a smooth adaptation of the solution phase protocol to the solid phase synthesis. After extensive washing of the resin, the detachment of the bicyclic structures **5**−**11** (Scheme 2) was accomplished as previously described (1 M methylamine in methanol, 23 °C, sonication).[1]

The extent of diastereofacial selectivity with the resin-supported asymmetric bias was found to be comparable with our solution phase results.[1] The induction of stereoselectivity of the auxiliary can be best illustrated by the chiral (−)-menthyl-based dipolarophile. The cycloaddition proceeded with a high degree of selectively in both the "matched" (>95% de) and even the "mismatched" case (90% de).

In every case, the ^1H NMR and HPLC of the liberated crude material indicated a remarkable purity of the aminolysis-derived products with the desired bicyclic species being the sole products of the multistep synthetic sequence. Unidentified nonpolar impurities, which appeared to originate from the polystyrene resin itself, were also present in the crude mixtures in varied quantities. Hence, only a gradient

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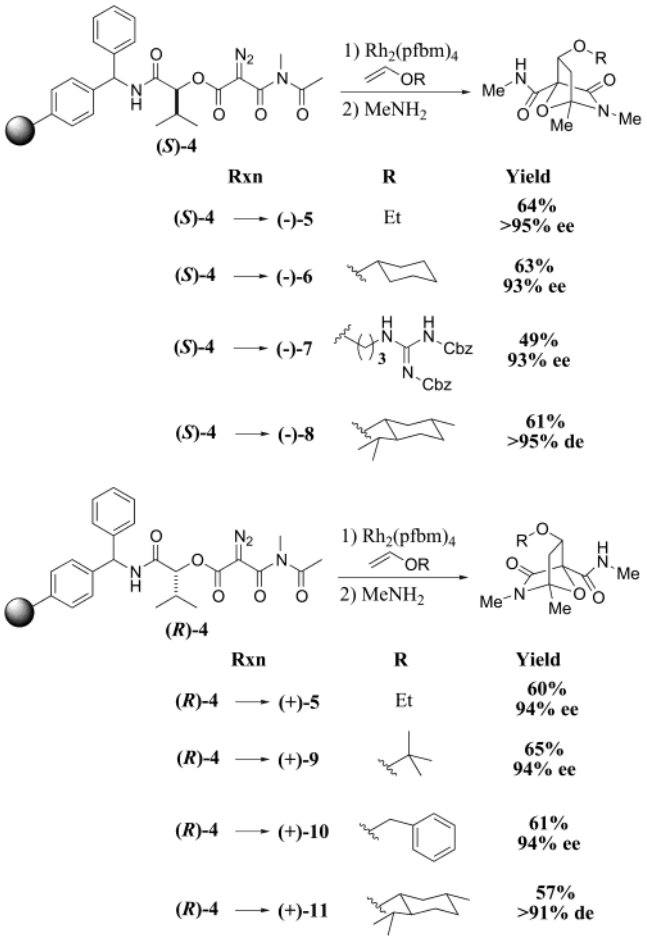
Scheme 2. Induction of Facial Selectivity with Chiral Resins

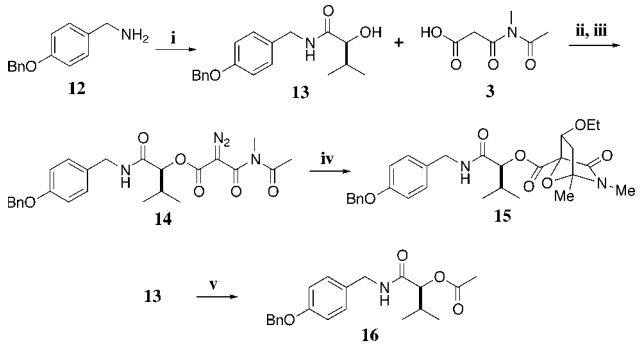


filtration through a short silica gel plug was required to afford analytically pure (>95% by HPLC and ^1H NMR) bicyclic substrates in 55−60% isolated yields after five synthetic steps.[10] As observed in our solution phase studies,[1] secondary amines, diethylamine and dibenzylamine, fail to liberate substrate from the resin.

The rate and purity of the resin cleavage stimulated our interest in investigating this unusual yet highly beneficial behavior. As an initial experiment, a comparative kinetic analysis was undertaken to ascertain and quantify the observed rate enhancement for the auxiliary cleavage. Three aminolysis substrates were envisioned, cycloadduct functionalized auxiliary (*S*)-**15**, acetyl functionalized substrate (*S*)-**16**, and methyl acetate itself. Benzyl-substituted auxiliary (*S*)-**13** (Scheme 3), designed to mimic the BHA solid phase attachment, was synthesized from benzoxy benzylamine **12** and L-hydroxyvaline. Subsequent diazotransfer and Rh(II) catalysis under standard conditions yielded cycloadduct (*S*)-**15** in good yield. Cleavage substrate (*S*)-**16** was generated from direct acylation of (*S*)-**13**.

(10) The overall yield is based on the initial loading of BHA resin (0.75 mmol/g). The solid phase products were compared with analogous solution phase substrates. The species liberated from the solid support matched well with the solution phase synthesized heterocycles in all physical properties, including optical rotation.

Scheme 3. Synthesis of Substrates for Kinetic Analysis[a]



[a] (i) L-Hydroxyvaline, BOP, HOBt, 85%; (ii) DIC, DMAP; (iii) MsN_3, Et_3N, 73%; (iv) $Rh_2(pfbm)_4$, ethyl vinyl ether, 83%; (v) Ac_2O, Et_3N, 82%.

Substrates (*S*)-**15** and (*S*)-**16**, along with methyl acetate, a kinetic control, were subjected to aminolysis with methylamine under pseudo-first-order conditions (25 equiv of $MeNH_2$, 23 °C) and the reaction course was monitored by ^1H NMR, until near completion (Figure 1). Ester (*S*)-**15** was

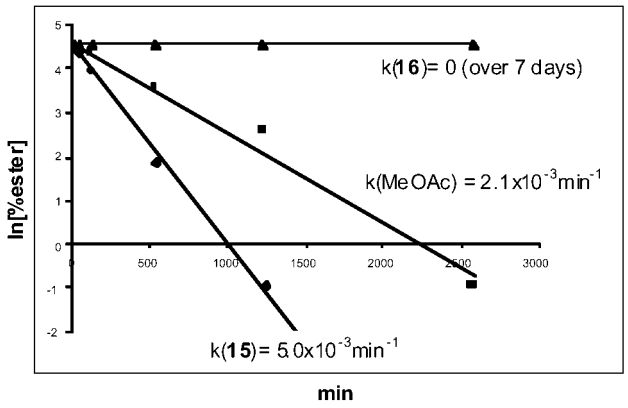


Figure 1. Kinetic analysis of cleavage substrates (*S*)-**16**, methyl acetate, and (*S*)-**15**.

cleaved significantly faster than the other two substrates. In fact, the rate was more than 2-fold greater for (*S*)-**15** compared to methyl acetate. In contrast, no aminolysis was observed for acetate (*S*)-**16**. These data suggest that the bicyclic product itself was playing a role in its cleavage from the auxiliary.

To ascertain the possibility and nature of a self-catalyzed aminolysis, a molecular mechanics investigation of the bicyclic scaffold and a primary amine was initiated using the MacroModel software package.[11] Using a Monte Carlo conformational search routine,[12] the amine was allowed to sample various binding arrangements via rotational/translational search with energetically accessible conformations of the bicyclic species. Thus, a set of the most favored arrangements was established, a great majority of which were small permutations of a single hydrogen-bonded conformation (Figure 2). A unique recognition event is predicted to

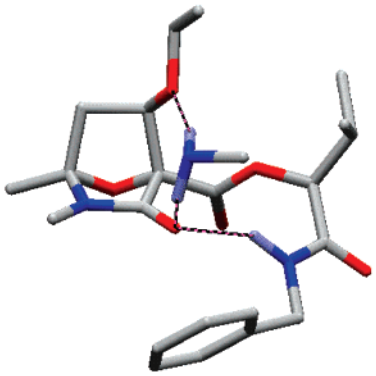


Figure 2. Computational model of nucleophilic attack.

occur between the primary amine and rigidly projected hydrogen-bond acceptors (i.e., the ether and carbonyl oxygens). These are positioned ideally for the formation of two hydrogen bonds with the primary amine, effectively fixing the nucleophile near the ester group.

An emerging model for this rate enhancement involves an amine nucleophile, entropically constrained in the immediate proximity of the electrophilic site, where it is presented to the ester carbonyl in a Burgi−Duntz type arrangement.[13] Hence, the reactivity of the bound amine is enhanced due to potential contributions from both proper orientation of the reagents and extra electron density on the amine provided by the polarization effect of the hydrogen-bond acceptors.[14]

In addition to rate enhancement, this system displays several characteristics that provide for chemoselective cleavage. First, since secondary and tertiary amines cannot form a bis-hydrogen bonding interaction, the auxiliary ester is immune to their attack (vide infra). Second, since the recognition element is not present until the cycloaddition step, none of the previous reaction byproducts that are carried through on the resin will undergo cleavage. In the absence of the complexation site, these esters would be guarded from cleavage by the bulk of the chiral auxiliary, as demonstrated in the kinetic study with (*S*)-**16**. This, in turn, ensures high purity of the liberated material.

Thus, a dual chemoselectivity is accomplished, whereby only a specific class of nucleophiles can react with only one type of electrophile, leaving potential byproducts attached to the solid support and sparing less reactive electrophilic

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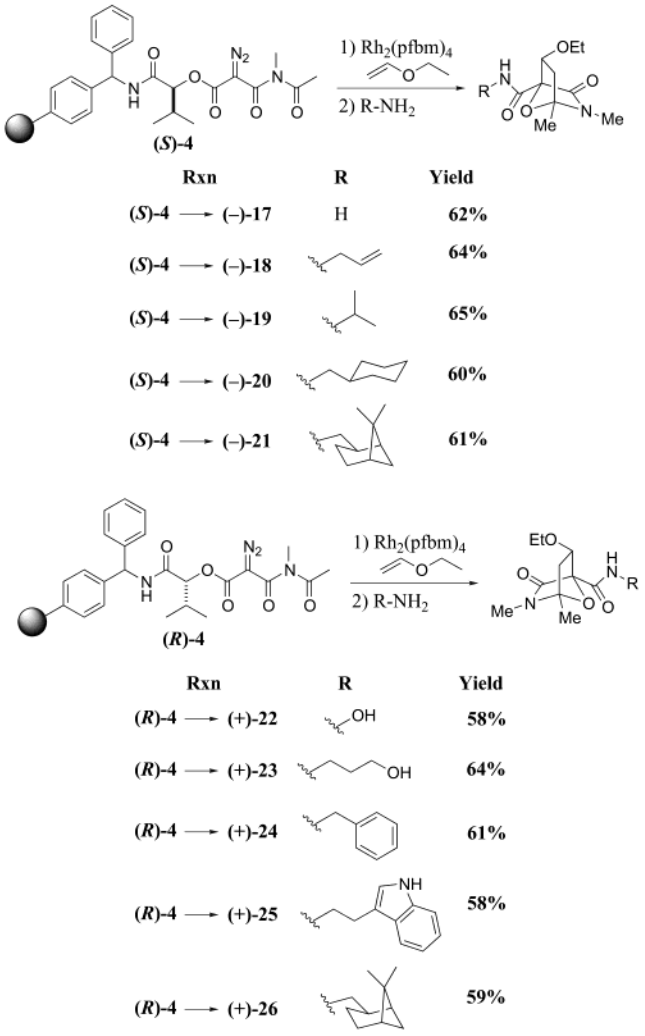
Scheme 4. Selective Resin Cleavage with Substituted Amines



functionalities. The cycloaddition, therefore, fulfills the function of a "safety-catch" trigger.[15] A unique linker strategy emerges when considering the chemoselectivity and rate enhancement of the cleavage, since the desired product can only be cleaved under mild conditions after completion of the cycloaddition step. Hence, the bicyclic structure acts similarly to an enzyme by (i) specifically "recognizing" its substrate, (ii) orienting it vis-à-vis the reactive functionality, and (iii) promoting the reaction via stereoelectronic and inductive incentives.

To demonstrate the potential of a simultaneous resin cleavage and diversity elaboration, polymer-supported diazoimides (*S*)-**4** and (*R*)-**4** were subjected to the cyclization−cycloaddition, followed by resin cleavage with a variety of primary amines (Scheme 4). After incubation with an amine scavenger (Amberlyst-15), the crude mixtures were filtered through a plug of silica gel to provide compounds **17**−**26**. The functionalized primary amines liberated product at rates comparable with methylamine. In fact, no relationship between cleavage rate and nature of the amine could be established, as α-branched, *β*-branched, and linear amines showed very similar reactivities. No byproducts from the substrate assembly were visible in the ^{1}H NMR spectrum, and no further chromatographic purification was required to achieve this high level of purity.

As a result, a library of bicyclic substrates was generated with primary amines serving as diversity elements. To quantify the diastereofacial selectivity of the cycloaddition step, (−)-*cis*-myrtanylamine was employed. In the case of resin (*S*)-**4**, the anticipated compound **21** was the only diastereomer observed in the ^{1}H NMR spectrum, indicating an exceptionally high (>95% de) level of diastereoselection. Similarly, the linker containing the opposite asymmetric bias (*R*)-**4** provided diastereomer **26** as the sole product.

In conclusion, we have demonstrated the adaptability of a 1,3-dipolar cycloaddition, utilizing a chiral auxiliary, to the solid phase synthesis of a diversity scaffold. In addition, we have discovered a novel, self-promoted, and chemoselective resin cleavage process. The synthesis and evaluation of scaffold-based libraries is currently underway.

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Supporting Information Available: Experimental details and characterization of compounds **5**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note added after ASAP: There were errors in Schemes 1−4 in the version posted ASAP March 30, 2002; the corrected version was posted April 9, 2002.

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