Dipeptide-Derived Chiral Tri- or Diammonium Salt-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition Reaction of Nitrones with α-(Acyloxy)acroleins

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Abstract. Organoammonium salts of dipeptide-derived chiral triamine or
diamine with TIOH catalyze the enantioselective 1,3-dipolar cycloaddition
reaction of α-acyloxyacroleins with nitrones to give the corresponding
adducts in good yields (up to 96%) with high diastereomeric and enantioselectivity
(up to 89% ee). Although α-[α-methoxybenzoyloxy]acrolein is rather
unstable under the reaction conditions, α-[3-pyrroline-1-
carbonyloxy]acrolein is stable enough to be smoothly converted to the
adducts with the aid of chiral organoammonium salt catalysts.

Key words α-(acyloxy)acrolein, 1,3-dipolar cycloaddition, enantioselective,
isoaxolidine, nitrone, organoammonium salt, tetrastituted carbon center

Isoxazolidine, a five-membered ring containing adjacent nitrogen and oxygen atoms, is an important structure in medicinal chemistry.1 It is also a useful building block since it can be easily converted to β-amino acids, β-lactams, or β-amino alcohols.2 Isoaxazolidines are generally synthesized through the 1,3-dipolar cycloaddition reaction of nitrones. Thus, for the stereoselective synthesis of isoxazolidines, many methods have been developed for the catalytic asymmetric 1,3-dipolar cycloaddition of nitrones.3 In many of these methods, α-unsubstituted α,β-unsaturated carbonyl compounds are used as 1,3-dipolarophiles (Scheme 1). On the other hand, when α-substituted α,β-unsaturated carbonyl compounds are used as 1,3-dipolarophiles, isoaxazolidines with a tetrastituted carbon center are obtained. Thus, several methods have been developed for the asymmetric 1,3-dipolar cycloaddition of nitrones with α-substituted α,β-unsaturated carbonyl compounds.4 However, in most of these reports, 1,3-dipolarophiles are limited to methacrolein or methaclyonitrile.

α-(Acyloxy)acrolein, an α-substituted acrolein, is highly useful as a dienophile for asymmetric cycloaddition reactions. For example, Ishihara’s group reported an enantioselective Diels-Alder reaction and [2+2] cycloaddition reaction with α-(acyloxy)acrolein.6-8 Chiral primary ammonium salt catalysts stereoelectively promote these reactions to give carbocyclic quaternary α-hydroxycarbonyl compound derivatives. Based on this study, we envisioned that chiral primary ammonium salts would stereoelectively promote the 1,3-dipolar cycloaddition of nitrones with α-(acyloxy)acroleins and give isoaxazolidines with an oxygen-containing tetrastituted carbon center. These isoaxazolidines could be new chiral building blocks with synthetic utility, since they could be easily converted to acyclic aminoalcohols via N–O bond cleavage under mild reducing conditions.9 We report here our study on the development of an enantioselective 1,3-dipolar cycloaddition reaction of nitrones with α-(acyloxy)acroleins.

Our study commenced with examination of the 1,3-dipolar cycloaddition reaction of nitrone 4a with α-(p-methoxybenzoyloxy)acrolein (2). According to the procedure for the Diels–Alder reaction with 2, the reaction of 4a (2 equiv) with 2 was conducted in the presence of a chiral triammonium salt 1a·2·8CuF5SO3H (10 mol%) in THF or EtNO2. However, the

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corresponding adduct 5a was not obtained, and almost all of 2 decomposed. By the screening of solvents, we found that the reaction proceeded slowly in CHCl₃ to give endo-5a as a major diastereomer (5:9:1 dr) with 75% ee, although the yield was poor (Table 1, entry 1). This low yield was attributed to the lower reactivity of 4a compared to dienes, and to the instability of 2 under the reaction conditions. Thus, the use of two equivalents of 2 relative to 4a improved the yield of 5a (52%) without decreasing the enantioselectivity (entry 2).

The ester group of 5a was also reduced to make the product more stable than 1a. To suppress the decomposition of 1,3-dipolarophiles, we next examined the cycloaddition with diammonium salts of which should be lower than those of the corresponding triammonium salts. We found that the use of diaminium salt 1b·2C₅F₅SO₃H or monoammonium salt 1c·C₅F₅SO₃H significantly suppressed the decomposition of 2 during the reaction course, and endo-5a was obtained with good enantionic excess (65 and 74% ees) (entries 3 and 4). However, the yield of 5a was not improved, and a significant amount of unreacted 2a was recovered. These results showed that the catalytic activities of 1b·2C₅F₅SO₃H and 1c·C₅F₅SO₃H were similar to that of 1a·2.8C₅F₅SO₃H.

Since acrolein 3 was found to be more stable than 2, we envisioned that ammonium salts of 1 with TIOH, a stronger acid than C₅F₅SO₃H, could be used as catalysts to show high activities without the decomposition of 3. As expected, the use of 1a·2.8TIOH or 1b·2TIOH successfully improved the yield of 6a (58 and 55%) (entries 8 and 9). In addition, the diastereoselectivity of 6a were also unexpectedly improved (14:1 dr, 86% ee and 20:1 dr, 80% ee). However, the use of 1b·2TfOH as a catalyst resulted in the significant decomposition of 3 to decrease the yield of 6a (entry 10).

With the optimal reaction conditions in hand, we next examined the substrate scope and limitations of the present enantioselective 1,3-dipolar cycloaddition reaction of nitroene 4 with α- (carbamoylox)acrolein 3 (Table 2). The electronic properties of the substituent on nitroene 4 significantly affected the reactivity. For example, in the presence of 1a·2.8TIOH as a catalyst, the reaction of nitrones 4b and 4c bearing an electron-rich aromatic substituent gave the corresponding adducts 6b and 6c in high yields (83 and 96%) with good enantioselectivities (86 and 76% ee) (entries 1 and 3). Although 1b·2TIOH showed catalytic activity similar to that of 1a·2.8TIOH in the reaction of 4a, the use of 1b·2TIOH gave 6b and 6c in moderate yields (66 and 50%) (entries 2 and 4). The absolute configuration of endo-6c was determined to be (3S,4S) based on an analysis of CD spectra. This stereochemistry could be explained by the transition state assemblies shown in Figure 1. As in the Diels–Alder reaction and [2+2] cycloaddition reaction with α-(acyloyloxy)acroleins, 7 (Z)-iminium ion intermediate would be generated from 1a·3TIOH 16 and 3 as an active species. This (Z)-iminium ion intermediate would be stabilized by intramolecular hydrogen bonding of the pyrrolidinium group with the carbamoyl group. In this active species, re-face of the iminium group is shielded by the benzyl group. Thus, nitrones 4 should approach the si-face of the iminium group to give (4S)-adducts preferentially. The result that the use of 3 improved the diaxial- and enantioselectivity might be attributed to the stronger intramolecular hydrogen bonding with the carbamoyl group than with the p-methoxybenzoyl group to make the asymmetric environment more rigid.
2-Furyl-substituted 4d showed unexpectedly poor reactivity despite the electron-rich furyl group, albeit the enantioselectivity was high (entries 5 and 6). In contrast to electron-rich nitrones, 4e and 4f bearing an electron-deficient aromatic substituent showed moderate to poor reactivities (entries 7–10).

In addition to aromatic substituents, a 2-phenylethynyl group could be successfully incorporated into adduct 6g with ca. 80% ee, although the yield was moderate (entries 11 and 12). Cyclopropyl-substituted adduct 6h was also obtained in moderate yield (44–45%) with moderate enantioselectivity (46–48% ee) (entries 13 and 14). Notably, 1b:2TIOH gave slightly better results than 1a:2TIOH in the reaction of less-reactive nitrones 4d–4g.

The 1,3-dipolar cycloadducts 6 are useful compounds for the synthesis of various chiral aminols with an oxygen-containing tetrasubstituted carbon center (Scheme 2). For example, reduction of the formyl group of endo-6a with NaBH₄ gave the corresponding carbamoyl-protected diol. The subsequent reductive removal of the 3-pyrrrole-1-carbonyl group with LiAlH₄ gave diol 7 in 71% yield (two steps). In addition, Wittig reaction of endo-6b with PhP=CHCO₂Et gave unsaturated ester 8 in 97% yield. Reductive N-O bond cleavage of 8 with Zn dust gave the corresponding acyclic aminol 9 in 81% yield.

In conclusion, we have developed a dipeptide-derived tri- or diamonium salt-catalyzed enantioselective 1,3-dipolar cycloaddition of α-(acyloxy)acroleins with nitrones to provide chiral isoxazolidines with an oxygen-containing tetrasubstituted carbon center. The ammonium salts of chiral trisamine 1a and diamine 1b with TIOH successfully promoted the reaction with high diastereo- and enantioselectivity.

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Supporting Information

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