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Ytterbium(III) trifluoromethanesulfonate catalyzed solid phase aza Diels–Alder reaction and subsequent facile adduct release

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Abstract

Ytterbium(III) trifluoromethanesulfonate has been demonstrated to catalyze the solid phase aza Diels–Alder reaction of an aldehyde, a diene, and immobilized benzylamine. The [4+2] adducts were cleaved from solid support efficiently using a 'trace-less' release methodology. The piperidine derivatives were obtained in excellent to reasonable yields with high levels of purity. © 1999 Elsevier Science Ltd. All rights reserved.

The aza Diels–Alder reaction (aza DA) is one of the most convenient and versatile synthetic routes to nitrogen containing heterocyclic compounds,[1] which are a class of organic molecules with biological significance and often used as pharmacophores. In a typical aza DA reaction, imine acts as a dienophile and reacts with a diene to yield a [4+2] adduct. In many cases, the imine can be prepared in situ. Even direct combination of three components, an iminium, an aldehyde, and a diene, can achieve very good reaction results. In recent years, the aza DA has attracted considerable attention due to its wide application. Chiral amines[2] and amino acids[3] have been employed as chiral directing groups for stereoselective preparation of *N*-heterocyclic compounds. Aqueous aza DA reactions have also been developed.[4,5] More recently, we have reported the aza DA reactions in aqueous media catalyzed by a unique type of Lewis acids, lanthanide(III) trifluoromethanesulfonates (lanthanide triflates).[6] Continuing our work in lanthanide catalysis, we describe here a solid phase aza DA reaction catalyzed by ytterbium(III) triflate and subsequent trace-less product release from the polymer support.

Solid phase synthesis has been successfully applied to the preparation of a variety of heterocyclic structures, such as benzopiperazinones,[7] pyrazolines,[8] pyrimidines,[9] etc. Solid phase Mannich–Michael reactions involving polymer-bound imines and the Danishefsky's diene have been recently reported.[10] In our approach of solid phase aza DA reaction, aminomethylated polystyrene resin (Nova-Biochem) was used directly, without modification or functionalization, as the immobilized amine component. Upon direct combination of the resin, diene, aldehyde, and lanthanide(III) triflate, the reaction proceeded smoothly. The product release was effected utilizing a tertiary amine *N*-dealkylation method involving 1-chloroethyl chloroformate (ACE-Cl) treatment and methanolic decomposition of the resulting carbamate.

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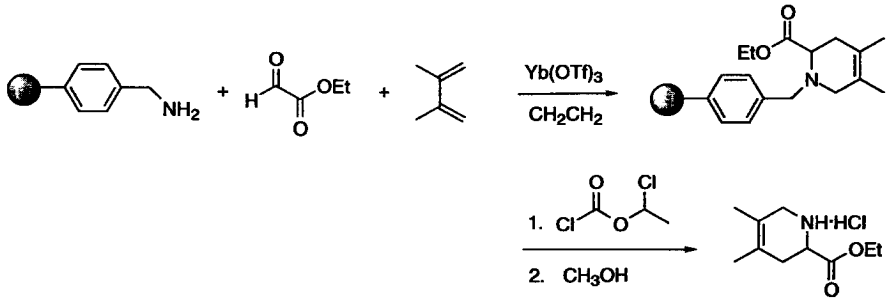
This mild and effective *N*-debenzylation approach has been used in solution chemistry and its feasibility of solid phase application has recently been demonstrated.[11] Taking advantage of this 'trace-less' procedure, the [4+2] adducts formed on solid phase were released from the polymer support with remarkable purity.

Lanthanide(III) triflates, a unique class of water-stable and active Lewis acids that were developed and commercialized recently, have been used by many researchers to catalyze a variety of reactions including aza DA reactions both in organic and aqueous media.[12] In our initial studies, we found that, in the presence of 0.1 equivalent of a lanthanide triflate, the aza DA reaction can proceed by simply mixing the amino resin, ethyl glyoxylate, and 2,3-dimethyl butadiene in CH_2Cl_2 at room temperature. We investigated the effectiveness of four lanthanide triflates (hydrated and/or anhydrous), $La(OTf)_3$, $Nd(OTf)_3$, $Dy(OTf)_3$, and $Yb(OTf)_3$ in catalyzing the reaction shown in Scheme 1 (Table 1) and compared with the reaction without a Lewis acid. There was no significant difference among the four lanthanide triflates in terms of the adduct yield although $Yb(OTf)_3$ seemed to have slight advantage over the other three, while the reaction with the absence of a Lewis acid did not yield any product. It is also worth mentioning that 0.1 equivalent of $AlCl_3$ or $MgCl_2$ did not show catalytic effect for this reaction. On the other hand, ytterbium triflate recovered (through aqueous extraction and drying) after the reaction was reused and exhibited the same catalytic activity.



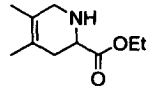
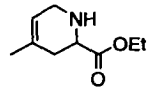
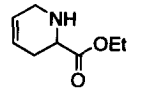
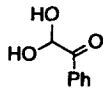
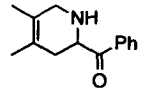
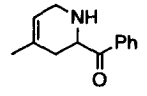
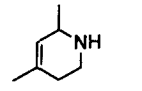
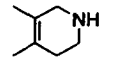
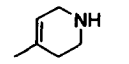
Scheme 1.

A typical procedure is as follows: To a suspension of 250 mg of polystyrene amino resin in 2 mL of CH_2Cl_2 in a peptide vessel, were added 1.2 equivalents of aldehyde, 2.5 equivalents of diene, and 10% mol of $Yb(OTf)_3$ (extra 1 equivalent of TFA for entries 6–8). The vessel was tightly capped and shaken for 12 to 48 h. The reaction was monitored using a Kaiser test. If the test result was positive after 12 h for entries 1–3, an additional 0.3 equivalent of glyoxylate was added to the reaction mixture and the reaction was allowed to continue. The resin was washed with CH_2Cl_2 (2×3 mL), triethylamine in CH_2Cl_2 (10%, 2×3 mL), CH_2Cl_2 (3×3 mL) successively, and then suspended in CH_2Cl_2. To the suspension was added 5 equivalents of 1-chloroethyl chloroformate and the mixture was gently shaken for 3 h, except for entry 6 where reflux in dichloroethane was needed. The resin was filtered off and the filtrate was concentrated.

Table 1
Effectiveness of lanthanide(III) triflates in catalyzing the solid phase aza DA reaction shown in Scheme 1

$Ln(OTf)_3$	No L.A.	La hydrate	Nd anhydrous	Dy anhydrous	Yb hydrate	Yb anhydrous
Yield %	0	85	92	82	91	93

Table 2
$Yb(OTf)_3$ catalyzed solid phase aza Diels–Alder reaction and product release

Entry	Diene	Aldehyde	Solvent[a]	Product	Yield %[b]	Purity %[c]
1			CH_2Cl_2		93	95
2		·	CH_2Cl_2		96	94
3		·	CH_2Cl_2		83	96
4			CH_2Cl_2		82	90
5		·	CH_2Cl_2		80	88
6			CH_2Cl_2, TFA		52[d]	90
7		·	CH_2Cl_2, TFA		70	94
8		·	CH_2Cl_2, TFA		62	93

[a] Solvents for solid phase aza DA reactions. One equivalent of trifluoroacetic acid was used for entries 6 - 8. [b] Based on original amino substitution rate of the resin. [c] Determined by C_8 reverse phase HPLC using CH_3CN/H_2O (25 - 40% H_2O containing 0.1% TFA) mixture. [d] Product release was carried out in refluxing dichloroethane.

The concentrated residue was dissolved in methanol and heated to reflux for 2 h. The solvent was removed to yield the cyclic secondary amine as a HCl salt (Table 2).[13]

Although it has been demonstrated that aza DA reactions in organic solvent are somewhat sensitive to water content (e.g., presence of more than 1 equivalent of H_2O retards the reaction while trace amount of H_2O actually promotes the reaction),[2a] we did not observe the negative effects of water on the reactions we investigated. We believe that the water produced from imine generation and brought in through $Ln(OTf)_3$ hydrate was tolerated by the system primarily due to the water stable nature of lanthanide triflates, which allows the reaction to proceed via direct combination of the three components. It is worth noting that even with the addition of a 37% aqueous solution of formaldehyde in entries 6–8, the reactions still gave reasonable yields. The drop in yield was caused mainly by incomplete solvation of the polymer support in the presence of relatively large amount of water. It is also interesting to notice that the hydrate form of phenylglyoxal worked well for the reaction (entries 4 and 5).

ACE-Cl dealkylation works best for cyclic tertiary amines, which perfectly fits the feature of the resin bound aza DA products. The fact that only desired [4+2] adducts, the cyclic tertiary amines, can be released from the polymer support enables a clean and 'trace-less' resin cleavage, which was demonstrated by high levels of purity of the adducts. Another advantage of ACE-Cl resin cleavage is the simultaneous debenzylation of the adducts with the double bond remaining intact for further synthetic manipulation. This cannot be achieved by the commonly used catalytic hydrogenation debenzylation method.

In conclusion, we have reported a new approach for solid phase aza DA reaction catalyzed by $Yb(OTf)_3$ utilizing polymer bound amine with in situ imine generation. The products were released cleanly from the polymer support by treatment with ACE-Cl. The piperidine derivatives were obtained in good yields and high levels of purity.

Acknowledgements

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13. NMR spectrum data for the final products, entry **1**: ^{1}H: (300 MHz, $CDCl_3$): 10.29 (s, 1H), 10.10 (s, 1H), 4.25 (q, J=7.0 Hz, 2H), 4.08 (q, J=7.5 Hz, 1H), 3.77 (d, J=16.5 Hz, 1H), 3.63 (d, J=16.5 Hz, 1H), 2.60 (s, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.28 (t, J=7.0 Hz, 3H); ^{13}C: (75 MHz, $CDCl_3$): 168.2, 124.1, 119.8, 62.7, 53.3, 45.0, 30.3, 18.9, 16.1, 14.2. **2**: ^{1}H: 10.20 (s, 1H), 10.08 (s, 1H), 5.36 (s, 1H), 4.25 (q, J=7.0 Hz, 2H), 4.11 (q, J=7.0, 1H), 3.89 (d, J=16.0 Hz, 1H), 3.73 (d,

J=16.0 Hz, 1H), 2.59 (m, 2H), 1.72 (s, 2H), 1.26 (t, J=7.0 Hz); ^{13}C: 168.1, 132.3, 114.4, 62.8, 53.4, 41.3, 29.3, 23.2, 14.2. **3**: ^{1}H: 10.27 (s, 1H), 10.22 (s, 1H), 5.89 (d, J=10.5 Hz, 1H), 5.72 (d, J=10.5, 1H), 4.28 (q, J=7.0 Hz, 2H), 4.13 (t, J=6.5, 1H), 3.98 (d, J=17.5 Hz, 1H), 3.82 (d, J=16.5 Hz, 1H), 2.75 (s, 2H), 1.29 (t, J=7.0 Hz, 3H); ^{13}C: 168.2, 124.2, 120.7, 62.9, 52.8, 41.4, 24.9, 14.2. **4**: ^{1}H: 10.17 (s, 1H), 10.11 (s, 1H), 7.88 (d, J=7.5 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 5.08 (q, J=7.0 Hz, 1H), 3.97 (d, J=16.0 Hz, 1H), 3.81 (d, J=16.0 Hz, 1H), 2.54 (s, 2H), 1.64 (s, 3H); ^{13}C: 194.9, 134.4, 133.7, 129.2, 123.6, 120.5, 57.1, 45.6, 32.0, 18.9, 16.1. **5**: ^{1}H: 10.10 (s, 2H), 7.89–7.86 (m, 2H), 7.65–7.60 (m, 1H), 7.51–7.46 (m, 2H), 5.52 (s, 1H), 5.04 (dd, J=10.0, 7.2 Hz, 1H), 4.15 (m, 1H), 3.92 (m, 1H), 2.48 (d, J=7.5 Hz, 2H), 1.75 (s, 3H); ^{13}C: 195.4, 134.7, 133.6, 132.6, 129.3, 128.9, 114.9, 57.2, 42.1, 31.4, 23.0. **6**: ^{1}H: 9.61 (s, 2H), 5.25 (m, 1H), 4.02 (d, J=13.5, 1H), 3.60 (d, J=13.5 Hz, 1H), 3.23 (s, 1H), 3.00 (m, 1H), 2.54 (m, 1H), 1.71 (s, 3H), 1.30 (d, J=6.6 Hz, 3H); ^{13}C: 132.5, 124.1, 57.4, 46.5, 28.8, 23.2, 19.0. **7**: ^{1}H: 9.67 (s, 2H), 3.48 (s, 2H), 3.23 (m, 2H), 2.34 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H); ^{13}C: 126.0, 119.1, 45.4, 41.0, 27.6, 18.9, 16.3. **8**: ^{1}H: 9.57 (s, 2H), 5.33 (s, 1H), 3.57 (s, 2H), 3.22 (m, 2H), 2.30 (s, 2H), 1.71 (s, 3H); ^{13}C: 134.1, 113.8, 41.6, 40.8, 26.4, 23.4.