

AgOTf-Catalyzed Aza-Diels–Alder Reactions of Danishefsky's Diene with Imines in Water

Catherine Loncaric, Kei Manabe, Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Fax: (+81)-3-5684-0634, e-mail: skobayas@mol.f.u-tokyo.ac.jp

Received: November 26, 2002; Accepted: January 8, 2003

Abstract: Aza-Diels–Alder reactions of Danishefsky's diene with imines in water took place smoothly in the presence of a catalytic amount of silver triflate to afford dihydro-4-pyridones in high yields. The silver triflate-catalyzed three-component reactions starting from aldehydes, amines, and Danishefsky's diene were also performed efficiently. In the three-component reactions with benzaldehyde, the addition of a non-ionic surfactant was found to be effective.

Keywords: aqueous reaction; aza-Diels–Alder reaction; Lewis acid; silver triflate; water

The increasing interest in the development of organic reactions in aqueous media is easily justified by economical, environmental, and safety issues. Thus, many aqueous reactions have been reported recently.^[1] On the other hand, aza-Diels–Alder reactions provide a powerful methodology for the construction of nitrogen-containing six-membered ring compounds.^[2] While recent progress has been made in a number of Lewis acid-catalyzed aza-Diels–Alder reactions in organic solvents,^[3–5] asymmetric versions using chiral catalysts have been also reported.^[6] Meanwhile, aza-Diels–Alder reactions in water have been limited to the use of iminium salts and water-stable dienes.^[1a,7] In the case of a water-sensitive reagent such as Danishefsky's diene,^[8] Brønsted acids have been used to catalyze this reaction.^[9] Considering the difficulty to attain mild reaction conditions as well as to design active chiral Brønsted acid catalysts, asymmetric aza-Diels–Alder reactions in water would be then mostly restricted to a chiral auxiliary methodology. In our effort to develop organic reactions in aqueous media, we have already demonstrated that some Lewis acids are effective catalysts for several carbon-carbon bond-forming reactions.^[10] To our best knowledge, except for aza-Diels–Alder reactions of iminium salts and alkyldienes promoted by lanthanides,^[11] no example of aza-Diels–Alder reactions of Danishefsky's diene and imines catalyzed by a Lewis acid in water has been yet reported in the literature. This communication reports our investigations on aza-Diels–Alder reactions in water with Danishefsky's diene in the

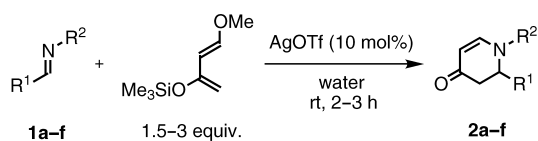
presence of a silver catalyst to afford dihydro-4-pyridones in high yields. Furthermore, silver triflate-catalyzed three-component reactions starting from aldehydes, amines, and Danishefsky's diene have also been efficiently performed.

In our preliminary study, silver triflate (AgOTf) was found to mediate an aza-Diels–Alder reaction in aqueous media (Table 1, entry 2),^[12] while no reaction proceeded without a catalyst (entry 1). Although some other Lewis acids were similarly effective,^[13] silver catalysts appeared to be suitable candidates in terms of yields.^[14] As shown in Table 1, a survey of the nature of silver catalysts confirmed that only AgOTf and AgClO₄ provided the highest yields in THF/water (entries 2 and 3). While lower yields were achieved with AgNO₃, AgSbF₆, or AgBF₄ (entries 4, 7, and 8), no reaction occurred with Ag₂CO₃ or AgOAc (entries 5 and 6).

Since our final interest is to perform organic reactions in water without using organic co-solvents, we then examined aza-Diels–Alder reactions in water as the sole solvent. The aza-Diels–Alder reaction of imine **1a** with Danishefsky's diene proceeded sluggishly without a catalyst (Table 2, entry 1), even though ¹H NMR analysis showed that approximately half of Danishefsky's diene still remained after one hour at room

Table 1. Silver catalysts for aza-Diels–Alder reaction of Danishefsky's diene with imine **1a** in THF/water.

Entry	Catalyst	Yield [%]
1	none	0
2	AgOTf	63
3	AgClO ₄	61
4	AgNO ₃	53
5	Ag ₂ CO ₃	0
6	AgOAc	0
7	AgSbF ₆	42
8	AgBF ₄	35

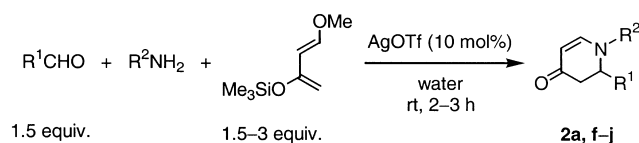
Table 2. AgOTf-catalyzed aza-Diels–Alder reactions of Danishefsky's diene with imines in water.

Entry	R ¹	R ²	Product	Yield [%]
1 ^[a,b]	Ph	Ph	2a	trace
2 ^[a]	Ph	Ph	2a	83
3 ^[a]	<i>p</i> -MeOC ₆ H ₄	Ph	2b	77
4 ^[a]	<i>p</i> -BrC ₆ H ₄	Ph	2c	75
5 ^[c]	<i>p</i> -BrC ₆ H ₄	Ph	2c	87
6 ^[c]	<i>p</i> -NO ₂ C ₆ H ₄	Ph	2d	69
7 ^[a]	Ph	Ph	2e	63
8 ^[c]	Ph	Ph	2e	92
9 ^[a]	Ph	Ph	2f	57
10 ^[a]	Ph	<i>p</i> -BrC ₆ H ₄	2f	83

^[a] 1.5 equiv. diene.^[b] Without catalyst.^[c] 3 equiv. diene.

temperature. On the other hand, the reaction proceeded smoothly in the presence of 10 mol % AgOTf to afford the dihydropyridone in 83% yield (entry 2). Moreover, it was revealed that the aza-Diels–Alder reaction using Danishefsky's diene in water was even more efficient than that in THF/water. The main reason for this high efficiency in water is probably the slower hydrolysis of the Danishefsky's diene under heterogeneous reaction conditions, which prevents formation of side products. The aza-Diels–Alder reactions using Danishefsky's diene were then investigated with a range of imines in water in the presence of 10 mol % of AgOTf. As shown in Table 2, the reactions with all imines **1a–f** afforded the corresponding cycloadducts in good to excellent yields. In some cases, the use of 3 equivalents of Danishefsky's diene improved the yields.

Three-component reactions starting from aldehydes, amines, and nucleophiles are synthetically useful not only because unstable imines can be generated *in situ*, particularly those derived from aliphatic aldehydes, but also the procedures are simplified. Accordingly, the three-component reaction starting from benzaldehyde, aniline, and Danishefsky's diene was investigated with AgOTf in water. The aldehyde was first allowed to react with the amine in water in the presence of 10 mol % of AgOTf at room temperature, and Danishefsky's diene was introduced successively. Only a trace amount of the desired cycloadduct was observed when the diene was added in one portion in the three-component reaction. However, slow addition of Danishefsky's diene to the mixture of the aldehyde and the amine over 45–60 min

Table 3. AgOTf-catalyzed three-component aza-Diels–Alder reactions in water.^[a]

Entry	R ¹	R ²	Product	Yield [%]
1 ^[b]	Ph	Ph	2a	63
2 ^[b,c]	Ph	Ph	2a	80
3 ^[c,d]	Ph	<i>p</i> -BrC ₆ H ₄	2f	90
4 ^[b,c]	Ph	<i>o</i> -MeOC ₆ H ₄	2g	56
5 ^[b]	<i>c</i> -C ₆ H ₁₁	Ph	2h	70
6 ^[b,c]	<i>c</i> -C ₆ H ₁₁	Ph	2h	51
7 ^[b]	Ph(CH ₂) ₂	Ph	2i	53
8 ^[b]	(CH ₃) ₂ CHCH ₂	Ph	2j	72

^[a] The diene was added slowly over 45–60 min.^[b] 1.5 equiv. diene.^[c] With 10 mol% Triton X-100.^[d] 3 equiv. diene.

improved the yield dramatically, while the addition time of the diene did not affect the yields significantly in the two-component aza-Diels–Alder reactions. Also, an excess of benzaldehyde to the amine, to facilitate the equilibrium formation of the imine in water, was found to increase the yield (Table 3, entry 1). Interestingly, the addition of 10 mol % Triton X-100, a non-ionic surfactant, further improved the yield to 80% (entry 2). The role of the surfactant is believed to help the formation of the imine in water, since the addition of 10 mol % of Triton X-100 did not improve the yield in the two-component reaction. Furthermore, an opposite effect was observed for aliphatic aldehydes. Indeed, the three-component aza-Diels–Alder reaction with cyclohexanecarboxaldehyde gave 70% yield, while a moderate result was obtained in the presence of Triton X-100 (entries 5 and 6). It is noteworthy that the three-component protocol was successfully performed in the reactions of aromatic and aliphatic aldehydes, and that the use of a slightly excess amount of the diene gave good to high yields of the desired adducts.

In conclusion, the aza-Diels–Alder reactions of Danishefsky's diene with imines have been found to proceed efficiently in water in the presence of a catalytic amount of AgOTf at room temperature to give the corresponding dihydro-4-pyridone derivatives in high yields. Three-component reactions of aldehydes, amines, and the diene were also conducted in water using a slow addition procedure of the diene. In the three-component reactions of benzaldehyde, yields were improved with the aid of a non-ionic surfactant Triton X-100. Further investigations on asymmetric aza-Diels–Alder reactions with a silver salt in water are under progress.

Experimental Section

Typical Procedure for Aza-Diels–Alder Reaction in THF/Water

Silver triflate (AgOTf, 7.7 mg, 0.03 mmol) and *N*-benzylideneaniline **1a** (54.4 mg, 0.3 mmol) were placed in a 5-mL round-bottom flask covered by aluminum foil. THF (0.54 mL), water (60 μ L), and Danishefsky's diene (66 μ L, 0.33 mmol) were then added successively. After stirring for 16 h at room temperature, the reaction mixture was treated with 2 mL of a saturated NaHCO₃ solution. The aqueous phase was extracted with CH₂Cl₂ and the combined organic phases were dried over Na₂SO₄. Purification of the crude mixture by preparative TLC (silica gel) afforded the cycloadduct **2a** in 63% yield.

Typical Procedure for Aza-Diels–Alder Reaction in Water

In a 5-mL round-bottom flask covered by aluminum foil was placed AgOTf (7.7 mg, 0.03 mmol) and *N*-benzylideneaniline **1a** (54.4 mg, 0.3 mmol). Water (0.6 mL) and Danishefsky's diene (90 μ L, 0.45 mmol) were then added successively. After stirring for 2–3 h, the reaction mixture was diluted with water, and the organic materials were extracted with CH₂Cl₂. The organic phases were combined and dried over Na₂SO₄. Purification of the crude mixture by preparative TLC (silica gel) afforded the cycloadduct **2a** in 83% yield.

Typical Procedure for the Three-Component Aza-Diels–Alder Reaction in Water

In a 5-mL round-bottom flask covered by aluminum foil was placed AgOTf (7.7 mg, 0.03 mmol). After introduction of water (0.6 mL), benzaldehyde (46 μ L, 0.45 mmol) and aniline (27 μ L, 0.3 mmol) were sequentially introduced. Danishefsky's diene (90 μ L, 0.45 mmol) was then added dropwise over 45–60 min. After stirring for 2 h, the reaction mixture was diluted with water, and the organic materials were extracted with CH₂Cl₂. The organic phases were combined and dried over Na₂SO₄. The purification of the crude mixture by preparative TLC afforded the cycloadduct **2a** in 80% yield.

Acknowledgements

This work was partially supported by CREST and SORST, Japan Corporation of Science and Technology and by a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science (JSPS).

References and Notes

[1] a) U. M. Lindstrom, *Chem. Rev.* **2002**, *102*, 2751; b) *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic and Professional, London, **1998**.

[2] S. M. Weinreb, *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming) Pergamon, Oxford, Vol. 5, p 401, **1991**.
[3] N. J. Patmore, C. Hague, J. H. Cotgreave, M. F. Mahon, C. G. Frost, A. S. Weller, *Chem. Eur. J.* **2002**, *8*, 2088.
[4] For aza-Diels–Alder reactions with Danishefsky's diene: a) J. Collin, N. Jaber, M. I. Lannou, *Tetrahedron Lett.* **2001**, *42*, 7405; b) H. Laurent-Robert, B. Garrigues, J. Dubac, *Synlett* **2000**, 1160; c) T. Ali, K. K. Chauhan, C. G. Frost, *Tetrahedron Lett.* **1999**, *40*, 5621; d) S. Kobayashi, H. Ishitani, S. Nagayama, *Synthesis* **1995**, 1195; e) S. Kobayashi, H. Ishitani, S. Nagayama, *Chem. Lett.* **1995**, 423. With a solid catalyst: R. Kumareswaran, B. Gopal Reddy, Y. D. Vankar, *Tetrahedron Lett.* **2001**, *42*, 7493. For inverse electron demand aza-Diels–Alder reactions: a) G. Sundararajan, N. Prabakaran, B. Varghese, *Org. Lett.* **2001**, *3*, 1973; b) J. S. Yadav, B. V. Subba Reddy, R. Srinivas, Ch. Madhuri, T. Ramalingam, *Synlett* **2001**, 240.
[5] Aza-Diels–Alder reactions in methanol without catalyst: Y. Yuan, X. Li, K. Ding, *Org. Lett.* **2002**, *4*, 3309.
[6] For recent review on asymmetric hetero-Diels–Alder reactions: K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, *39*, 3558.
[7] For recent review on Diels–Alder reactions in aqueous media: F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* **2001**, 439.
[8] S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc.* **1974**, *96*, 7807.
[9] a) T. Akiyama, K. Matsuda, K. Fuchibe, *Synlett* **2002**, 1898; b) T. Akiyama, J. Takaya, H. Kagoshima, *Tetrahedron Lett.* **1999**, *40*, 7831; c) K. Manabe, Y. Mori, S. Kobayashi, *Tetrahedron* **2001**, *57*, 2537.
[10] a) K. Manabe, S. Kobayashi, *Chem. Eur. J.* **2002**, *8*, 4095; b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209; c) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15; d) S. Kobayashi, *Synlett* **1994**, 689, and references cited therein.
[11] L. Yu, D. Chen, P. G. Wang, *Tetrahedron Lett.* **1996**, *37*, 2169.
[12] A silver salt catalyzed a Mukaiyama aldol reaction in aqueous media: S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, *120*, 8287.
[13] For example, the aza-Diels–Alder reaction of 1.1 equivalents of Danishefsky's diene with imine **1a** in the presence of 10 mol % of the catalyst in THF/water (9/1): Sc(OTf)₃: 58% yield, InCl₃: 52% yield, BiCl₃: 41% yield, CuCl₂: 50% yield.
[14] We have recently found that a chiral silver salt effectively catalyzes Michael reactions in water: S. Kobayashi, K. Kakumoto, Y. Mori, K. Manabe, *Israel J. Chem.* **2001**, *41*, 247; also, catalytic enantioselective allylation reactions of aldehydes in aqueous medium have been reported; T.-P. Loh, J.-R. Zhou, *Tetrahedron Lett.* **2000**, *41*, 5261; in addition, a substoichiometric amount of water seemed to enhance an aza-Diels–Alder reaction in dichloromethane in the presence of silver phosphane partnered with carborane.^[3]