Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 4749–4753

Tetrahedron Letters

Cascade and one-pot processes providing substituted quinolines from aldimines and allylsilanes: auto-tandem catalysis of triflic imide

Naoya Shindoh, Hidetoshi Tokuyama* and Kiyosei Takasu*,†

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

Received 5 April 2007; revised 26 April 2007; accepted 1 May 2007
Available online 22 May 2007

Abstract—We have demonstrated cascade and one-pot reactions, which constitute inverse electron demand hetero-Diels–Alder reaction and oxidative aromatization, to provide substituted quinolines to form aryl aldimines and allylsilanes. The cascade process involves an auto-tandem catalysis; Tf_2NH activates these mechanistically distinct reactions. We have found that a multicomponent process starting from aniline, aldehyde, and allylsilane is also available.

Classes of cascade and one-pot reactions, which include multiple bond formation and/or transformation of functional groups, provide powerful and useful methods for the synthesis of structurally complex molecules.[1] Cascade and one-pot reactions, if possible, the catalytic variants, would give a number of opportunities to improve chemical transformations, such as reduction of the number of reaction operations, saving reagents, energy, time and labor, and minimum generation of waste. Therefore, development of efficient cascade processes would lead to significant economical and ecological impact.

Several groups depicted the significant utility of triflic imide (Tf_2NH) in the catalytic carbon–carbon (C–C) bond formation reactions, such as aldol reactions,[2] Mannich reactions,[3] Diels–Alder reactions,[4] and so on.[5] Recently, we have independently reported Tf_2NH shows good catalytic performance in several cycloaddition and cascade reactions.[6] In the processes, Tf_2NH acts as a strong Brønsted acid, as well as a precursor of the strong Lewis acidic silyl triflic imide,[7] which is generated in situ by reaction with silylated substrates, such as silyl enol ethers and allylsilanes. For instance, we have recently reported Tf_2NH-catalyzed imino Diels–Alder reaction of imines with 2-siloxydienes or its analogous three-component reaction to provide multi-substituted piperidin-4-ones.[6e] As a part of our continuous efforts, we were intrigued that Tf_2NH would display good catalytic activity in an inverse electron demand hetero-Diels–Alder reaction of 2-azadienes with electron-rich olefins.[8] In the reaction, we have also found that the same catalyst, Tf_2NH, activates dehydrogenation of tetrahydroquinolines in the presence of imine. We wish to report herein a cascade hetero-Diels–Alder reaction and oxidative aromatization, catalyzed by Tf_2NH, to construct substituted quinolines. In addition, we wish to describe a one-pot process that provides quinolines by the assistance of DDQ.

Benzylideneaniline **1a** (1.0 equiv) was treated with allyltriisopropylsilane (**2a**, 1.0 equiv) in the presence of Tf_2NH (10 mol %) in CH_2Cl_2 (DCM) at 60 °C for 24 h. Tetrahydroquinoline **3aa** was obtained in 51% yield as a mixture of two diastereomers (trans:cis = 10:9), together with quinoline **4aa** (12% yield), which resulted from oxidation of **3aa** (Table 1, run 1). The stereochemistry of both diastereomers of **3aa** was determined by the coupling constants of ^1H NMR. At the same time, production of amine **5** was observed. We believed that hydrogen transfer between the yielded tetrahydroquinoline **3aa** and imine **1a** would take place in this reaction. Thus, when the reaction of **2a** (1.0 equiv) with an excess amount of **1a** (3.0 equiv) in

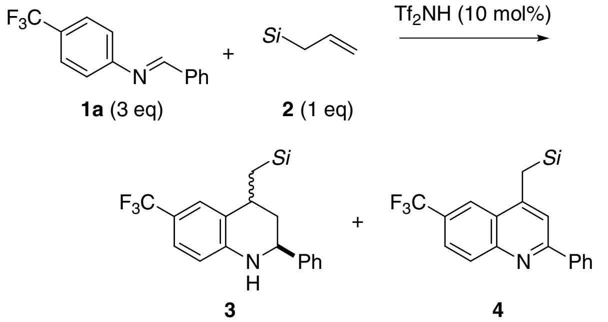
---

* Corresponding authors. E-mail addresses: kay-t@mail.pharm.tohoku.ac.jp; kay-t@pharm.kyoto-u.ac.jp

† Present address: Graduate School of Pharmaceutical Sciences, Kyoto University, Japan.

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.032

Table 1. Reaction of aldimine **1a** and allylsilanes **2** in the presence of Tf_2NH[a]



Run	**2** (Si)	Solvent	Yield[b] (%)		
			3 (trans:cis)[c]	**4**	Total (**3** + **4**)
1[d]	**2a** (TIPS)	DCM	51 (53:47)	12	63
2	**2a**	DCM	48 (74:26)	31	79
3[e]	**2a**	DCM	36 (100:0)	48	84
4	**2a**	DCE	49 (76:24)	37	86
5	**2a**	Toluene	32 (71:29)	44	66
6[f]	**2b** (TMS)	Toluene	10 (73:27)[g]	Trace	10
7	**2c** (TBS)	Toluene	32 (66:34)	39	71

[a] Reaction conditions: **1a** (3.0 equiv), **2** (1.0 equiv), Tf_2NH (10 mol %), 12 h.

[b] Isolated yields. All chemical yields are calculated based on **2**.

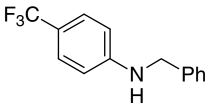
[c] The diastereomeric ratios were determined by ^1H NMR.

[d] Reaction conditions: **1a** (1.0 equiv), **2** (1.0 equiv), Tf_2NH (10 mol %), 12 h.

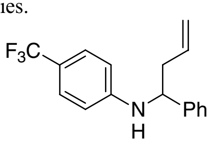
[e] Reaction conditions: **1a** (3.0 equiv), **2** (1.0 equiv), Tf_2NH (15 mol %), 6 days.

[f] Compound **5** was obtained in 22% yield as a byproduct.

[g] The yield has ~10% error owing to contamination of inseparable impurities.



5



6

the presence of Tf_2NH was carried out, the chemical yield of **4aa** increased to 31%, whereas production of **3aa** decreased to 48% and its trans/cis ratio was changed to 3:1 (run 2). When the reaction time was prolonged to six days using 15 mol % of Tf_2NH, *trans*-**3aa** as a single diastereomer and **4aa** were obtained in 36% and 48% yield, respectively (run 3). These results indicate kinetic resolution of two diastereomers of **3aa** proceeds in the oxidation process, and the reaction rate of *cis*-**3aa** is much faster than that of *trans*-**3aa**. In fact, no reaction occurred when the isolated *trans*-**3aa** was exposed to a similar reaction conditions (with 2.0 equiv of **1a** in the presence of 10 mol % of Tf_2NH in DCM). Next, the solvent effect was examined. Production of **4aa** slightly increased in 1,2-dichloroethane (DCE) and toluene (runs 4 and 5). Notably, we found the rate of the hetero-Diels–Alder reaction of **1a** with **2a** in DCE was faster than that in toluene, but, in contrast, oxidation of **3aa** smoothly proceeded in toluene rather than in DCE. Reaction in polar solvents, such as THF, CH_3CN and AcOEt, resulted in no formation of **4aa** and poor production of **3aa**, but generation of homoallylamine **6** was observed. When allyltrimethylsilane (**2b**) was employed, both **3ab** and **4ab** were obtained in low yield,[9] but the Hosomi–Sakurai type adduct **6** was obtained (run 6). In contrast, allyl-*tert*-butyldimethylsilane (**2c**) bearing a sterically demanding silyl group suppressed formation of **6** and thereby furnished heterocyclic compounds **3ac** and **4ac** (run 7).

We have considered that the cascade process involves an auto-tandem catalysis, in which Tf_2NH activates both hetero-Diels–Alder reaction of **1** with **2** and oxidation of **3**. The term ‘auto-tandem catalysis’ is defined as one catalyst which promotes two or more mechanistically distinct reactions in a cascade reaction process.[10] Recently, an auto-tandem catalysis received significant attention in its synthetic efficiency.[6d,11,12] It was also made clear that the oxidative aromatization was promoted by the assistance of both imine **1** and Tf_2NH. In the absence of either **1** or Tf_2NH, no formation of the dehydrogenated product from tetrahydroquinoline **3aa** (as a 1:1 diastereomeric mixture) was observed. The inverse electron demand hetero-Diels–Alder reaction of aryl aldimines with allylsilanes was reported by Akiyama and his co-workers as a rare example.[13] In the literature, stoichiometric amounts of $SnCl_4$ promoted the reaction to give tetrahydroquinolines. Moreover, to the best of our knowledge, no example for successive dehydrogenation to furnish quinolines from tetrahydroquinolines has been reported.[14]

For the practical synthesis of quinoline derivatives, we established an alternative oxidative conversion of *trans*-**3aa** into **4aa** using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Thus, treatment of *trans*-**3aa** with two equivalents of DDQ in DCE at ambient temperature for 1 h, 78% yield of qinoline **4aa** was obtained in the presence of 10 mol % of Tf_2NH.[15] Since Tf_2NH was compatible to these oxidative conditions, we extended the reaction sequence to a one-pot quinoline synthesis with DDQ. After treatment of a mixture of imine **1a** (1.25 equiv) and allylsilane **2a** (1.0 equiv) with a catalytic amount of Tf_2NH (10 mol %) in DCE, DDQ (2.0 equiv) was added to the reaction mixture to furnish quinoline **4aa** in 84% yield (Scheme 1). The one-pot reaction would be an alternative method to provide quinolines against the above auto-tandem catalysis procedure.

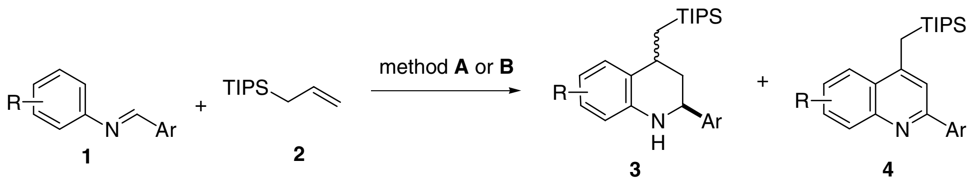
With two standard conditions in hand, we investigated the scope of the hetero-Diels–Alder reaction and successive oxidation reaction. Some of the typical results are summarized in Table 2. In all the cases, Tf_2NH acts as an auto-tandem catalyst to give quinoline **4**. In method A (in the presence of an excess amount of imine), the chemical yield of **4** resulted in low to moderate yield, and tetrahydroquinoline **3**, in which the trans diastereomer was enriched, was obtained (runs 1, 2, 4, 5, 7, 9, and 10). Imine **1h**, which was prepared from electron-donating *p*-anisidine and electron-withdrawing *p*-nitrobenzaldehyde, afforded quinoline **4ha** in 47% yield by method A (run 10). In method B (consequent addition of 2.0 equiv DDQ), quinoline **4** was obtained in good yield (runs 3, 6, 8, 11, and 12). It should be noted that the reaction of substrates containing halogen or nitro groups, which make possible further derivatization, occurred smoothly.

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{DDQ (2 eq), rt, 10 min}]{Tf_2NH\text{ (10 mol\%)}, \text{ DCE, 60 °C, 3 h;}} \underset{\text{84\% yield}}{\mathbf{4aa}}$$

Scheme 1.

It is sometimes difficult to isolate and handle an alkyl aldimine prepared from an aliphatic aldehyde, owing to its instability. To avoid these problems, we envisaged to elaborate the cascade reaction to the multicomponent variant. When a mixture of **2a** (1.0 equiv), aniline **7** (3.0 equiv), and isobutylaldehyde (**8**) (3.0 equiv) in the presence of Tf_2NH (10 mol %) in toluene was stirred at 60 °C (under method A-like conditions), only tetrahydroquinoline **3ka** was obtained in 60% yield as a 1:1 diastereomeric mixture (Scheme 2a). However, no formation of **4** was observed, despite the excess amount of imine that would be formed in the reaction. On the other hand, quinoline **4ka** could be synthesized under method B-like conditions. Thus, heating a mixture of **2a** (1.0 equiv), **7** (1.25 equiv) and **8** (1.25 equiv) in DCE at 60 °C, followed by addition of DDQ (2.0 equiv)

Table 2. Scope of the auto-tandem catalysis procedure[a]



Run	**1** (R, Ar)	Method	Products	Yield[b] (%)		
				3 (trans:cis)[c]	**4**	Total (**3** + **4**)
1	**1b** (H, Ph)	A	**3ba**, **4ba**	11 (72:28)	28	39
2	**1c** (*p*-NO_2, Ph)	A	**3ca**, **4ca**	60 (60:40)[d]	28[d]	88
3	**1c**	B	**4ca**	0	83	83
4	**1d** (*p*-Cl, Ph)	A	**3da**, **4da**	16 (84:16)	39	55
5	**1e** (*p*-Br, Ph)	A	**3ea**, **4ea**	15 (79:21)	41	66
6	**1e**	B[e]	**4ea**	0	60	60
7	**1f** (*o*-Br, Ph)	A	**3fa**, **4fa**	47 (60:40)	19	66
8	**1f**	B[e]	**4fa**	0	72	72
9	**1g** (*p*-MeO, Ph)	A	**3ga**, **4ga**	5 (91:9)	34	39
10	**1h** (*p*-MeO, *p*-$NO_2C_6H_4$)	A	**3ha**, **4ha**	27 (62:38)	47	74
11	**1i** (*p*-Br, *o*-$NO_2C_6H_4$)	B[f]	**4ia**	0	68	68
12	**1j** (*o*-Br, *o*-$NO_2C_6H_4$)	B[g]	**4ja**	0	66	66

[a] Reaction conditions: method A; **1** (3.0 equiv), **2a** (1.0 equiv), Tf_2NH (10 mol %), toluene, 60 °C, 24 h. method B; **1** (1.25 equiv), **2a** (1.0 equiv), Tf_2NH (15 mol %), DCE, 60 °C, 3 h; then DDQ (2.0 equiv), rt, 10 min.

[b] Isolated yields. All chemical yields are calculated based on **2**.

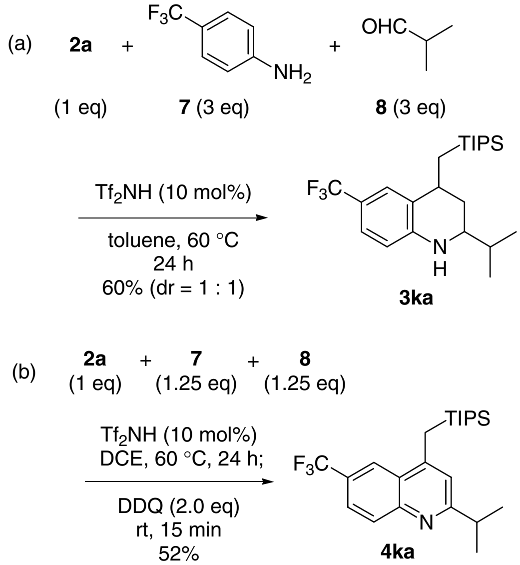
[c] The diastereomeric ratios were determined by ^1H NMR.

[d] The yield has ~10% error owing to contamination of inseparable impurities.

[e] Hetero-Diels–Alder reaction was carried out for 24 h.

[f] Hetero-Diels–Alder reaction was carried out for 1 h.

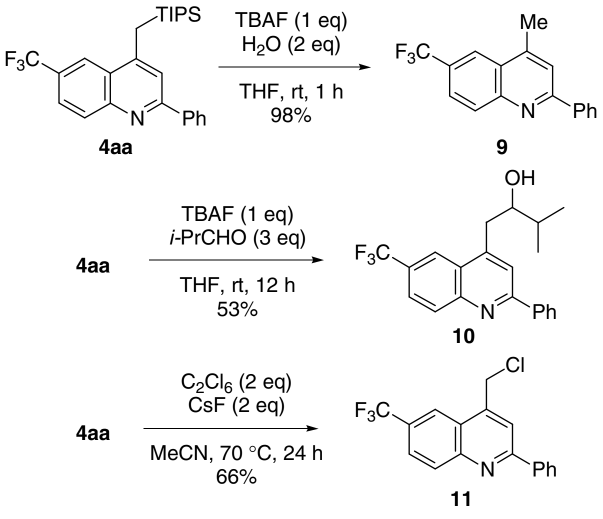
[g] Hetero-Diels–Alder reaction and DDQ-oxidation were carried out for 45 min and 1 h, respectively.



Scheme 2. Multicomponent reaction.

at rt, successfully furnished **4ka** in 52% yield (Scheme 2b).

Quinolines are important ring systems present in a variety of natural products, pharmaceuticals, and agrochemicals. To demonstrate the synthetic utility of the products in the above cascade process, transformation reactions of **4** were summarized in Scheme 3. Protodesilylation of **4aa** can be accomplished by the treatment of tetrabutylammonium fluoride (TBAF) in the presence of H_2O to give methylquinoline **9** in quantitative yield. In the presence of an aldehyde, instead of H_2O as an electrophile, alcohol **10** was obtained in 53% yield from **4aa** with formation of a new C–C bond. Moreover, the reaction of **4aa** with CsF in the presence of hexachloroethane as an electrophile[16] afforded **11**, whose chloromethyl moiety would be a trigger for further chemical transformation.



Scheme 3. Desilylative transformation of **4**.

In summary, we have found Tf_2NH acts as an auto-tandem catalyst, which activates an inverse electron demand hetero-Diels–Alder reaction and successive oxidative aromatization, to give substituted quinolines **4** from aldimines **1** with allylsilanes **2**. Notably, a multi-component strategy is also available. In the course of this study, we made clear two new catalytic aspects of Tf_2NH. To the best of our knowledge, Tf_2NH is the first example of a catalyst for inverse electron demand hetero-Diels–Alder reactions of aryl aldimines with allylsilanes. Second, tetrahydroquinoline **3** can be oxidized into **4** by the assistance of imine as an oxidant in the presence of catalytic amounts of Tf_2NH. As an alternative way to access substituted quinolines, we found a one-pot reaction adding DDQ as an oxidant would be effective. Further extension of the auto-tandem catalysis procedure into rapid synthesis of biologically active compounds is in progress.

Acknowledgments

This work was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

1. Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.
2. (a) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45–48; (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48–49.
3. Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 5335–5337.
4. (a) Nakashima, D.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1251–1253; (b) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 375–378.
5. (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204–10205; (b) Sun, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13512–13513.
6. (a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668–3669; (b) Takasu, K.; Ishii, T.; Inanaga, K.; Ihara, M. *Org. Synth.* **2006**, *83*, 193–199; (c) Takasu, K.; Hosokawa, N.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2006**, *47*, 6053–6056; (d) Takasu, K.; Nagao, S.; Ihara, M. *Adv. Synth. Cat.* **2006**, *340*, 2376–2380; (e) Takasu, K.; Shindoh, N.; Tokuyama, H.; Ihara, M. *Tetrahedron* **2006**, *62*, 11900–11907.
7. Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219–8226.
8. For a representative review on imino Diels–Alder reaction, see: Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
9. Desilylated quinoline **9**, which would be transformed from **4ab**, was also obtained in 6% yield.
10. Definition of 'auto-tandem catalysis': Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.
11. Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020.
12. Recent representative examples for auto-tandem catalysis, see: (a) Field, L. D.; Messerle, B. A.; Wren, S. L. *Organometallics* **2003**, *22*, 4393–4395; (b) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*, 1352–1353; (c) Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465–9477; (d) Enders, D.; Huttl,

M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863; (e) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770–11771.

13. Akiyama, T.; Suzuki, M.; Kagoshima, H. *Heterocycles* **2000**, *52*, 529–532.
14. As an exceptional example, Kobayashi and his co-workers reported on a direct formation of quinoline (3% yield) from aryl aldimine and alkyl enol ether in the presence of Yb(OTf)$_3$. However, the process constitutes hetero-Diels–Alder reaction, elimination of alcohol and dehydrogenation: see: Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423–424.
15. In the absence of Tf$_2$NH, 84% yield of **4aa** was obtained by DDQ-oxidation of **3aa** under the similar conditions.
16. Smith, A. P.; Lamba, J. J. S.; Faser, C. L. *Org. Synth.* **2002**, *78*, 82–87.