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# Auto-Tandem Catalysis in the Synthesis of Substituted Quinolines from Aldimines and Electron-Rich Olefins: Cascade Povarov−Hydrogen-Transfer Reaction

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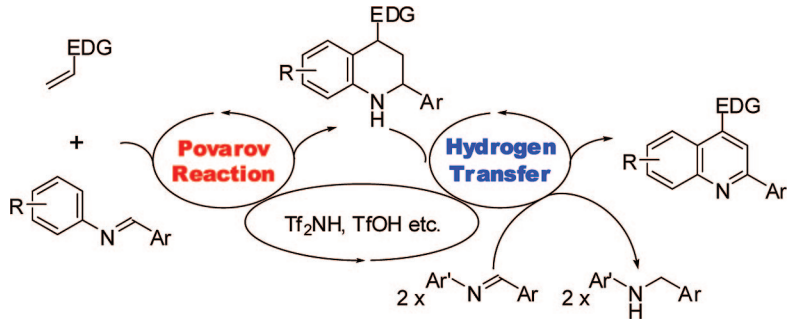


We demonstrated a catalytic cascade inverse electron demand hetero-Diels−Alder reaction (Povarov reaction) and hydrogen-transfer process. The reaction of electron-rich olefins and excess amount of imines in the presence of acid catalysts under appropriate conditions affords substituted quinolines in a single operation. In the cascade process, the catalysts, such as $Tf_2NH$, TfOH, and Lewis acids, catalyze two mechanistically distinct reactions (auto-tandem catalysis). We also describe the synthetic utility of the prepared quinolines.

## Introduction

The quinoline nucleus is a common heterocyclic ring found in a broad range of natural and unnatural compounds. A number of them are reported to have biologically activities,[1] including antimalarial, antimicrobial, antifungal, and antineoplastic, as well as inhibitory effects on HIV integrase. Owing to their medicinal importance, great attention has been paid to the synthesis of substituted quinoline compounds.[2] Classical methods, such as the Skraup reaction, Combes quinoline synthesis, Friedländer synthesis, and Doebner−Miller reaction, are widely recognized for the preparation of quinolines from anilines.[3] Recent progress in transition-metal-catalyzed reactions has led to the development of several efficient methods for the synthesis of quinolines from anilines and acetylenes.[4] Moreover, the cycloaddition followed by oxidation approach has also been shown to afford a quinoline nucleus. For example, the hetero-Diels−Alder reaction of imines, derived from anilines and aryl aldehydes, with dienophiles gives 1,2,3,4-tetrahydroquinolines.[5,6] The cycloaddition favors the inverse electron demand Diels−Alder reaction mode. Thus, electron-rich olefins, such as vinyl ethers and enamines, can promote the reaction (Povarov reaction); on the contrary, electron-withdrawing olefins show much less reactivity. The cycloaddition can be activated in the presence of an acid catalyst, such as $BF_3 \cdot Et_2O$, $SnCl_4$, lanthanide triflates, and *p*-toluenesulfonic acid. The obtained tetrahydroquinolines could be transformed into quinolines by treatment with oxidants.

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(1) (a) Ward, S. A.; Bray, P. G.; Mungthin, M.; Hawley, S. R. *Ann. Trop. Med. Parasit.* **1995**, *89*, 121–124. (b) Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. *Bioorg. Med. Chem.* **2007**, *15*, 1280–1288. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246.

(2) Kouznetsov, V. V.; Méndez, L. V.; Gómez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141–161.

(3) Yamashkin, S. A.; Oreshkina, E. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 701–718.

(4) (a) Zhang, X.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766. (b) Luo, Y.; Li, Z.; Li, C.-J. *Org. Lett.* **2005**, *7*, 2675–2678. (c) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877. (d) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109–1112.

(5) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670.

(6) For a review of tetrahydroquinoline synthesis, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.

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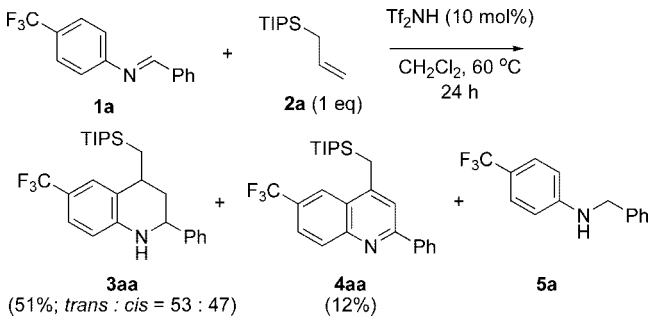
**SCHEME 1**




In recent years, cascade, multicomponent, and one-pot reactions have been significantly focused on as powerful and useful synthetic tools in drug discovery and process chemistry.[7] These reactions, if the catalytic variants are possible, would give a number of opportunities to improve chemical transformations, such as improvement of atom-economy, reducing of the number of operations, and saving reagents, energy, time, and labor. Therefore, the development of classes of cascade, multicomponent, and one-pot reactions would have a significant impact on the field. As a related chemistry, auto-tandem catalysis has also received great interest for synthetic efficiency.[8−10] The term "auto-tandem catalysis" is defined as one catalyst which promotes two or more mechanistically distinct reactions in a cascade reaction process. We recently reported the auto-tandem catalysis of $EtAlCl_2$ and triflic imide ($Tf_2NH$) in a cascade cycloaddition.[11] The catalysts independently activate two different cycloadditions, such as Diels−Alder reaction and [2 + 2] cycloaddition, in the cascade process.[11a] The reaction enables high-throughput synthesis of structurally complex compounds from simple and readily available substrates. We envisaged that the discovery of new auto-tandem catalysis reactions, which activate Povarov reaction and successive oxidative aromatization, would provide a new method to give substituted quinolines from readily available substrates in a single operation. In a recent paper, we have reported the auto-tandem catalysis of $Tf_2NH$ in the synthesis of substituted quinolines in which $Tf_2NH$ catalyzes Povarov reaction giving 1,2,3,4-tetrahydroquinolines and then the oxidation of the cycloadducts to yield quinolines.[12] Herein, we report a detailed account of auto-tandem catalysis in the reaction of arylaldimines and electron-rich olefins, such as allylsilanes and styrenes. In addition, the one-pot synthesis of quinolines by a catalytic Povarov reaction followed by DDQ-oxidation is reported below.

## Results and Discussion

**Cascade Povarov−Hydrogen-Transfer by Acid Catalyst (Auto-tandem Catalysis).** 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 using a sealed tube for 24 h. Tetrahydroquinoline **3aa** was obtained in 51% yield as a mixture of two diastereomers (*trans/cis* = 53: 47) together with quinoline **4aa** (12% yield), which resulted from the oxidation of **3aa** (Scheme 1). At the same time, production of amine **5a** was observed. We supposed that hydrogen-transfer between the obtained tetrahydroquinoline **3aa** and imine **1a** would take place in this reaction. We have examined the details of the oxidation process of the isolated **3aa** (mixture of diastereomers). Oxidation of **3aa** did not take place under an oxygen atmosphere at 60 °C, either in the presence or absence of catalyst. On the other hand, 64% conversion of **3aa** into **4aa** was observed at 60 °C for 12 h in the presence of 2 equiv of imine **1a** and $Tf_2NH$ (15 mol%). However, in the absence of catalyst, no hydrogen-transfer occurred at all. These results suggest imine **1a** acts as an oxidant and $Tf_2NH$ activates hydrogen-transfer to imine **1a** from **3aa** in the formation of **4aa**. In other words, $Tf_2NH$ acts as an auto-tandem catalysis activating two mechanistically distinct reactions in the cascade Povarov−hydrogen-transfer reaction (Figure 1). We found two new catalytic aspects of $Tf_2NH$. To the best of our knowledge, $Tf_2NH$ is the first example of a catalyst for Povarov reaction 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 $Tf_2NH$.

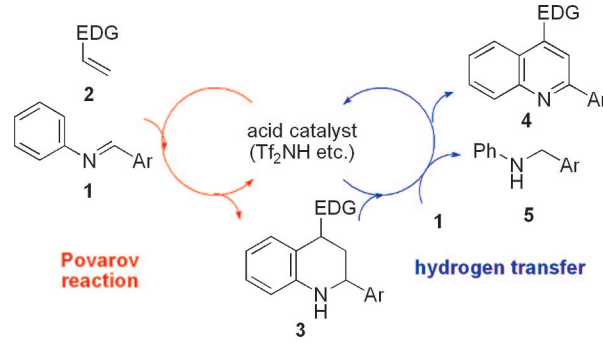



**FIGURE 1.** auto-tandem catalysis in the synthesis of quinoline.

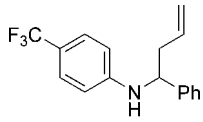
We were intrigued that the reaction with an excess amount of imine would improve the chemical yield of quinoline. When the reaction of **2a** (1.0 equiv) with 3 equiv of **1a** in the presence of $Tf_2NH$ (10 mol %) was carried out at 60 °C for 12 h, the chemical yield of **4aa** increased to 31%. On the other hand, production of **3aa** decreased to 48% and its *trans/cis* ratio was changed to 74:26 (Table 1, entry 1). Optimization of the reaction conditions, such as reaction temperature, reaction time, and solvent, were examined. At ambient temperature, allylsilane **2a** was completely consumed within 1.5 h to give **3aa** (59%, *trans/cis* = 55: 45; as an inseparable mixture of diastereomers), but quinoline **4aa** was produced in less than 11% yield (entry 2). On the contrary, the reaction at more than 80 °C resulted in the formation of unidentified byproduct (entry 3). When the reaction time was prolonged to 6 days at 60 °C, *trans*-**3aa** as a single diastereomer and **4aa** were obtained in 36% and 48% yields, respectively (entry 4). The stereochemistry of both diastereomers of **3aa** was assigned by the coupling constants of $^1H$ NMR. The yielding of **3aa** with only the *trans* isomer indicates that the kinetic resolution of the two diastereomers of **3aa** proceeds in the hydrogen-transfer process and that the reaction rate of *cis*-**3aa** is much faster than that of *trans*-**3aa**. In fact, no reaction

(7) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.
(8) Definition of "auto-tandem catalysis": Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.
(9) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020.
(10) For recent representative examples for auto-tandem catalysis, see: (a) Field, L. D.; Messerle, B. A.; Wren, S. L. *Organometallics* **2003**, *22*, 4393–4395. (b) Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465–9477. (c) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. (d) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770–11771.
(11) (a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*, 1352–1353. (b) Takasu, K.; Nagao, S.; Ihara, M. *Adv. Synth. Catal.* **2006**, *348*, 2376–2380. (c) Takasu, K.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2008**, *49*, 4220–4222. (d) Takasu, K. *Synth. Org. Chem., Jpn.* **2008**, *66*, 554–563.
(12) A part of this work was published as a preliminary communication: Shindoh, N.; Tokuyama, H.; Takasu, K. *Tetrahedron Lett.* **2007**, *48*, 4749–4753.

**TABLE 1. Reaction of Aldimine 1a and Allylsilane 2a in the Presence of $Tf_2NH$[a]**

| | | | | % yield[b] | |
|---|---|---|---|---|---|
| entry | solvent | *T* (°C) | time (h) | **3aa** (*trans/cis*)[c] | **4aa** |
| 1 | DCM | 60 | 24 | 48 (74:26) | 31 |
| 2 | DCM | rt | 12 | 59 (55:45) | 11 |
| 3 | DCM | 80 | 24 | 47 (71:29) | 31 |
| 4[d] | DCM | 60 | 144 | 36 (100:0) | 48 |
| 5 | DCE | 60 | 24 | 49 (76:24) | 37 |
| 6 | toluene | 60 | 24 | 32 (71:29) | 44 |
| 7 | toluene | 0 | 60 | 56 (28:72) | 8 |
| 8[e] | toluene | 0 to 60 | 240 | 25 (88:12) | 69 |
| 9 | $CH_3CN$ | 60 | 24 | 60 (59:41) | 3[f] |

[a] Reaction conditions: **1a** (3.0 equiv), **2a** (1.0 equiv), $Tf_2NH$ (10 mol %). [b] Isolated yields. All chemical yields are calculated on the basis of **2a**. [c] The diastereomeric ratios were determined by $^1H$ NMR. [d] $Tf_2NH$ (15 mol%) was used. [e] Reaction was carried out at 0 °C for 120 h and then at 60 °C for 120 h. [f] Homoallylamine **6a** was obtained in 11% yield.




**6a**

occurred when the isolated *trans*-**3aa** was exposed under similar reaction conditions (with 2.0 equiv of **1a** in the presence of 10 mol % of $Tf_2NH$ in DCM). Next, solvent effects were examined. Production of **4aa** slightly increased in 1,2-dichloroethane (DCE) and toluene (entries 5 and 6). Careful study taught us the following solvent effects. First, the rate of Povarov reaction of **1a** with **2a** in DCE is faster than that in toluene; in contrast, the oxidation of **3aa** proceeds more smoothly in toluene than that in DCE. Second, the reaction temperature does not have an affect on diastereoselectivity in Povarov reaction occurring in DCE or DCM; however, in toluene, the cis selectivity increases at low temperature. When the reaction was carried out at 0 °C in toluene, **3aa** was obtained in 56% with 72:28 selectivity (*cis/trans*) along with **4aa** in 8% for 60 h (entry 7). These findings suggest that the chemical yield could be improved by controlling the reaction temperature. Thus, after the completion of Povarov reaction at 0 °C for 6 days to furnish *cis*-**3aa** as a major diastereomer, the reaction temperature was raised to 60 °C giving quinoline **4aa** in 69% yield (entry 8). When the reaction was carried out in polar solvents, such as THF, $CH_3CN$, and AcOEt, homoallylamine **6a** was obtained in 11% yield ($CH_3CN$) along with **3aa** and **4aa** (entry 9). The formation of homoallylamine indicates that Povarov reaction under the tested conditions proceeds in a stepwise manner rather than as a concerted cycloaddition. In a polar solvent, the zwitterionic intermediate given by the Hosomi−Sakurai-type addition of allylsilanes to imines would be stabilized and would result in the formation of olefin by the elimination of the neighboring silyl group.

Next, the scope of auto-tandem catalysis in cascade Povarov−hydrogen-transfer reaction was investigated under the standard conditions in hand. The results are summarized in Table 2. With allyltriisopropylsilane **2a**, reaction of benzylideneimine **1b**−**h** gave quinolines **4ba**−**ha** in low to moderate yield (19−47% yield) along with tetrahydroquinoline **3ba**−**ha** (10−68% yield), in which the *trans* diastereomer was enriched. The Povarov reaction (the first step in the cascade reaction) promoted all in good yield, except for **1b** and **1g**, as can be seen in the total yields in Table 2. The electronic nature of the aromatic rings of imine **1** affects the reactivity of Povarov reaction. Thus, the electron-rich aromatic ring of the aniline portion shows poor reactivity (entries 1 and 8). However, introduction of an electron-withdrawing substituent on the benzilidene moiety can restore the chemical yield (entries 9 and 10). Thus, the reaction of imine **1h**, which was prepared from electron-donating *p*-anisidine and electron-withdrawing *p*-nitrobenzaldehyde, in toluene afforded quinoline **4ha** in 47% yield (entry 10). When allyltrimethylsilane (**2b**) was employed, a Hosomi−Sakurai-type adduct **6a** was obtained in 26% yield along with tetrahydroquinoline **3ab** (22% yield) and desilylated quinoline **7a** (9% yield), which would be converted from **4ab** by means of protodesilylation (entry 11). In contrast, allyl-*tert*-butyldimethylsilane (**2c**), bearing a sterically demanding silyl group, suppressed both the formation of **6a** and the desilylation into **7a**, thereby furnishing the heterocyclic compounds **3ac** and **4ac** (entry 12). Reaction with styrenes **2d** and **2e**, instead of allylsilanes, also furnishes quinolines **4ad** and **4ae**, respectively, in the presence of $Tf_2NH$ (entries 13 and 14). When reaction of *N*-vinyl-2-pyrroridone (**2f**) as an electron-rich olefin was carried out under the same conditions, *cis*-tetrahydroquinoline **3af** and quinoline **7b** were obtained in 27% and 54% yields, respectively (entry 15). No desired quinoline **4af** was formed. In this case, $\beta$-elimination of **3af** giving **7b** and 2-pyrroridone would be preferable to the hydrogen-transfer reaction leading to **4af**. Production of only the cis diastereomer of **3af** can be reasonably explained: because both substituents of *cis*-**3af** at C(2) and C(4) atoms would exclusively orient at the equatorial position, conformation of an appropriate transition state for $\beta$-elimination would be unfavorable.

We next examined the cascade Povarov−hydrogen-transfer reaction using various acidic catalysts (Table 3). Lewis acids also act as a catalyst for the cascade reaction to give quinolines **4aa** in moderate yield (entries 1−4). Akiyama and his co-workers reported the Povarov reaction of equimolar amounts of aldimines and allylsilanes in the presence of a stoichiometric amount of $SnCl_4$ at 0 °C to give tetrahydroquinolines in excellent yield, but without information as to the production of quinolines.[13] We have assessed that the result is reproducible under the reported conditions.

However, quinoline **4aa** was obtained in 38% yield under our tested conditions (10 mol% $SnCl_4$, 60 °C; entry 3). Hydrochloric acid and camphorsulfonic acid (CSA) are inactive in the Povarov reaction under the tested conditions (entries 5 and 6), whereas triflic acid (TfOH) functions in auto-tandem catalysis in the cascade reaction (entries 7 and 8). Although there are several studies on the Povarov reaction of imines with electron-rich olefins to give tetrahydroquinolines, to the best of our knowledge, very limited examples have been reported to furnish quinolines by cascade Povarov−oxidation reaction under similar conditions.[14,15]

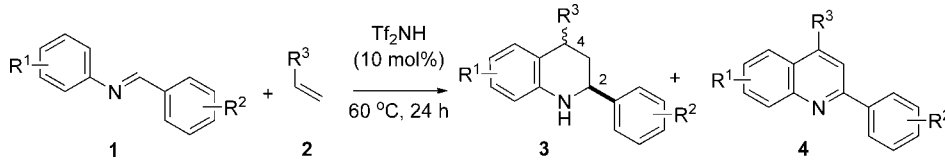
**One-Pot Synthesis of Quinolines Using DDQ.** Both *trans*- and *cis*-**3aa** could be oxidized into **4aa** by treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in DCE at ambient

(13) Akiyama, T.; Suzuki, M.; Kagoshima, H. *Heterocycles* **2000**, *52*, 529–532.

(14) After publication of our preliminary communication (ref 12), Mahajan and his co-workers reported an interesting synthetic study using Povarov−hydrogen-transfer reaction in the presence of Lewis acids; see: Bhargave, G.; Mohan, C.; Mahajan, M. P. *Tetrahedron* **2008**, *64*, 3017–3024.

(15) Hydrogen-transfer between 1,2-dihydroquinolines and imines has been reported by several groups; see: (a) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G.; Ruggieri, F. *J. Org. Chem.* **1992**, *57*, 1842–1848. (b) Tanaka, S.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800–803. (c) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423–424.

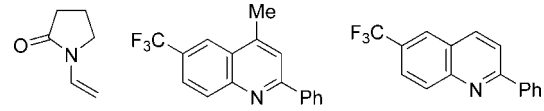
**TABLE 2. Scope of the Cascade Povarov−Hydrogen-Transfer Reaction in Auto-Tandem Catalysis[a]**




1 2 3 4

| entry | 1 ($R^1$, $R^2$) | 2 ($R^3$) | solvent | products 3 | products 4 | % yield[b] 3 (*trans/cis*)[c] | % yield[b] 4 | % yield[b] total[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1b** (H, H) | **2a** ($CH_2TIPS$) | DCE | **3ba** | **4ba** | 19 (71:29) | 29 | 48 |
| 2 | **1c** (*p*-$NO_2$, H) | **2a** | DCE | **3ca** | **4ca** | 68 (70:30)[e] | 19[e] | 87[e] |
| 3 | **1d** (*p*-Cl, H) | **2a** | DCE | **3da** | **4da** | 29 (79:21) | 36 | 65 |
| 4 | **1d** | **2a** | toluene | **3da** | **4da** | 16 (84:16) | 39 | 55 |
| 5 | **1e** (*p*-Br, H) | **2a** | DCE | **3ea** | **4ea** | 30 (78:22) | 39 | 69 |
| 6 | **1e** | **2a** | toluene | **3ea** | **4ea** | 15 (79:21) | 41 | 56 |
| 7 | **1f** (*o*-Br, H) | **2a** | DCE | **3fa** | **4fa** | 47 (60:40) | 19 | 66 |
| 8 | **1g** (*p*-MeO, H) | **2a** | DCE | **3ga** | **4ga** | 10 (88:12) | 31 | 41 |
| 9 | **1h** (*p*-MeO, *p*-$NO_2$) | **2a** | DCE | **3ha** | **4ha** | 35 (69:31) | 33 | 68 |
| 10 | **1h** | **2a** | toluene | **3ha** | **4ha** | 27 (62:38) | 47 | 74 |
| 11 | **1a** (*p*-$CF_3$, H) | **2b** ($CH_2TMS$) | DCE | **3ab** | **4ab** | 22 (75:25)[e] | 0 | 22[e,f] |
| 12 | **1a** | **2c** ($CH_2TBS$) | DCE | **3ac** | **4ac** | 48 (63:37) | 29 | 77 |
| 13 | **1a** | **2d** (*p*-$MeOC_6H_4$) | DCE | **3ad** | **4ad** | 32 (75:15) | 50 | 82 |
| 14[g] | **1a** | **2e** (*p*-$BrC_6H_4$) | DCE | **3ae** | **4ae** | 0 (−) | 64 | 64 |
| 15 | **1a** | **2f** (pyrrolidone) | DCE | **3af** | **4af** | 27 (0:100) | 0 | 27[h] |

[a] Reaction conditions: **1** (3.0 equiv), **2** (1.0 equiv), $Tf_2NH$ (10 mol %), 60 °C, 24 h. [b] Isolated yields. All chemical yields are calculated based on **2**. [c] The diastereomeric ratios were determined by $^1H$ NMR. [d] Sum of the %yields of **3** and **4**. [e] The yield has ∼10% error owing to contamination of inseparable impurities. [f] In the reaction, homoallylamine **6a** and quinoline **7a** were obtained in 22 and 9% yield, respectively. [g] Reaction was carried out with $Tf_2NH$ (20 mol%) for 48 h. [h] In the reaction, quinoline **7b**, which possesses no substituent on the C(4), was obtained in 54% yield.



**2f** **7a** **7b**

**TABLE 3. Catalytic Activity in the Reaction of 1a with 2a[a]**

| entry | catalyst | % yield **3aa** (*trans/cis*)[c] | % yield **4aa** | % yield total[b] |
|---|---|---|---|---|
| 1 | $BF_3\cdot OEt_2$ | 37 (74:26) | 42 | 79 |
| 2 | $Sc(OTf)_3$ | 20 (85:15) | 37 | 57 |
| 3 | $SnCl_4$ | 30 (88:12) | 38 | 68 |
| 4 | $Yb(OTf)_3$ | 23 (80:20) | 37 | 60 |
| 5 | HCl | 0 (−) | 0 | 0 |
| 6 | CSA | 0 (−) | 0 | 0 |
| 7 | TfOH | 24 (90:10) | 56 | 80 |
| 8[d] | TfOH | 14 (100:0) | 69 | 83 |

[a] Reaction conditions: **1a** (3.0 equiv), **2a** (1.0 equiv), catalyst (10 mol %), toluene, 60 °C, 24 h. [b] Isolated yields. All chemical yields are calculated on the basis of **2a**. [c] The diastereomeric ratios were determined by $^1H$ NMR. [d] Sum of the % yields of **3** and **4**. [e] Catalyst (20 mol %), 144 h.

**SCHEME 2**


**3aa** **4aa**

temperature for 5 min (84% yield; Scheme 2). Further study indicates that $Tf_2NH$ is compatible with DDQ-oxidation. We envisaged that quinoline **4aa** would be obtained in good yield by a one-pot sequence. Thus, a mixture of **1a** (1.25 equiv) with **2a** (1.0 equiv) in DCE was treated with a catalytic amount of $Tf_2NH$ at 60 °C for 3 h. After completion of the Povarov reaction (monitored by TLC), DDQ (2.0 equiv) was added to the mixtures at ambient temperature and stirred for 10 min to furnish **4aa** in 84% yield (Table 4, entry 1). The one-pot reaction would be an alternative method to provide quinolines against the above auto-tandem catalysis procedure. We examined the possibility that the oxidation of **3** with DDQ would be activated by $Tf_2NH$, but only a slight rate enhancement (ca. 1.1 times) was observed. With the alternative conditions in hand, we tested the sequential Povarov reaction and successive oxidation reaction. Substituted quinolines **4** were obtained in good yield in one pot (Table 4, entries 2−7).

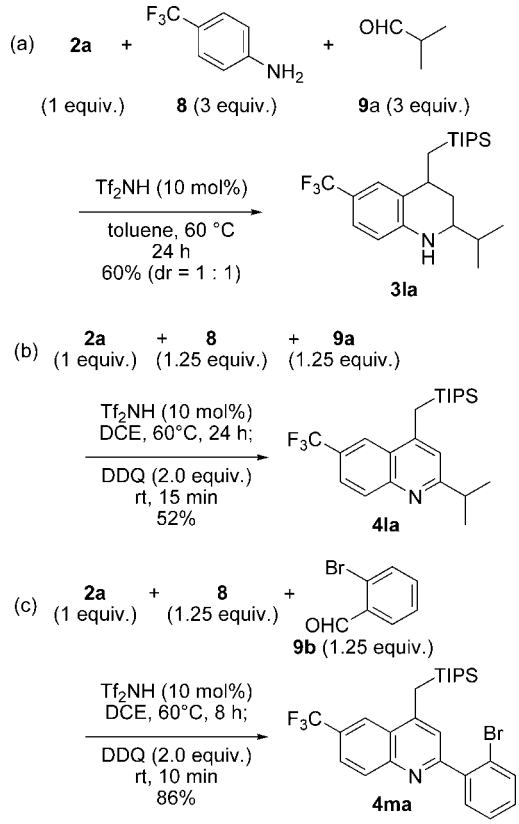
**TABLE 4. One-Pot Synthesis of Quinolines 4 by a Sequential Procedure**

| entry | 1 ($R^1$, $R^2$) | % yield of **4** |
|---|---|---|
| 1 | **1a** (*p*-$CF_3$, H) | 84 |
| 2 | **1c** (*p*-$NO_2$, H) | 83 |
| 3[a] | **1e** (*p*-Br, H) | 60 |
| 4[b] | **1f** (*o*-Br, H) | 72 |
| 5[c] | **1i** (*p*-$CF_3$, *o*-$NO_2$) | 87 |
| 6[d] | **1j** (*p*-Br, *o*-$NO_2$) | 68 |
| 7[e] | **1k** (*o*-Br, *o*-$NO_2$) | 66 |

[a] Reaction conditions: **1** (1.25 equiv), **2a** (1.0 equiv), $Tf_2NH$ (15 mol %), DCE, 60 °C, 3 h; then DDQ (2.0 equiv), ambient temperature, 10 min. [b] Povarov reaction for 24 h, DDQ oxidation for 10 min. [c] Povarov reaction for 1 h, DDQ oxidation for 10 min. [d] Povarov reaction for 45 min, DDQ oxidation for 1 h. [e] Povarov reaction for 1 h, DDQ oxidation for 1 h.

**Three-Component Reactions Affording Quinolines.** It is sometimes difficult to isolate and handle alkyl aldimines prepared from aliphatic aldehydes, owing to their instability. To avoid these problems, we envisaged elaboration of the cascade reaction to the multicomponent variant. When a mixture of **2a** (1.0 equiv), aniline **8** (3.0 equiv), and isobutylaldehyde

**SCHEME 3**

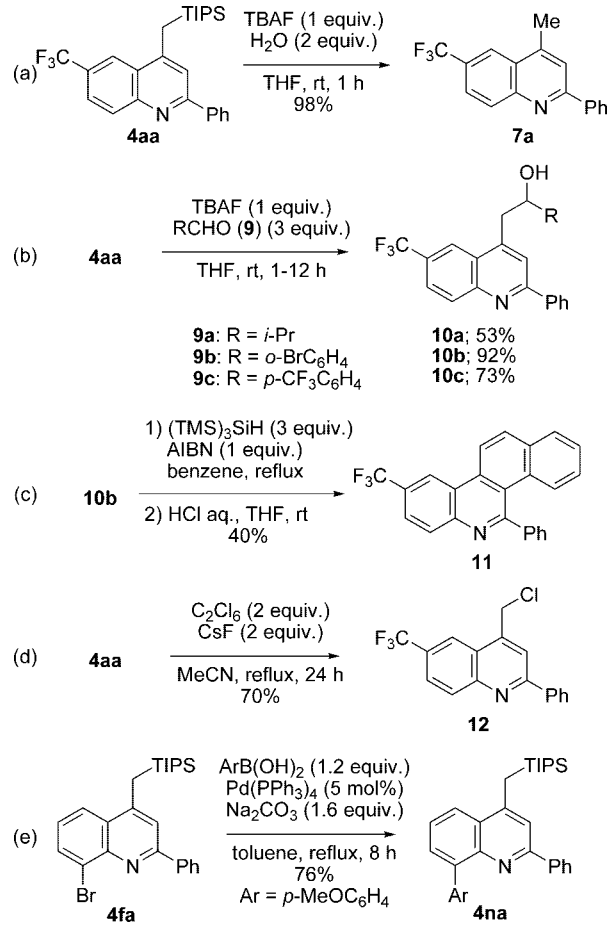



(**9a**) (3.0 equiv) in the presence of $Tf_2NH$ (10 mol%) in toluene was stirred at 60 °C, only tetrahydroquinoline **3la** was obtained in 60% yield as a 1:1 diastereomeric mixture (Scheme 3a). However, no formation of **4** was observed, although the excess amount of imine was employed. On the other hand, quinoline **4la** could be synthesized under one-pot synthesis conditions using DDQ. Thus, heating a mixture of **2a** (1.0 equiv), **8** (1.25 equiv), and **9a** (1.25 equiv) in DCE at 60 °C, followed by the addition of DDQ (2.0 equiv) at ambient temperature, successfully furnished **4la** in 52% yield (Scheme 3b). In the process, completion of the Povarov reaction was monitored by TLC. The method is applicable in the reaction with aromatic aldehyde **9b** to furnish quinoline **4ma** in 86% yield (Scheme 3c).

**Synthetic Application of Substituted Quinolines.** To demonstrate the synthetic utility of the products in the above quinoline synthesis, transformation reactions of **4** were summarized in Scheme 4. Protodesilylation of **4aa** can be accomplished by the treatment of tetrabutylammonium fluoride (TBAF) in the presence of $H_2O$ to give methylquinoline **7a** in quantitative yield (Scheme 4a). In the presence of aldehydes **9**, instead of $H_2O$ as an electrophile, the corresponding alcohols **10** were obtained in 53−92% yield from **4aa** with the formation of a new C−C bond (Scheme 4b). Obtained alcohol **10b** can be transformed into tetracyclic heteroaromatic compound **11** by means of radical cyclization−dehydration. Namely, treatment of **10b** with tris(trimethylsilyl)silane and AIBN in refluxed benzene,[16] followed by treatment with hydrochloric acid, furnished benzo[*i*]phenanthridine **11** in 40% yield (Scheme 4c).

(16) Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3899–3901.

**SCHEME 4**




Moreover, the reaction of **4aa** with CsF in the presence of hexachloroethane as an electrophile[17] afforded **12**, whose chloromethyl moiety would be a trigger of further chemical transformation (Scheme 4d). Suzuki−Miyaura coupling of bromoquinoline **4fa** with boronic acid successfully gave diarylquinoline **4na** (Scheme 4e). Recently, its structurally related diarylquinolines have been reported to be potential drug candidates for rheumatoid arthritis.[18]

Cadogan and co-workers reported the synthesis of carbazoles from 2-nitrobiphenyls by treatment with phosphite or phosphine via the formation of nitrenes.[19] We were intrigued that the application of Cadogan's method to synthesized 2-(*o*-nitrophenyl)quinolines **4ia**−**ka** gave tetracyclic heterocycles. According to the literature, two groups individually reported the reaction of 2-(*o*-nitrophenyl)quinoline with excess amounts of $P(OEt)_3$.[20] Although the reaction was carried out under nearly identical conditions, Ray's group and Reddy's group reported the production of different products, benzo-δ-carboline[19a] and indazolo[2,3-*a*]quinoline,[20b] respectively, in good yield. Our interest is directed toward which heterocycles would be obtained

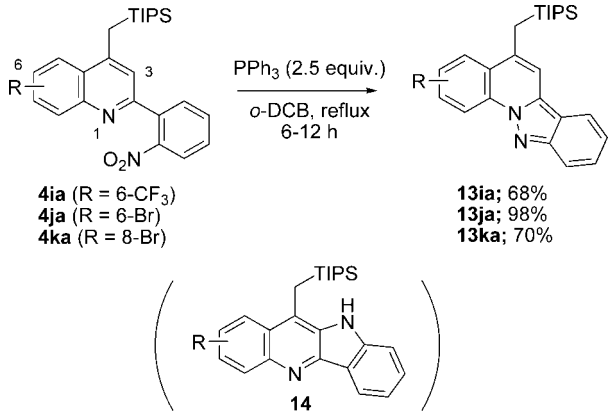
(17) Smith, A. P.; Lamba, J. J. S.; Fraser, C. L. *Org. Synth.* **2002**, *78*, 82–90.

(18) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H. H.; Keith, Jr., J. C.; Nickerson-Nutter, C.; Shilling, A.; Young-Sciame, R.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 21–39.

(19) (a) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831–4837. (b) Bouchard, J.; Wakim, S.; Leclerc, M. *J. Org. Chem.* **2004**, *69*, 5705–5711. (c) Freeman, A. W.; Urvoy, M.; Criswell, M. E. *J. Org. Chem.* **2005**, *70*, 5014–5019.

(20) (a) Dutta, B.; Some, S.; Ray, J. K. *Tetrahedron Lett.* **2006**, *47*, 377–379. (b) Reddy, Y. P.; Reddy, K. K. *Indian J. Chem.* **1988**, *27B*, 563–564.

**SCHEME 5**




from our synthesized quinolines **4ia**−**ka**. When **4ia**−**ka** were reacted with 2.5 equiv of triphenylphosphine in refluxing *o*-dichlorobenzene, indazolo[2,3-*a*]quinolines **13ia**−**ka** were obtained in 68−98% yield but no formation of benzo-*δ*-carbolines **14** was observed (Scheme 5). The structure of **13** was fully assigned by DEPT techniques. In our case, steric hindrance of the silylmethyl moiety of the C(4) position of **4** would suppress the approach of the nitrene group at the C(3) position, leading to N−N bond formation preferred to result in the production of indazolo[2,3-*a*]quinolines **13**. Indazolo[2,3-*a*]quinolines have been reported to show inhibitory effects on reverse transcriptase.[21]

## Conclusions

In summary, we have found that several acid catalysts, such as $Tf_2NH$, TfOH, and Lewis acids, activate two mechanistically distinct reactions, such as the inverse-electron-demand hetero-Diels−Alder reaction (Povarov reaction) and oxidative aromatization, in a cascade reaction process. As a result, the reaction of benzaldimines **1** and electron-rich olefins **2** in the presence of the catalyst could afford substituted quinolines **4**. As an alternative way to access substituted quinolines, we found that a one-pot reaction with the addition of DDQ as an oxidant would be effective. The described approach in this paper would suggest a rapid entry to synthesize substituted quinolines.

## Experimental Section

**Typical Procedure for $Tf_2NH$-Catalyzed Cascade Povarov−Hydrogen-Transfer Reaction (Table 1, Entry 5).** To a stirred solution of allyltriisopropylsilane (**2a**) (41.7 mg, 0.21 mmol) and aldimine **1a** (160 mg, 0.64 mmol) in 1,2-dichloroethane (0.9 mL) was added $Tf_2NH$ (0.4 M solution in toluene, 52 $\mu$L, 21 $\mu$mol, 10 mol%) at ambient temperature. The reaction mixture was stirred at 60 °C for 24 h, diluted with $CHCl_3$, and cooled to ambient temperature. The mixture was quenched with satd $NaHCO_3$, and the aqueous phase was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (2: 3 $CHCl_3$−hexane with 0.5% $NEt_3$, then $CHCl_3$ with 0.5% $NEt_3$) to afford 1,2,3,4-tetrahydroquinoline **3aa** (46.4 mg, 49%, *trans/cis* = 76:24) and quinoline **4aa** (34.1 mg, 37%), which was further purified by silica gel flash column chromatography (1:8 AcOEt−hexane).

(21) Sharples, D.; Hajós, G.; Riedl, Z.; Csányi, D.; Molnár, J.; Szabó, D. *Arch. Pharm.* **2001**, *334*, 269–274.

**(2*R**,4*S**)-6-Trifluoromethyl-4-(triisopropylsilyl)methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (*trans*-3aa).** colorless viscous oil; IR (neat) 1618, 1329, 1271, 1109, 1070 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.22 (m, 7H), 6.53 (d, $J$ = 8.5 Hz, 1H), 4.62 (t, $J$ = 7.0 Hz, 1H), 4.38 (bs, 1H), 3.13−3.08 (m, 1H), 1.97 (dd, $J$ = 7.0, 4.1 Hz, 2H), 1.11−1.04 (m, 23H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 146.0, 144.0, 128.8, 127.8, 127.6, 126.6, 125.7 (q, $^3J_{(C,F)}$ = 3.3 Hz), 125.0 (q, $^1J_{(C,F)}$ = 271.2 Hz), 124.1 (q, $^3J_{(C,F)}$ = 4.1 Hz), 118.4 (q, $^2J_{(C,F)}$ = 31.1 Hz), 113.2, 52.1, 37.4, 31.7, 19.1, 19.0, 18.9, 11.8; LRMS (APCI) *m*/*z* 448 ($M^+$ + 1). Anal. Calcd for $C_{26}H_{36}F_3NSi$: C, 69.76; H, 8.11; N, 3.13. Found: C, 69.52; H, 8.03; N, 3.00.

**6-Trifluoromethyl-4-(triisopropylsilyl)methyl-2-phenylquinoline (4aa).** colorless plates; mp 104−106 °C; IR (KBr) 1591, 1470, 1312, 1119 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.37 (s, 1H), 8.22 (d, $J$ = 8.8 Hz, 1H), 8.14 (d, $J$ = 7.1 Hz, 2H), 7.85 (d, $J$ = 8.8 Hz, 1H), 7.75 (s, 1H), 7.56−7.46 (m, 3H), 2.75 (s, 2H), 1.19−1.12 (m, 3H), 1.10 (d, $J$ = 7.2 Hz, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.3, 150.8, 149.6, 139.4, 131.6, 129.7, 128.9, 127.6, 127.1 (q, $^2J_{(C,F)}$ = 32.0 Hz), 125.9, 124.9 (q, $^3J_{(C,F)}$ = 3.3 Hz), 124.4 (q, $^1J_{(C,F)}$ = 272.8 Hz), 122.2 (q, $^3J_{(C,F)}$ = 4.1 Hz), 119.5, 18.5, 16.5, 11.5; LRMS (APCI) *m*/*z* 444 ($M^+$ + 1). Anal. Calcd for $C_{26}H_{32}F_3NSi$: C, 70.39; H, 7.27; N, 3.16. Found: C, 70.48; H, 7.24; N, 3.01.

**Typical Procedure for One-Pot Reaction of $Tf_2NH$-Catalyzed Povarov Reaction and DDQ-Mediated Oxidation (Table 4, Entry 1).** To a stirred solution of **2a** (40.8 mg, 0.21 mmol) and **1a** (64.6 mg, 0.26 mmol) in 1,2-dichloroethane (0.2 mL) was added $Tf_2NH$ (0.4 M solution in toluene, 77 $\mu$L, 31 $\mu$mol, 15 mol%) at ambient temperature. The reaction mixture was stirred at 60 °C for 3 h and then cooled to ambient temperature followed by addition of 2,3-dichloro-5,6-dicyano-1,2-benzoquinone (DDQ, 94.0 mg, 0.41 mmol) in one portion. The brown reaction mixture was stirred at the same temperature for 10 min (exothermic), diluted with $CHCl_3$, and filtered through pad of Celite. The organic layer was added saturated aqueous solution of $NaHCO_3$, and the aqueous phase was extracted twice with $CHCl_3$. Combined organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by silica gel flash column chromatography (3: 2 $CHCl_3$−hexane with 0.5% $NEt_3$) to afford **4aa** (76.3 mg, 84%).

**3-Bromo-5-(triisopropylsilyl)methylindazolo[2,3-*a*]quinolone (13ja).** Quinoline **4ja** (2.00 g, 4.00 mmol) and $PPh_3$ (2.66 g, 10.1 mmol) were dissolved in 10 mL of *o*-dichlorobenzene and heated to reflux for 10 h. The solvent was removed under high vacuum, and the crude product was purified by silica gel column chromatography (3:1 CHCl−-hexane with 0.25% $NEt_3$) to afford **13ja** (1.83 g, 98%) as yellow solids: mp 149−151 °C; IR (KBr) 2941, 1632, 1545, 1356 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.81 (d, $J$ = 8.0 Hz, 1H), 8.16 (s, 1H), 7.98 (d, $J$ = 8.0 Hz, 1H), 7.87 (d, $J$ = 8.0 Hz, 1H), 7.82 (d, $J$ = 8.0 Hz, 1H), 7.64 (s, 1H), 7.52 (t, $J$ = 8.0 Hz, 1H), 7.19 (t, $J$ = 8.0 Hz, 1H), 2.53 (s, 2H), 1.16−1.11 (m, 3H), 1.01 (d, $J$ = 6.8 Hz, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 149.3, 133.4, 132.5, 132.1, 128.2, 126.5, 120.2, 119.8, 119.3 × 2, 116.2, 115.8, 114.4, 18.7, 15.7, 11.6; LRMS (EI) *m*/*z* 466, 468 ($M^+$, $M^+$ + 2). Anal. Calcd for $C_{25}H_{31}BrN_2Si$: C, 64.23; H, 6.68; N, 5.99. Found: C, 63.89; H, 6.67; N, 5.98.

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**Supporting Information Available:** Experimental procedures, full spectral data for all new compounds, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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