A New Methodology for Combinatorial Synthesis. Preparation of Diverse Quinoline Derivatives Using a Novel Polymer-Supported Scandium Catalyst

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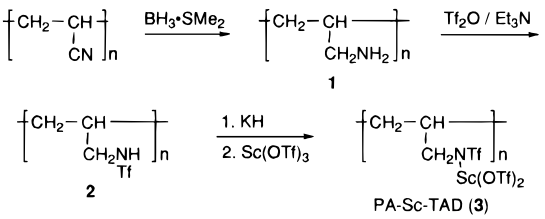
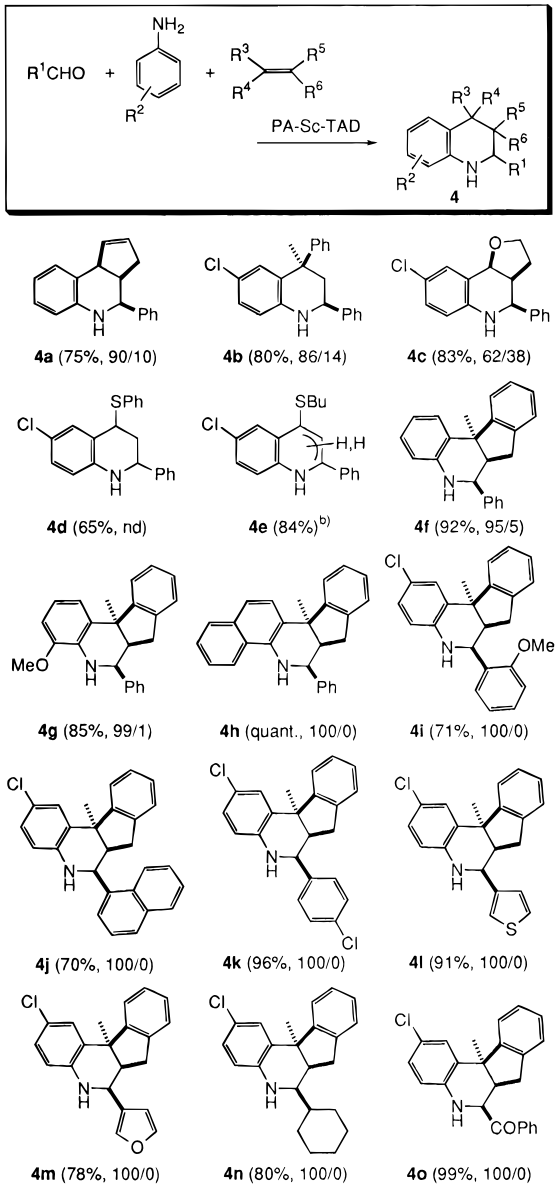
Combinatorial synthesis, a synthetic strategy which leads to large chemical libraries, is beginning to make a significant impact, especially on the drug discovery process.[1] Although polymer-supported substrates (reagents) have often been employed for library construction,[2] there are some disadvantages to this method. First, the reactions of polymer-supported reagents are sometimes slow, and differences in reactivity between the substrates lead to a lack of diversity of the library in some cases. Second, the loading level of polymer-supported substrates is generally low (<0.8 mmol/g) and large-scale preparation is difficult. To overcome these problems, we have developed a new methodology for combinatorial synthesis.[3] In this paper, we report a new method for preparation of a quinoline library using a novel polymer-supported scandium catalyst. According to this method, a large number of quinoline derivatives can be rapidly prepared in quantities greater than 100 mg.

The quinoline library synthesis[4] is based on our recently reported three-component coupling reactions using a lanthanide triflate as a catalyst.[5,6] Many combinations of aldehydes, amines, and olefins are used in this reaction, and a large quinoline library could be prepared on the basis of these combinations.[7] Although liquid phase combinatorial synthesis may be possible, our attention was focused on reactions using a polymer catalyst.

Scheme 1



Scheme 2[a]



[a] Yield and diastereomer ratio are shown in parenthesis. Relative stereochemical assignment was made by ^{1}H NMR analysis (see supporting information). Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the scheme. [b] Butyl ethynyl sulfide was used as a dienophile.

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(7) For the utility of multiple-component reactions for combinatorial synthesis, see: (a) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. See also: refs 5b and 5c.

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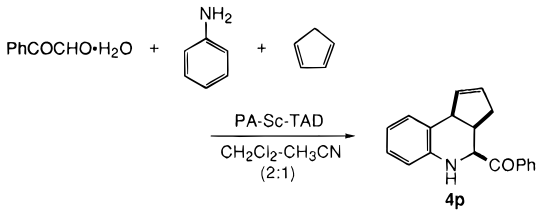
Use of polymer-supported catalysts[8] offers several advantages such as simplification of product workup, separation, isolation, reuse of the catalyst, etc., and may be useful for parallel library construction. On the other hand, one of the drawbacks of polymer-supported catalysts is their low reactivity. Bearing in mind that the low reactivity may be ascribed to the insolubility of the catalysts, we searched for a new polymer-supported catalyst which is partially soluble in an appropriate solvent and is precipitated after completion of the reaction and recovered quantitatively by filtration. After several trials, we have finally developed a new scandium catalyst, (polyallyl)scandium trifylamide ditriflate (PA-Sc-TAD). The synthetic route of PA-Sc-TAD is shown in Scheme 1. Polyacrylonitrile[9] was treated with $BH_3 \cdot SMe_2$ in diglyme for 36 h at 150 °C. The resulting amide **1** was reacted with Tf_2O in the presence of Et_3N in 1,2-dichloroethane for 10 h at 60 °C to afford sulfonamide **2**.[10] After **2** and KH were combined, $Sc(OTf)_3$ was added and the mixture was stirred in THF for 48 h at room temperature to give **3**.[11] PA-Sc-TAD (**3**) is gummy, but is dispersed and partially soluble in a $CH_2Cl_2-CH_3CN$ mixed solvent. The dispersed catalyst assemblies again when hexane is added.

In the presence of PA-Sc-TAD (**3**, 56.0 mg), an aldehyde (0.40 mmol), an aromatic amine (0.40 mmol), and an alkene (0.44 mmol) were mixed in $CH_2Cl_2-CH_3CN$ (2:1, 2.4 mL) at 40 °C for 15 h. Hexane (20 mL) was then added, and the catalyst was filtered. The filtrate was concentrated *in vacuo* to afford a crude adduct. After purification by column chromatography, the desired quinoline derivative was obtained in a high yield.

This method is especially useful for construction of a quinoline library (Scheme 2). The procedure is very simple: just mix the catalyst (PA-Sc-TAD), an aldehyde, an aromatic amine, and an alkene (alkyne). After filtration, the filtrates are concentrated to give almost pure quinoline derivatives in most cases.[12] It is noted that PA-Sc-TAD is water-tolerant[12,13] and that substrates having water of crystallization can be used directly. PA-Sc-TAD can be easily recovered and continuous use is possible without any loss of activity (see below).



1st use, 90%; 2nd use, 91%; 3rd use, 93% yield

A characteristic feature of the present method compared to conventional combinatorial synthetic technology using polymer-supported reagents is that more than hundred milligrams scale syntheses with a large array of diverse molecular entries have been achieved with high purities (high yields and high selectivities). The number of commercially available aromatic aldehydes, aliphatic aldehydes, heterocyclic aldehydes, and glyoxals and glyoxylates is more than 200, and more than 200 aromatic amines and 50 alkenes (and alkynes)[14] are commercially available. Therefore, a quinoline library of more than a million compounds with high quantity and quality could be prepared by using an automation system based on this method.[15]

In summary, a new method for combinatorial synthesis has been developed using a new polymer-supported scandium catalyst. It has been shown that a quinoline library of high quality and quantity can be readily prepared. This method using a polymer catalyst would be useful for construction of other compound libraries, and research projects along this line are now in progress.

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Supporting Information Available: Experimental procedures and physical data of the products (6 pages). See any current masthead page for ordering and Internet access instructions.

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(9) Purchased from Aldrich Chemical Co., Inc.

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(11) PA-Sc-TAD (**3**) is fully characterized by elemental analysis. For **3**: C, 23.51; H, 3.62; N, 3.33; F, 12.5; S, 6.74; Sc, 2.0. Precise experimental procedures for the preparation of **3** is shown in supporting information.

(12) Dehydrating agents such as molecular sieves (4A) and $MgSO_4$ are not necessary.

(13) We have found that lanthanide triflates (including scandium triflate) are water-tolerant Lewis acids and efficient catalysts in several synthetic reactions in aqueous media. (a) Kobayashi, S. *Synlett* **1994**, 689. (b) Kobayashi, S. *Chem. Lett.* **1991**, 2187. (c) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755. (d) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. (e) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379.

(14) Electron deficient dienophiles will not work under the conditions, since the present reactions are based on inverse electron-demand aza Diels–Alder reactions.

(15) The tetrahydroquinoline derivatives thus obtained are easily oxidized to dihydroquinoline or quinoline derivatives, which could double the size of the library.