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Highly enantioselective aldehyde–nitroolefin Michael addition reactions catalyzed by recyclable fluorous (*S*) diphenylpyrrolinol silyl ether

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Abstract—A recyclable and reusable (*S*) diphenylpyrrolinol silyl ether **I** organocatalyst bearing a *n*-C_8F_{17} fluorous tag has been demonstrated for promoting the asymmetric Michael addition reactions of a wide range of aldehydes with both aryl and alkyl-substituted nitroolefins and excellent levels of enantio- and diastereoselectivities are achieved. The catalyst **I** can be conveniently recovered by fluorous solid-phase extraction and subsequently reused (up to eight cycles) without significant loss of its catalytic activity and stereoselectivity for the process.

Interest in organocatalysis has increased dramatically as a result of both the novelty of the concept and, more significantly, the high efficiencies and selectivities of many organocatalytic reactions that often exceed those seen with other methods.[1,2] Consequently, operationally simple organocatalytic processes, which circumvent the use of toxic transition metals, have become powerful tools in the construction of biologically interesting substances and therapeutic agents.[3] With the scope of organocatalysis rapidly expanding, it is important to fully recognize the potential limitations and disadvantages associated with the use of these catalysts. One problem is that high organocatalyst loadings (10–20 mol %) are generally required to effect the desired transformations in reasonable timescales.[1,2] The costs of expensive chiral materials used to prepare the catalysts can be a major concern especially when the catalysts are used for a large scale of syntheses. Owing to these limitations, the development of recyclable and reusable organocatalysts has great significance in the context of the ever-growing applications of organocatalysis as an environmentally benign technology in fine chemical synthesis. However, few attempts have been made to devise general strategies to recover and reuse organocatalysts.[4]

Recently, fluorous chemistry has emerged as a new powerful strategy for facilitating catalyst recovery.[5–7] In 1997, Curran reported the first example of the application of solid–liquid separations based on fluorous silica gel (silica gel with a fluorocarbon bonded phase).[8] He showed that these separations are operationally convenient and are applicable to substances that contain only relatively few fluorine atoms (i.e., light-fluorous substances).[9] This is a key finding since light-fluorous reagents and catalysts have chemical and physical properties that are similar to their non-fluorous counterparts. This new technology has been applied recently to the development of recoverable organometallic catalysts.[10] We envisioned that this important concept could be also employed in designing recyclable organocatalysts. Below, we report the results of a recent effort targeted at the development of a recyclable and subsequently reusable fluorous (*S*)-diphenylpyrrolinol silyl ether as an organocatalyst for highly enantio- and diastereoselective Michael addition reactions of aldehydes with nitroolefins.

(*S*)-Diphenylprolinol TMS ether was selected as a model to test the feasibility of the recyclable light-fluorous organocatalyst concept. This substance and its relatives

Keywords: Asymmetric organocatalysis; Diphenylpyrrolinol silyl ether; Fluorous chemistry; Michael addition reaction; Nitroolefin.
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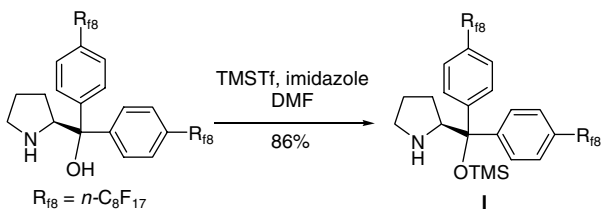
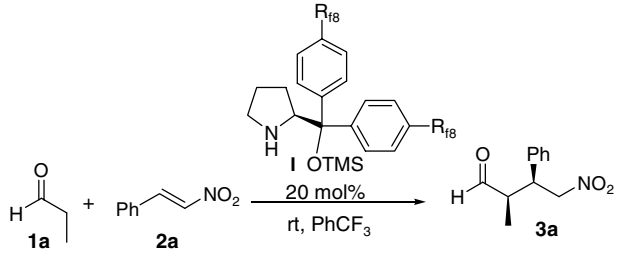
have been shown to promote a variety of asymmetric organic processes such as α-sulfenylation[11] and α-fluorination[12] of aldehydes, epoxidation[13] of α,β-unsaturated aldehydes and Michael addition of aldehydes to nitroolefins.[14] A recyclable fluorous version of (*S*)-diphenylprolinol TMS ether must meet two important criteria. Specifically, it must be catalytically active under the same reaction conditions used in processes promoted by the parent prolinol derivative, and it must be readily separable from reactants and products. To achieve these goals, the new catalyst must be sufficiently fluorous so that it can be separated by solid–liquid separation methods, but not too highly fluorinated so that it retains acceptable catalytic properties. We believed that attachment of a *n*-C_8F_{17} group at the *para*-position of the phenyl group in (*S*)-diphenylprolinol TMS ether, as in **I** (Scheme 1), would not have a detrimental effect on catalytic activity,[15,16] and would lead to ready separation by using fluorous solid–liquid extraction.

To test this proposal, we prepared the new fluorous organocatalyst **I** from the corresponding alcohol by treatment with TMSOTf in the presence of imidazole (Scheme 1).[16a] The activity of fluorous-tagged organocatalyst **I** for promotion of the Michael addition reaction of propionaldehyde **1a** with *trans*-β-nitrostyrene **2a** (Table 1) was evaluated.[14,17] Reaction of these substrates in the presence of 10 mol % **I**, under the reaction conditions used by Hayashi[14] (in hexane at room temperature instead of 0 °C, however), gave the desired product **3a** in 65% yield and a 98% ee. However, a long reaction time (15 h) was needed to complete the process and a low 2/1 *syn*/*anti* ratio was obtained. Changing the solvent to trifluoromethylbenzene caused a significant improvement in the diastereoselectivity (21:1 dr) and reaction rate (4 h) while at the same time maintaining an excellent ee (>99%) and high yield (89%) (Table 1, cycle 1). This observation indicated that the strongly electron withdrawing, fluorous tag *n*-C_8F_{17} in **I** had little effect on its catalytic activity. The fluorous organocatalyst **I** could be conveniently recovered (>90% recovery in each run) by using simple fluorous solid-phase extraction and repeatedly. For this process, 20 mol % **I** was used in order to increase the accuracy of evaluating catalyst recovery (see Supplementary data). The recovered catalyst retained its high activity for the Michael addition process, even after six cycles (Table 1). In each reuse cycle, excellent levels of enantioselectivity (99% ee) and diastereoselectivity (⩾20:1 dr) and high yields were observed (cycles 2–6).



Scheme 1. Structure of fluorous (*S*) diphenylpyrrolinol TMS ether **I** and its preparation.

Table 1. Recycling and reuse of organocatalyst **I** in promoting Michael addition of propionaldehyde **1a** to *trans*-β-nitrostyrene **2a**[a]



Cycle	*t* (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	4	89	>99	21:1
2	5	86	>99	24:1
3	10	90	>99	23:1
4	20	90	>99	24:1
5	23	89	>99	23:1
6	36	86	>99	28:1

[a] Unless otherwise specified, the reaction was carried out using **1a** (1.5 mmol) and **2a** (0.15 mmol) in the presence of 20 mol % (0.03 mmol) catalyst **I** in 0.75 mL of $PhCF_3$ at rt. Procedure for catalyst recovery by fluorous silica gel is provided in Supplementary data section.

[b] Isolated yields after chromatographic purification.

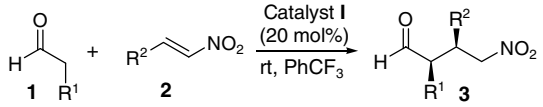
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).

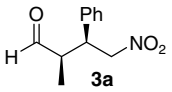
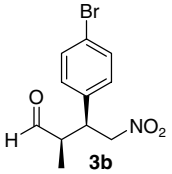
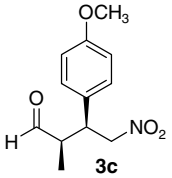
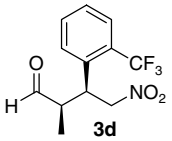
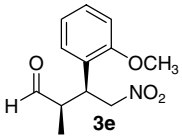
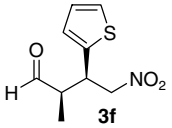
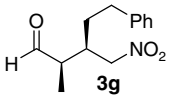
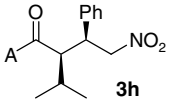
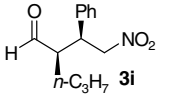
[d] Determined by ^1H NMR.

Having established that the fluorinated prolinol derivative **I** can be easily separated and repeatedly used, we next examined its ability to promote Michael addition reactions between a range of aldehydes and aromatic and aliphatic nitroalkenes. The results of this exploratory study (Table 2) show that **I** catalyzes reactions of a wide range of Michael donors and acceptors. In all cases, adducts **3** are obtained in remarkably high ee (⩾97%) and good to excellent *syn* diastereoselectivities (up to 29:1 dr). Both aryl- and alkyl-substituted nitroolefins participate in this catalytic process. Moreover, **I** catalyzes reactions of *trans*-β-nitrostyrenes, which possess either electron-withdrawing (entries 2 and 4) or donating (entries 3 and 5) groups and a variety of substitution patterns (*para*- and *ortho*-, entries 2–5) with excellent enantioselectivity (⩾99% ee), high degree of diastereoselectivity (6:1 to 29:1 dr) and high efficiencies. Heteroaromatic nitroolefins (e.g., thiophene, entry 6) can also be used as substrate in this process to generate adduct (e.g., **3f**) in high yield and enantioselectivity. Of greater importance is the observation that these processes take place efficiently with aliphatic nitroalkenes. For example, *trans*-$Ph(CH_2)_2=CHNO_2$ participates in this catalytic reaction to produce adduct **3g** in high yield and excellent ee and dr (Table 2, entry 7).[18] Finally, several aldehydes undergo highly enantio- and diastereoselective **I**-catalyzed Michael reactions with this nitroolefin (entries 8 and 9).

In summary, the study described above has led to the development of the first easily separated and reusable light-fluorous organocatalyst, diphenylprolinol TMS ether **I**, that promotes highly enantio- and diastereoselective Michael addition reactions of aldehydes with nitroalkenes. This effort has demonstrated that **I** is a

Table 2. Results of organocatalyst **I** promoted Michael addition reactions of aldehydes **1** to nitroolefins **2**[a]



Entry	Product	*t* (h)	Yield[b] (%)	ee[c] (%)	dr[d]
1	 **3a**	4	89	>99	21:1
2	 **3b**	2	81	>99	19:1
3[d]	 **3c**	5	84	99	14:1
4	 **3d**	8	84	>99	29:1
5	 **3e**	12	85	>99	6:1
6	 **3f**	4	84	97	5:1
7	 **3g**	13	82	>99	18:1
8	 **3h**	36	86	>99	16:1
9	 **3i**	26	92	98	25:1

[a] See footnote a in Table 1 and the Supplementary data.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H, AD or Chiralcel OD-H).
[d] Determined by ^{1}H NMR.

robust catalyst that can be readily separated and reused without significant loss of catalytic activity and stereoselectivity. This investigation demonstrates a new and important strategy for recovering expensive chiral organocatalysts. Given the rapidly ascending importance of both fluorous chemistry and organocatalysis, the strategy described here represents a general approach that should expand the scope of organocatalytic processes.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.067.

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18. Using (*S*) pyrrolidine trifluoromethanesulfonamide as catalyst we developed (see Ref. 17a), only 22% ee was observed for the same reaction.