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# Catalytic Stereoselective Synthesis of Highly Substituted Indanones via Tandem Nazarov Cyclization and Electrophilic Fluorination Trapping

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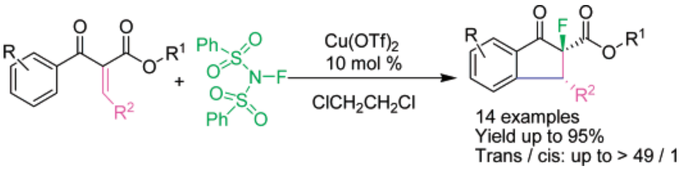
## ABSTRACT



**A new catalytic stereoselective tandem transformation via Nazarov cyclization/electrophilic fluorination has been accomplished. This sequence is efficiently catalyzed by a Cu(II) complex to afford fluorine-containing 1-indanone derivatives with two new stereocenters with high diastereoselectivity (trans/cis up to 49/1). Three examples of catalytic enantioselective tandem transformation are presented.**

The unique properties of organofluorine molecules have provided a major impetus for the development of efficient methods for their construction.[1,2] In general, the synthesis approach to organofluorine compounds has usually focused on a stepwise bond formation process. In contrast to this “stop and go” sequence of individual reactions, tandem or cascade transformation is a very appealing strategy as it enables a rapid increase in molecular complexity from readily available starting compounds.[3] Furthermore, the advantage of these transformations is the formation of several bonds in one pot by using a single catalyst. However, a survey of the literature reveals that catalytic tandem reactions for the construction of organofluorine molecules are rare.[4] Therefore, development of catalytic tandem protocols applicable to the synthesis of organofluorine compounds is in great demand but still remains a challenging goal.

Indanone derivatives are useful compounds serving as building blocks for the synthesis of natural products, medicines, and agrochemicals.[5] Although there have been a few reports on the synthesis of fluorine-containing indanone compounds by stepwise bond formation,[6] there are no examples of catalytic tandem reactions for their construction. Currently, our interest focuses on the design of catalytic

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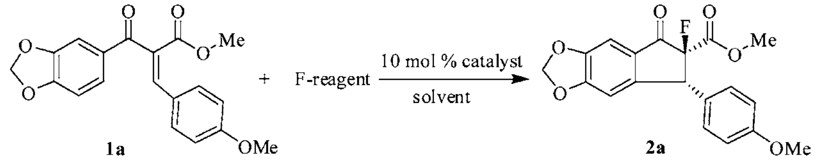
**Table 1.** Catalytic Tandem Nazarov Cyclization/Sequential Fluorination Trapping[a]

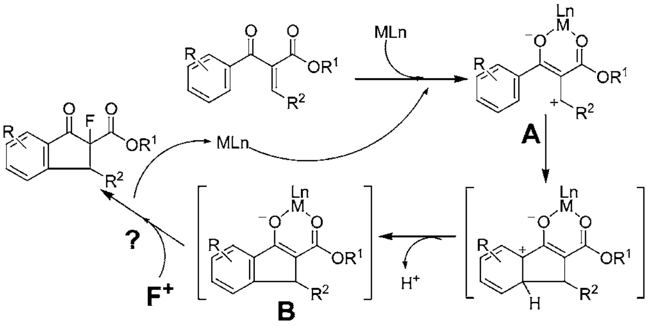


| entry | catalyst (mol %) | fluorinating reagent | solvent | yield[b] (%) | trans/cis[c] |
|---|---|---|---|---|---|
| 1 | Cu(OTf)$_2$ (10) | Selectfluor | DCE | <5 | |
| 2 | Cu(OTf)$_2$ (10) | NFPY-OTf | DCE | <5 | |
| 3 | Cu(OTf)$_2$ (10) | NFSI | DCE | 77 | 32/1 |
| 4 | Mg(ClO$_4$)$_2$ (10) | NFSI | DCE | 0 | |
| 5 | Zn(OTf)$_2$ (10) | NFSI | DCE | <5 | |
| 6 | Pd(OAc)$_2$ (10) | NFSI | DCE | 0 | |
| 7 | Cu(OTf)$_2$ (10) | NFSI | THF | 10 | |
| 8 | Cu(OTf)$_2$ (10) | NFSI | toluene | <5 | |
| 9 | Cu(OTf)$_2$ (10) | NFSI | MeNO$_2$ | 15 | |
| 10[d] | Cu(OTf)$_2$ (10) | NFSI | CH$_2$Cl$_2$ | 30 | 32/1 |
| 11 | Cu(OTf)$_2$ (10) | NFSI | solvent-free | 36 | 24/1 |
| 12[d] | Cu(OTf)$_2$ (10) | NFSI | DCE | 42 | 32/1 |
| 13[e] | Cu(OTf)$_2$ (10) | NFSI | DCE | 95 | 32/1 |
| 14[e] | Cu(OTf)$_2$ (5) | NFSI | DCE | 74 | 32/1 |

[a] Catalyst, substrate, and fluorinating reagent were mixed in the solvent at 60 °C for 24 h. [b] Yield of isolated product. [c] Determined by $^1$H NMR or $^{19}$F NMR. [d] Reaction temperature: 40 °C for 72 h. [e] Reaction temperature: 80 °C for 8 h.

tandem processes for the synthesis of fluorine-containing 1-indanone derivatives with a single catalyst. It is well-known that incorporation of cyclopentanone rings onto aromatic compounds via Nazarov cyclization is one of the most direct methods for the synthesis of indanone derivatives.[7] However, some shortcomings have limited the synthetic utility of Nazarov cyclization: stoichiometric amounts of protic acid or strong Lewis acid are necessary for best results, and the poor regioselectivity of the elimination led to a mixture of product isomers. Recently, a significant breakthrough was achieved by several research groups by using polarized enones as substrates under exceptionally mild catalytic conditions.[8] In this context, most of these transformations involve coordination of a transition-metal catalyst to alkylidene $\beta$-ketoesters via two-point binding to form the oxyallyl cation **A**, followed by 4$\pi$-electrocyclization, deprotonation, and reprotonation to afford the Nazarov products (Scheme 1). We envisioned that capture of the metal-bound enolate intermediate **B** might be implemented by using an appropriate electrophilic fluorinating agent to give the desired fluorinated compounds in one pot. In this paper, we describe the development of a highly stereoselective Lewis acid-catalyzed tandem transformation of polarized enones into fluorine-containing 1-indanone derivatives via Nazarov cyclization and electrophilic fluorination reaction.

**Scheme 1.** Catalytic Nazarov Cyclization of Polarized Enone



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Initially, we conducted a tandem reaction of alkylidene $\beta$-ketoester **1a** in the presence of 10 mol % Cu(OTf)$_2$ and Selectfluor as fluorinating reagent in dichloroethane (DCE) at 60 °C (Table 1, entry 1). The $^{19}$F NMR analysis of the crude reaction mixture revealed that only a trace amount of fluorinated product **2a** was detected, and most of the fluorinating reagent was not consumed. The use of *N*-fluoropyridinium triflate (NFPY-OTf) gave the similar result (entry 2). It is noteworthy that treatment of **1a** with the neutral fluorinating reagent *N*-fluorobenzenesulfonimide (NFSI) gave the single regioselective tandem product **2a** in good yield with high diastereoselectivity (trans/cis: 32/1) (entry 3). Other metals such as Mg(II), Zn(II), and Pd(II) complexes did not display reactivity in this tandem transformation (entries 4−6). A substantial change of the solvent had a significant effect on the yield (entries 3 and 7−10). Good results were attained when dichloroethane was used as solvent in the tandem reaction. Interestingly, under solvent-free conditions the tandem transformation also proceeded in moderate product yield with high diastereoselectivity (entry 11, trans/cis 24/1). In addition, higher temperature accelerated the reaction considerably (entries 12 and 13). Last, the effect of catalyst loading was examined, and reducing the amount of catalyst from 10 to 5 mol % caused a drop in yield (95% to 74%), although without any influence on the stereoselectivity (entry 14).

Gratifyingly, the single regio- and stereoisomer was isolated from the tandem product **2a** by fractional recrystallization using ethyl acetate/petroleum. X-ray structure analysis revealed the trans relationship between the F-atom and $\beta$-substituent R$^2$ (4-MeOPh) of the ketoester (Figure 1).[9]

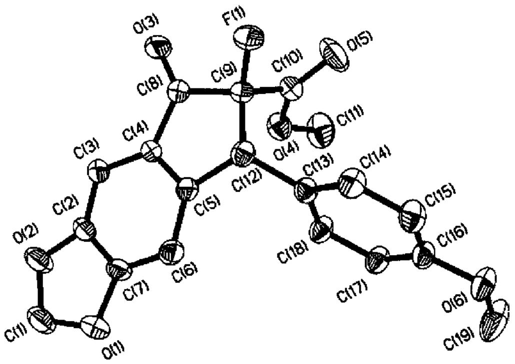
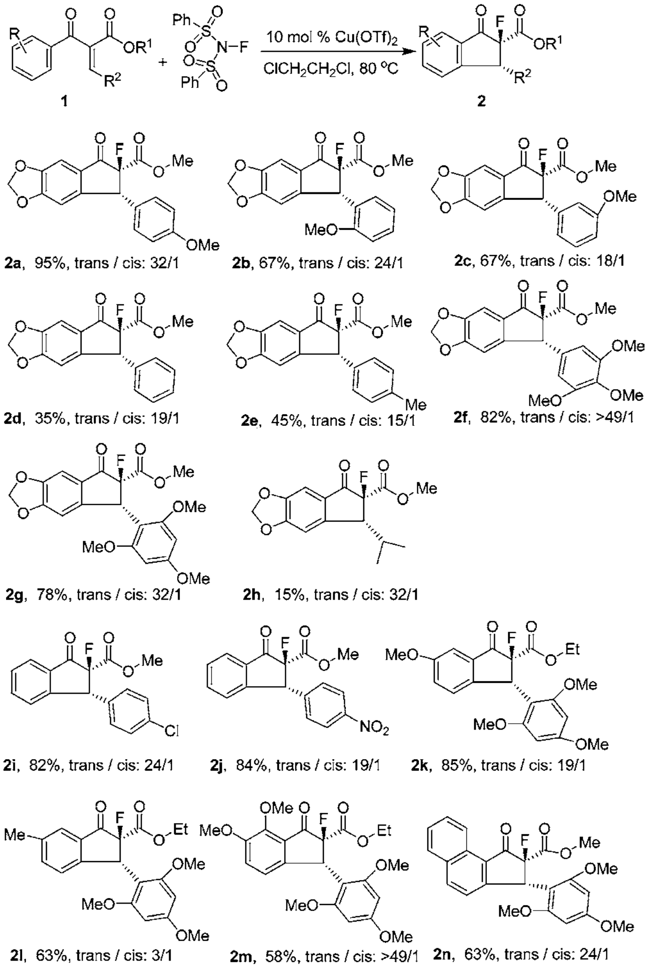


**Figure 1.** ORTEP illustration for the trans isomer of **2a**.

The stereochemical assignment of the major isomer indicated that the trans-product was predominantly formed, and the cis attack of the subsequent fluorination to Nazarov cyclization intermediate **B** was sterically restricted by $\beta$-aromatic group of R$^2$.

To determine the scope of the tandem reaction, we subjected a series of alkylidene $\beta$-ketoesters to the optimized reaction conditions (Scheme 2). It appears that the position and the electronic property of the substituents on the phenyl ring of alkylidene moiety have a very limited effect on the stereoselection of tandem transformation. No matter whether electron-donating, -neutral, or -withdrawing substituents on the phenyl ring were used, the tandem reactions proceeded to give excellent stereoselectivity in moderate to high yields (**2a**−**j**). While this reaction can also be applied to aliphatic alkylidene $\beta$-ketoesters (derived from aliphatic aldehyde and $\beta$-ketoesters) in high stereoselectivity, the low yield obtained appears to reflect formation of large amounts of insoluble polymeric material (**2h**). A variation of aromatic $\beta$-ketoesters was probed next. The corresponding fluorinated indanone derivatives were obtained with good to high stereoselectivities (**2i**−**m**). Additionally, in the case of the tandem reaction

**Scheme 2.** Catalytic Tandem Reaction Scope



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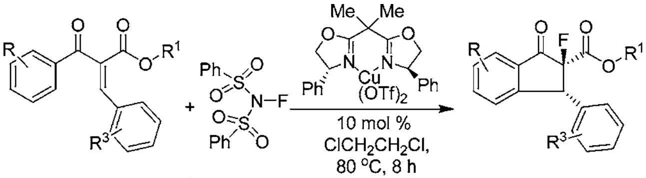
(9) CCDC 634975 contains the supplementary crystallographic data for the product **2a**. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

using 1-naphthalene-derived ketoester, high stereoselectivity was also obseved (**2n**).

Preliminary attempts to extend this protocol to a catalytic enantioselective tandem transformation were promising (Scheme 3). The use of $Cu(OTf)_2$/(*R*)-Ph-bis(oxazoline) with alkylidene $\beta$-ketoester **1b** afforded the tandem product in good yield with moderate enantioselectivity. Improved enantioselectivities were observed with substrates **1g** and **1m** bearing a bulky group at $R^2$ (95.5% ee for **2g** and 71% ee for **2m**, respectively). Interestingly, compared with the previous examples of Nazarov cyclizations that have employed stoichiometric amounts of chiral Lewis acid,[8f] the new electrophilic fluorination trapping as a terminating step for Nazarov cyclization may facilitate catalyst turnover. To the best of our knowledge, this is the first example of catalytic enantioselective tandem transformation for synthesis of organofluorine compounds with adjacent carbon- and fluorine-substituted quaternary and tertiary stereocenters.[6,10]

**Scheme 3.** Catalytic Enantioselective Tandem Transformation



**1b** R = 3,4-$OCH_2O$, $R^1$ = Me,
$R^3$ = 2-MeO
**1g** R = 3,4-$OCH_2O$, $R^1$ = Me,
$R^3$ = 2, 4, 6-$(MeO)_3$
**1m** R = 2,3-$(MeO)_2$, $R^1$ = Et
$R^3$ = 2, 4, 6-$(MeO)_3$

**2b** 69% yield, trans / cis: *19 / 1*
trans: *43.5%* ee
**2g** 80% yield, trans / cis: > 49 / 1
trans: 95.5% ee
**2m** 60% yield, trans / cis: > 49 / 1
trans: 71% ee

In conclusion, the new catalytic tandem Nazarov cyclization−fluorination transformation described above serves as an efficient method for preparation of fluorine-containing 1-indanone derivatives. This process proceeds with excellent diastereoselectivity and creates two new stereocenters. The stereocenters of tandem products can be controlled by a chiral catalyst. Further extension of the tandem reaction by using other halogenation reagents and different substrates, as well as full development of the enantioselective Cu (II)-catalyzed reaction are underway and will be reported in due course.

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**Supporting Information Available:** Experimental details and spectral data of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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