Stereoselective construction of fluorinated indanone derivatives *via* a triple cascade Lewis acid-catalyzed reaction†

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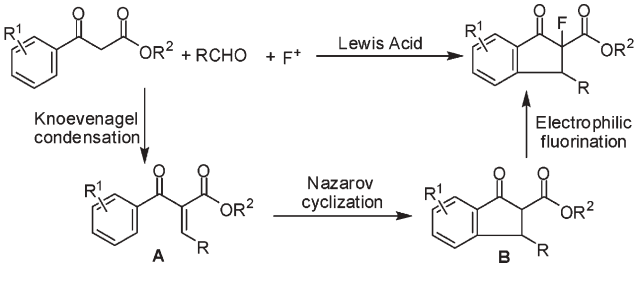
A one-pot three-component cascade reaction proceeds by way of a Lewis acid-catalyzed Knoevenagel condensation/Nazarov cyclization/electrophilic fluorination sequence to afford fluorinated 1-indanone derivatives in moderate to good yields with high diastereoselectivities.

Organofluorine compounds have attracted considerable attention because they show distinctive characteristics in comparison with their nonfluorinated analogues.[1] Construction of the structural complex and diverse organofluorine molecules has become the focus of intense research efforts for synthetic organic, medicinal and material chemists.[2] Traditionally, the synthesis approach to organofluorine compounds has most usually focused on stepwise bond formation processes. In contrast to this "stop and go" sequence of individual reactions, cascade or tandem transformation is a very appealing strategy as it favors the formation of several bonds in one pot by using a single catalyst, without the need for isolation of the intermediates.[3] Furthermore, cascade reactions also enable a rapid increase in molecular complexity from readily available starting compounds. However, survey of the literature reveals that cascade transformations for the construction of organofluorine molecules are rare.[4] Therefore, the design of multi-component cascade reactions for the synthesis of complex organofluorine compounds is a continuing challenge at the forefront of fluorine chemistry.

Indanone derivatives are useful compounds serving as building blocks for the synthesis of natural products, medicines and agrochemicals.[5] Over the past few years, there have been a few reports on the construction of fluorine-containing indanone molecules by stepwise bond formation.[6] We have an interest in developing cascade protocols that give access to fluorinated 1-indanone derivatives involving a minimum number of isolation and purification steps.

It is well established that Knoevenagel condensation of aromatic β-ketoesters and aldehydes with Lewis acid catalysts gives alkylidene β-ketoesters,[7] followed by Nazarov cyclization to form 1-indanone derivatives.[8] In addition, reports for fluorination reactions of β-ketoesters catalyzed by Lewis acids,[9] such as zinc, titanium, aluminium, palladium, copper and nickel salts, suggested us that a cascade Knoevenagel condensation/Nazarov cyclization/electrophilic fluorination process might be possible by using a single catalyst. In this communication, we present a new cascade transformation for the one-pot synthesis of fluorinated 1-indanone derivatives. The reaction sequence that we have devised is depicted in Scheme 1. This cascade transformation is a three-component reaction comprising an aromatic β-ketoester **1**, an aldehyde, a fluorinating agent and a simple Lewis acid, which is capable of catalyzing each step of this triple cascade. Initial screening of electrophilic fluorinating reagents was done with $AlCl_3$, methyl benzoylacetate and benzaldehyde in nitroethane. It was found that *N*-fluorobenzenesulfonimide (NFSI) was the only fluorinating reagent to provide the desired cascade product in 68% yield with excellent diastereoselectivity (*trans*/*cis*: 29/1). Commercially available fluorinating reagents Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)) and *N*-fluoropyridinium triflate were minimally reactive, and gave very low yields (<10%). Therefore, NFSI was used for subsequent reactions. Following this selection of an electrophilic fluorinating reagent, a Lewis acid screen was undertaken. The screening results revealed that other Lewis acids, such as $TiCl_4$, $SnCl_4$, BF_3 and $Pd(OAc)_2$, did not display reactivity for this cascade transformation.

To determine the scope of this cascade reaction, we subjected a series of aromatic β-ketoesters and aldehydes to the optimized conditions (Table 1). Not only electron-neutral and -donating (entries 1–3) but also electron-withdrawing substituents (entries 4 and 5) on the phenyl ring of aldehydes were tolerated for this triple cascade transformation to give the corresponding fluorinated indanone derivatives in good yields (62–71%) with good to high diastereoselectivities (*trans*/*cis*: 3/1–29/1). For these aromatic aldehydes with multi-substituents, low cascade yields were obtained probably owing to steric hindrance (entries 6 and 7). A variation of aromatic β-ketoesters was probed next. It appears that the nature of the electronic properties of the substituents in the aromatic systems have a remarkable effect on this cascade reaction. Substrates possessing the electron-neutral (entries 1–5) and -donating groups (entries 6–14) on the aromatic rings were



Scheme 1 Lewis acid-catalysed triple cascade reaction.

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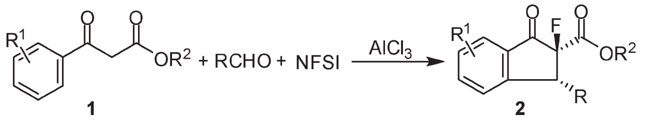
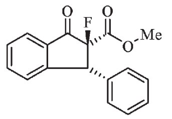
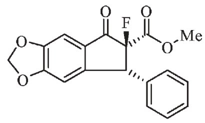
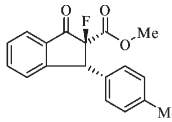
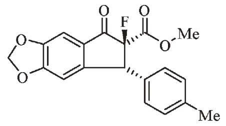
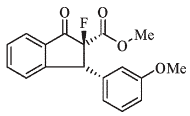
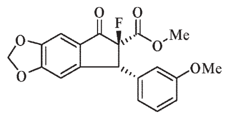
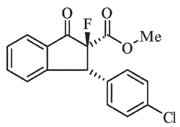
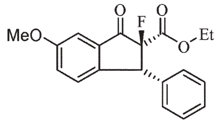
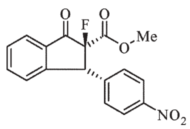
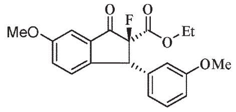
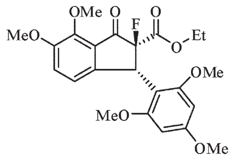
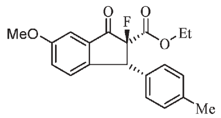
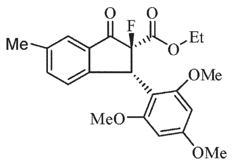
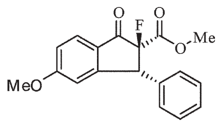
Table 1 One-pot three-component cascade reaction



Entry	Product^{a}		Yield^{b} (%)	*Trans*/*cis*^{c}	Entry	Product^{a}		Yield^{b} (%)^{a}	*Trans*/*cis*^{c}
1		**2a**	68	29/1	8		**2h**	72	29/1
2		**2b**	62	29/1	9		**2i**	45	29/1
3		**2c**	60	26/1	10		**2j**	65	24/1
4		**2d**	70	24/1	11		**2k**	50	25/1
5		**2e**	71	3/1	12		**2l**	59	24/1
6		**2f**	15	24/1	13		**2m**	48	21/1
7		**2g**	12	3/1	14		**2n**	46	29/1

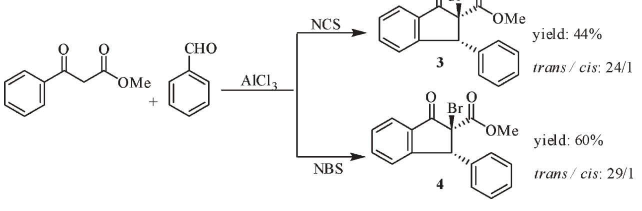
^{a} β-Ketoester (1 eq.), aldehyde (1 eq.) and $AlCl_3$ (1.2 eq.) in $EtNO_2$ at room temperature for 24–48 h, then NFSI (1.5 eq.) was added and stirred for 2–6 h at 110 °C. ^{b} Isolated yield. ^{c} Determined by ^{1}H NMR or ^{19}F NMR.

transformed with good to excellent diastereoselectivities. For β-ketoesters with electron-withdrawing substituents (such as F, Cl and NO_2) on the aromatic rings, the desired products were not observed in the cascade reaction.

Notably, when NFSI was replaced by chlorination and bromination reagents for extension of this triple cascade transformation, preliminary results were promising (Scheme 2). In the presence of $AlCl_3$, the reaction of methyl benzoylacetate and benzaldehyde with NCS and NBS affords the cascade products **3** and **4** in moderate to good yields with excellent diastereoselectivities (for **3**: *trans*/*cis* 24/1 with 44% yield and for **4**: *trans*/*cis* 29/1 with 60% yield, respectively).

The major diastereomers for the cascade products **2d** and **3** were recrystallized in pure form by using an ethyl acetate–petroleum mixture. The relative stereochemistry confirmed by X-ray crystallography (Fig. 1)‡ indicates that subsequent halogenation occurs *trans* to the R group of Nazarov cyclization intermediate **B**, and the *cis* attack was sterically restricted by the β-aromatic group of R.

In summary, we have reported the first examples of a triple cascade Knoevenagel condensation/Nazarov cyclization/electrophilic fluorination process. This Lewis acid-catalyzed sequence



Scheme 2 Lewis acid-catalysed cascade Knoevenagel condensation/ Nazarov cyclization/electrophilic chlorination and bromination.

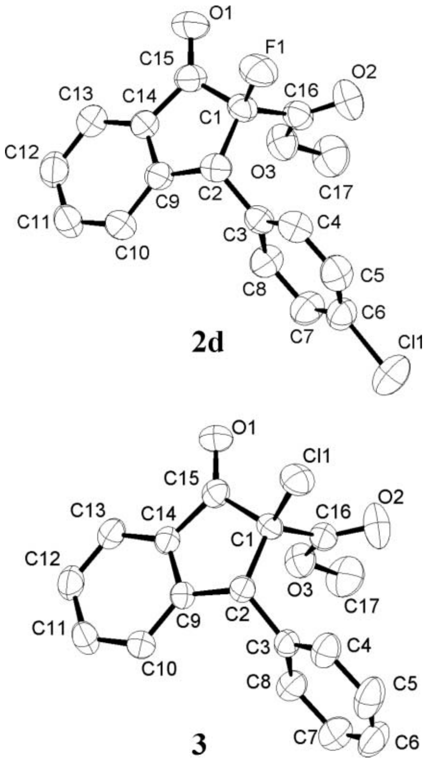


Fig. 1 X-Ray crystal structure of the major diastereomers for the fluorinated indanone **2d** and chlorinated indanone **3** (ORTEP).

proceeds with high stereoselectivity to afford *trans* fluorinated 1-indanone derivatives. The further development of catalytic enantioselective systems and the full extension of this triple cascade with other halogenation agents will be reported in due course.

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Notes and references

‡ *Crystal data* for **2d**: $C_{17}H_{12}ClFO_3$, M = 318.72, colorless prism, crystal size: 0.24 × 0.20 × 0.10 mm, monoclinic, space group $P2_1/c$, a = 17.213(4), b = 8.458(2), c = 10.468(2) Å, β = 96.925(4)°, T = 294(2) K, Reflections collected/unique: 8209/3082, final R indices were $R1$ = 0.0421 and $wR2$ = 0.0941 Selected bond lengths (Å): F(1)–C(1) 1.395(2), C(1)–C(2) 1.547(3), C(2)–C(9) 1.518(3); bond angles (°): F(1)–C(1)–C(16) 106.86(16), F(1)–C(1)–C(15) 109.72(16), F(1)–C(1)–C(2) 110.65(16); torsion angles (°): F(1)–C(1)–C(2)–O(1) −45.6(3), F(1)–C(1)–C(2)–C(3) −96.4(2), C(16)–C(1)–C(2)–C(3) 24.1(2). *Crystal data* for **3**: $C_{17}H_{13}ClO_3$, M = 300.72, colorless prism, crystal size: 0.24 × 0.14 × 0.10 mm, monoclinic, space group $P2_1/c$, a = 16.228(4), b = 8.599(2), c = 10.594(3) Å, β = 98.122(5)°, T = 294(2) K, Reflections collected/unique: 8103/2968, final R indices were $R1$ = 0.0438 and $wR2$ = 0.0702. Selected bond lengths (Å): Cl(1)–C(1) 1.781(2), C(1)–C(16) 1.532(3), C(2)–C(9) 1.515(3); bond angles (°): C(16)–C(1)–Cl(1) 108.82(14), C(2)–C(1)–Cl(1) 110.55(13), C(16)–C(1)–C(15) 109.62(16); torsion angles (°): C(16)–C(1)–C(2)–C(3) 27.4(2), C(9)–C(2)–C(3)–C(4) –152.26(19), Cl(1)–C(1)–C(15)–O(1) 46.6(2). CCDC 635729 and 635730. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b702114c

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