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COMMUNICATION
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COMMUNICATION

Photo-induced energy transfer relay of N-heterocyclic carbene catalysis: An asymmetric α-fluorination/isomerization cascade

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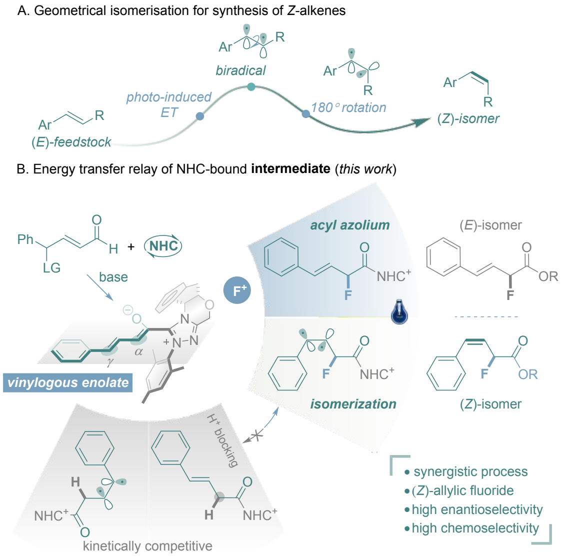
Geometric configuration of olefin products is often driven by thermodynamic control in synthesis. Methods enabling switching cis/trans selectivity are rare. Recently, photosensitized approaches emerge as a powerful tool for accomplish this task. In this report, we report an in situ isomerization of N-heterocyclic carbene (NHC)-bound intermediate by a photo-induced energy transfer process that leads to selective access of chiral allylic fluorides with cis-olefin geometry. In the absence of a photocatalyst or light, the reaction proceeds smoothly to give (*E*)-olefin products, while the (*Z*)-isomer can be obtained under photosensitizing conditions. Preliminary mechanistic experiments suggest an energy transfer process might be operative.

Allylic fluorides are important structural motifs that are not only versatile synthetic intermediates towards complexed structures but are also prevalent among bioactive molecules.[1] Chiral allylic fluorides are particularly useful synthons for radioactive probes for positron emission tomography (PET) imaging, pharmaceuticals, agrochemicals and materials.[1,2,3] Towards this important class of molecules, asymmetric installation of a fluorine atom at the allylic position of an olefin have made substantial progress in the past decade.[2] Transition-metal-catalyzed allylic fluorination, mostly via an electrophilic π-allyl-metal intermediate, has been developed as a powerful strategy to chiral allylic fluorides.[3] Products with (*E*)-olefinic geometry were frequently obtained. The complementary electrophilic fluorination using organocatalysts have also been developed.[4] For example, Toste and co-workers reported asymmetric fluorination of allylic alcohol using a chiral phosphoric acid as phase transfer catalyst.[4c] In this case, thermodynamically more stable olefin isomers were obtained as well. So far, access to chiral allylic fluorides with kinetic olefin geometry remains highly challenging. We were wondering whether cooperative catalysis merging visible-light-chemistry and organocatalysis would yield a straightforward solution to address this problem.



Scheme 1. Energy transfer relay of NHC-bound intermediate.

It has been well established that photosensitized energy transfer processes can manipulate olefin geometry that often leads to energetically unfavorable alkene isomers (**Scheme 1A**).[5,6] In 2014, Weaver et al. reported photosensitized isomerization of aryl-substituted (*E*)-allylamines to thermodynamically less stable (*Z*)-isomers.[6a] Inspired by (-)-riboflavin mediated (*Z*→*E*) isomerization, Gilmour and coworkers accomplished (*E*/*Z*) inversion of polarized

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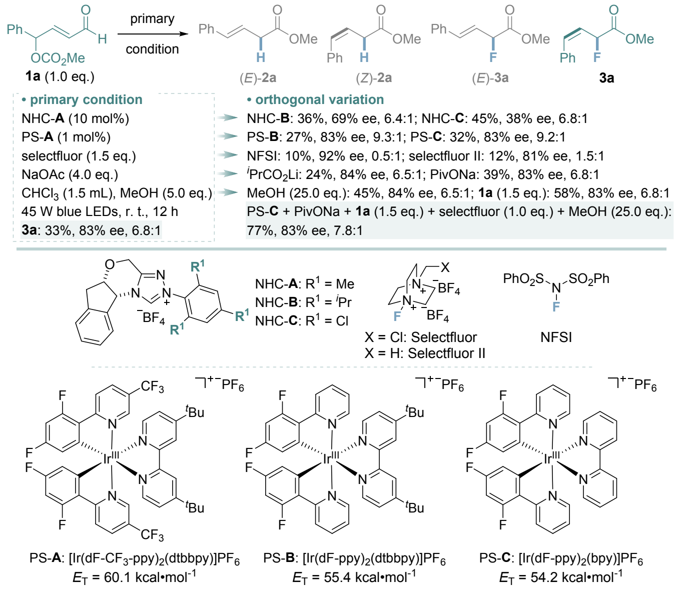
alkenes, a strategy that was further expanded to allylic alcohols and styrenyl boron compounds.[6c] However, photosensitized isomerization of allylic fluorides remains elusive. Recently, Rueping et al. reported a double functionalization of terminal alkynes using a combination of photoredox/nickel catalysis.[6f] The authors observed complete (*E*)-olefin selectivity when a Ru photocatalyst was used. In sharp contrast, switching to an Ir-based photosensitizer led to the corresponding (*Z*)-olefin. The authors postulated that double bond (*Z*→*E*) isomerization might be operative before the second functionalization. This development inspired us to probe a reaction involving energy-transfer-mediated double bond isomerization of an NHC-derived vinylogous enolate intermediate that might lead to access to chiral (*Z*)-allylic fluorides.

It has been reported that vinylogous enolates can react with an electrophilic fluorinating reagent to give the corresponding allylic fluorides.[7] Such chiral enolates can be generated from a chiral NHC catalyst and an α,β-unsaturated aldehyde bearing a γ-leaving group. We envisioned that upon fluorination, the olefinic acyl azolium intermediate might undergo photosensitized energy transfer to invert the double bond geometry before releasing the NHC catalyst. This in-cycle *contra*-thermodynamic isomerization might allow us to access chiral (*Z*)-allylic fluorides selectively. Several issues need to be addressed, however. Although reports merging NHC and photocatalysis is evolving rapidly, robust systems allowing for precise control of the photoactivation step within the NHC-catalytic cycle are still lacking.[8] Photosensitizers are generally redox reactive and might promote single-electron-transfer processes that disrupt the initial fluorination step. In addition, racemization might be a serious problem as the α-allyl-α-fluoro ester moiety is quite acidic and the reaction is basic.

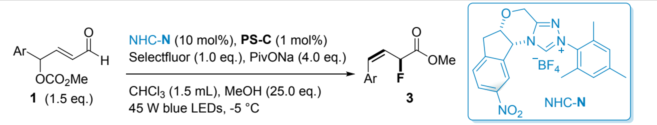


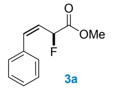
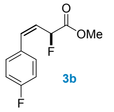
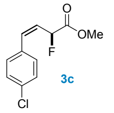
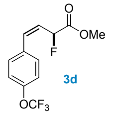
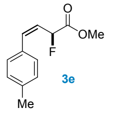
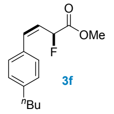
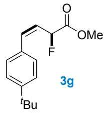
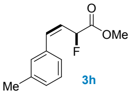
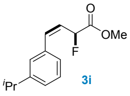
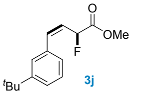
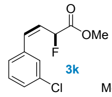
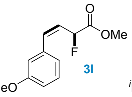
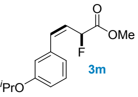
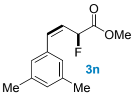
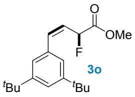
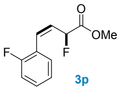
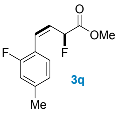
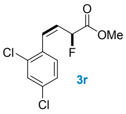
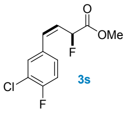
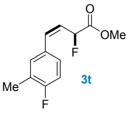
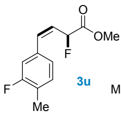
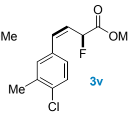
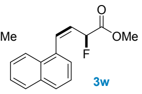
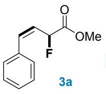
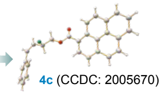
Scheme 2. First round of conditions survey for synergistic energy transfer catalysis.

We started our investigation using a model reaction between substrate **1a** and Selectfluor. Initial attempt using NHC-**A** and [Ir(dF-CF$_3$-ppy)$_2$(dtbbpy)]PF$_6$ (PS-**A**) was encouraging that (*Z*)-allylic fluoride **3a** was obtained in moderate yield (33%), good *Z*/*E* ratio (6.8:1) and decent ee (83%). The combined yield of the undesired side products, **(*E*)-2a**, **(*Z*)-2a** and **(*E*)-3a**, was 10%. Reaction parameters were screened orthogonally to identify key factors for the desired reaction pathway. Presumably, triplet–triplet energy transfer for the isomerization is operative. The triplet state energy (E_T) of photosensitizer might impact both chemoselectivity and efficiency of the double bond isomerization. Photocatalysts with E_T of 50~55 kcal mol^{-1} afforded the highest (*Z*/*E*) ratio and yield.[6g] Those with low E_T, Ru(bpy)$_3$Cl$_2$ (E_T = 46.8 kcal mol^{-1}) failed to promote formation of the (*Z*)-allylic fluoride.[6f] Both the **(*E*)-3a** and **(*E*)-2a** were isolated in 17% and 19%, respectively. PS-**C** was found to improve this process (*Z*/*E* = 9.2:1) without eroding yield and enantioselectivity (see **Table S1** for more details). Noteworthily, alternating Selectfluor with its type-II variant and NFSI resulted in dramatically decreased (*Z*/*E*) ratio (0.5:1 and 1.5:1, respectively) and yield (10% and 12%, respectively).[9] In order to suppress the competing α-protonation process, various additives were examined. In agreement with our previous reports on hydrofluorination reactions, PivONa delivered the highest H vs F selectivity (**Table S2**).[7d] Screening the ratio of the mixed solvents revealed that CHCl$_3$ (1.5 mL)/MeOH (25.0 eq.) was ideal for this reaction (**Table S3**). Further increasing the amount of methanol erodes (*Z*/*E*)-selectivity, likely due to rapid NHC turnover so that the (*E*)-acylazolium intermediate is converted into **(*E*)-3a** before undergoing olefin isomerization. The results also indicated that using Selectfluor as limiting reagent could dexterously balance the reactivity and controllability via avoiding the start material decomposition. (**Table S4**). Further tuning reaction variables other than NHC led to a suboptimum reaction with 77% yield, 83% ee and 7.8:1 (*Z*/*E*) ratio (**Scheme 2**).

At this stage, we believed that further improving yield and selectivity might be accomplished by modification of the NHC catalyst. A series of NHC precursors were explored under the optimized α-fluorination/isomerization cascade reaction (**Table S5**).[10] The N-aryl substituent was systematically modified. Electron-withdrawing groups on N-Ar improved yield, but negatively impacted ee. Higher (*Z*/*E*) ratio and ee was generally observed for N-Ar with electron-donating groups. Two ortho-substituents on N-Ar were essential for high (*Z*/*E*)-selectivity and enantioselectivity. More sterically hindered N-aryl groups, those with *ortho*-substituted MeO or Et group, afforded particularly high (*Z*/*E*) ratio (> 10:1). The indanol motif of the NHC was further optimized. Gratifyingly, we demonstrated NHC-**N**, with a *meta*-NO$_2$ group at the indanol aryl, demonstrated an overall balanced catalytic profile (92% yield, 94% ee, 7.9:1 *Z*/*E* ratio). The particularly high ee might be attributed to possible π-π interaction between the electron-deficient indanol arene and the electron-rich dienolate.[11] The stereoselectivity can be further improved by lowering reaction temperature to -5 ºC. Under the optimized reaction conditions, the substrate scope of enals were explored in the α-fluorination/isomerization cascade process. As shown in **Table 3**, substitutions are well tolerated at the *para*- (**3b-3g**), *meta*- (**3h-3m**), and *ortho*-position (**3p-3r**) of the γ-aryl group. An *ortho*-substituted halogen atom did not infer with photosensitized geometric isomerization (**3p-3r**). It appears that electro-deficient aromatic substituents generally led to slightly higher yield and (*Z*/*E*) ratio. A second substituent on the γ-aryl was also examined and most of such substrates performed similarly as their mono-substituted counterparts. Lower ee was observed for substrates with two electro-withdrawing groups on the γ-aryl (**3r** and **3s**), which might be due to weakened π-π interaction with the electron-deficient indanol aryl. When the phenyl group being expanded to a naphthyl group, geometric isomerization was affected and the (*E*)-olefinic product was isolated as the major isomer (**3w**). However, the reaction channel was totally obstructed when an alkyl group being forged in lieu of the aforementioned γ-aryl moiety. The optically enriched (*Z*)-allylic fluoride **3a** can be reduced under Luche reduction conditions and further derivatized by sulfonylation and acylation.[12] Upon acylation using 1-pyrenoic acid, the resulting ester **4c** was crystalline and its structure was confirmed by X-ray crystallography.

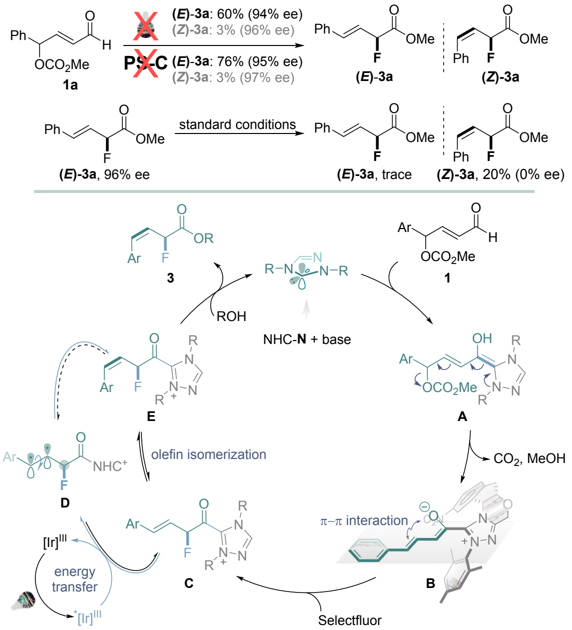
Table 1. Substrate scope of the enantioselective α-fluorination/isomerization cascade.



 **3a**	 **3b**	 **3c**	 **3d**	 **3e**
81 (98), 9:1	70 (97), 10:1	71 (92), 6:1	61 (94), 9:1	58 (98), 6:1
 **3f**	 **3g**	 **3h**	 **3i**	 **3j**
50 (94), 5:1	75 (95), 6:1	84 (95), 9:1	68 (96), 8:1	52 (97), 8:1
 **3k**	 **3l**	 **3m**	 **3n**	 **3o**
63 (94), 7:1	75 (93), 8:1	73 (95), 7;1	79 (97), 7:1	55 (96), 5:1
 **3p**	 **3q**	 **3r**	 **3s**	 **3t**
52 (95), 9:1	68 (94), 9:1	69 (88), 9:1	60 (88), 3:1	73 (96), 8:1
 **3u**	 **3v**	 **3w**	 **3a**	 **4c** (CCDC: 2005670)
72 (96), 6;1	73 (96), 5:1	25 (97), 1:2	Structural confirmation	

Reaction conditions: enal **1** (0.15 mmol), Selectfluor (0.1 mmol), NHC-**N** (10 mol%), PS-**C** (1 mmol%), PivONa (0.4 mmol), $CHCl_3$/MeOH (1.5 mL/0.1 mL), irradiation with 45 W blue LEDs, -5 ºC, 18 h. Numbers outside parentheses are isolated yield using Selectfluor as limiting reagent, and numbers inside parentheses are ee value for isolated product (determined by chiral GC), followed by (*Z*/*E*) ratio (determined by GC).

To further understand the isomerization details, several control experiments were carried out (**Scheme 3**). In the absence of either light or PS-**C**, the reaction proceeded with high (*E*)-selectivity and ee. A trace amount of (*Z*) -product was observed, likely due to internal electron transfer processes via formation of electron-donor-acceptor (EDA) complexes. When the (*E*)-isomer, allylic fluoride **(*E*)-3a**, was subjected to the standard reaction conditions, decomposition was predominant, and the corresponding (*Z*)-isomer was obtained in 20% yield as racemates. This result strongly suggests that the (Z)-selectivity of this reaction is not a result of photosensitized isomerization of the (*E*)-product. The olefin isomerization likely occurred prior to the NHC-turnover step. Presumably, a homoenolate intermediate **A** is generated by nucleophilic addition of NHC to the enal substrate, followed by a hydride shift. Upon releasing of CO_2 and methanol, dienolate **B** is formed that reacts with Selectfluor to give the acyl azolium intermediate **C**. The (*E*)-acyl azolium intermediate **C** is speculated as the key species that undergoes double bond isomerization by energy transfer from the triplet state of the excited photocatalyst, [Ir]*^{III}. Finally, the dominant (*Z*)-acyl azolium **E** react with MeOH to yield the product and regenerate the NHC catalyst. At this stage, we cannot rule



Scheme 3. Control experiments and speculated catalytic cycle.

out the possibility of olefin isomerization might also occur to dienolate intermediate **B**. From steric perspective, α-fluorination might have been slower for the (*Z*)-isomer of **B** than its (*E*)-isomer ($A^{1,3}$-strain) and therefore less likely.

In conclusion, we report an NHC/photosensitization relay catalysis that promotes photo-induced energy transfer of an NHC-bounded intermediate to yield (*Z*)-allylic fluorides with good stereochemical control. Systematic investigations of influence by both NHC catalysts and photosensitizers were carried out. Upon a highly enantioselective α-fluorination step, the key (*E*)-acyl azolium intermediate undergoes *in situ* photoisomerization prior to NHC turnover. It is suspected that π-π interactions between NHC and olefin may enhance asymmetric control and the choice of photocatalyst is important to control the rate and stage of isomerization. The unprecedented cooperation of photosensitization with NHC organocatalysis demonstrates unique advantages for accessing thermodynamically unfavored olefin isomers, especially those bearing multiple functional groups.

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Conflicts of interest

The authors declare no competing financial interests.

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