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Enantioselective N-Heterocyclic Carbene Catalysis via the Acyl Azolium without Exogenous Oxidants.

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ABSTRACT: An approach to the α,β–unsaturated acyl azolium has been developed that exploits N-heterocyclic carbenes (NHCs) and acyl fluorides, without additional oxidants, bases, or preactivated pro-nucleophiles. These conditions have been applied in 4-classes of NHC catalyzed reaction. In all cases the expected products were produced with high yield and enantioselectivity, using two sets of closely related reaction conditions, without additional optimization.

Keywords: Enantioselective catalysis; N-heterocyclic carbene; α,β–unsaturated acyl azolium; (3 + 3)-annulation; (3 + 2)-annulation; (4 + 2) annulation.

In recent years the versatility of acyl fluorides in organic synthesis has become more broadly recognised.[1] This can be traced to studies by Carpino who demonstrated their utility as alternatives to acyl chlorides in peptide coupling reactions.[2] Strikingly it was found that amide formation with or without exogenous base, occurred with similar yield and rate (Figure 1A).[2a] In addition to amide formation, the fluoride, acyl, or (after decarbonylation) alkyl fragments, derived from acyl fluorides have been exploited in various reaction designs.[1] In 2007 Lewis base catalysis with acyl

fluorides[3a] was reported by Levacher who demonstrated that acyl pyridinium fluoride can be generated in esterification reactions.[3a] Leveraging this observation we have found that α,β–unsaturated acyl fluorides (i.e. **1**) when exposed to N-heterocyclic carbenes (NHCs) can deliver α,β–unsaturated acyl azoliums (i.e. **2**) which engage in various bond forming cascades.[4] This was first demonstrated in 2009 with the annulation of TMS-enol ethers to give dihydropyranones **3** (Figure 1B).[4a] While such chemistry has proven valuable this approach suffers from limitations. Most notably, silicon masked nucleophiles, such as **4**, are required. For example when the TMS enol ether **4** is replaced by cyclohexanone the annulation reaction fails.

In contrast to the approach outlined above (Figure 1B) most NHC-organocatalysis[5] involving the α,β–unsaturated acyl azolium,[6] is achieved by oxidation of the Breslow-intermediate (i.e. **5**). Specifically, this involves either redox isomerisation of aldehydes containing reducible functionality,[7] or the use of enals (such as **6**) in the presence of an external oxidant (Figure 1C).[8] Most commonly the Kharasch oxidant (**7**), as introduced by Studer,[8a] is exploited, often with a superstoichiometric base, to both generate the NHC and deprotonate the pro-nucleophilic partner. While this strategy is common it exploits a high molecular weight oxidant that is relatively expensive, and in its reduced form, must be removed. While efforts to introduce alternate oxidants have been made,[9] surprisingly a general oxidant free approach to the acyl azolium is yet to be established.

Recently we considered whether acyl fluorides could serve as acyl azolium precursors in the absence of preactivated nucleophiles. If viable then such a scenario would provide an approach to the acyl azoliums that avoids oxidants, bases, and the intermediacy of the Breslow intermediate. Specifically, we postulated that by using an exogenous fluoride trap the acyl azolium could be formed directly from the acyl fluoride (Figure 1D). In addition, having trapped the fluoride anion

the resultant adduct might serve as a base to deprotonate the pro-nucleophile, thereby replacing any additional base additives. Herein, we report studies on this concept that have been showcased in the context of four NHC-catalyzed reactions. Using two sets of conditions, reactions of the α,β–unsaturated acyl azolium **2** acyl azolium dienolate **8**, and the, dienyl acyl azolium **9**, have been achieved. The approach is operationally simple and has been deployed in all designs using the same azolium precatalyst, and without additional optimization.

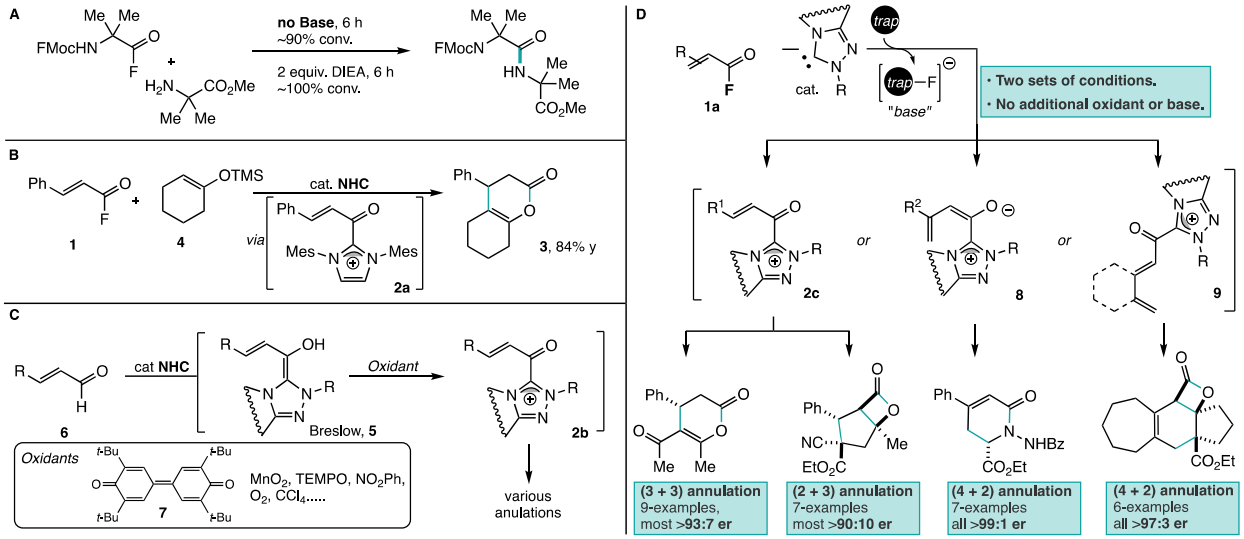


Figure 1. A) Peptide coupling with acyl fluorides. B) Annulation of the α,β–unsaturated acyl azolium using acyl fluorides. C) The α,β–unsaturated acyl azolium is commonly formed by oxidation of the Breslow intermediate. D) Reaction design in which acyl azoliums are formed with an exogenous trap for fluoride.

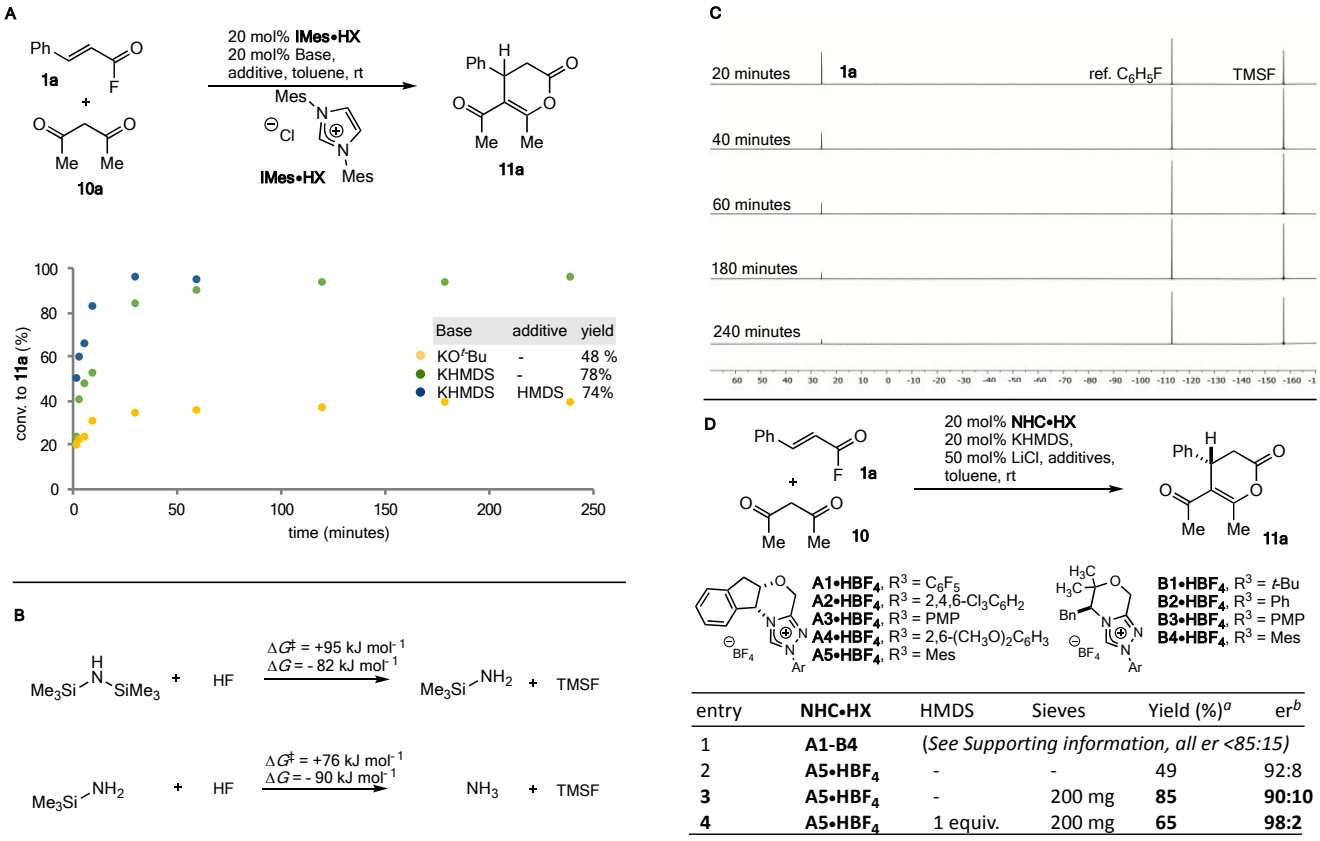
Reaction discovery commenced by examining the **IMes** catalysed annulation of cinnamoyl fluoride (**1a**) with acetoacetone (**10**) in the absence of additives. Using KO^{t}Bu to generate the NHC a 48% yield of dihydropyranone **11a** was obtained (Figure 2A). This result suggests that potentially

the design does not need an exogenous fluoride trap, and that fluoride itself can serve as a base, although accumulation of HF likely quenches the catalyst. Using potassium hexamethyldisilazide (KHMDS) to generate the NHC provides HMDS that we reasoned could serve to trap HF and allow full conversion. In the event full conversion was observed after 4 hours, with dihydropyranone **11a** formed in 78% yield. When the same reaction was performed with additional HMDS the yield was decreased slightly, but the reaction rate increased (Figure 2A). Next we examined the viability of HMDS to serve as a fluoride trap computationally.[10] From these studies it was possible to identify two thermodynamically and kinetically viable reactions between HF and HMDS providing 2 equivalents of TMSF and one of ammonia (Figure 2B and supporting information). Consistent with these predictions, when the reaction was monitored by ^{19}F-NMR, formation of TMSF was observed as the acyl fluoride is consumed (Figure 2C).

Exploiting these insights we next developed an enantioselective version of the reaction (Figure 2D). In studies by Studer α,β–unsaturated acyl azolium annulations have been found to benefit from LiCl,[11] thus the reaction of cinnamoyl fluoride (**1**) with acetoacetone (**10**) was examined with a series of azolium salts, using KHMDS as base, and LiCl as additive. These studies identified the Mes-indanol NHC **A5** as being well suited to this chemistry providing **11a** in 49% yield and 92:8 er (Figure 2D, entry 2). The yield was increased by the addition of molecular sieves (Figure 2D, entry 3),[8g] while introduction of an equivalent of HMDS increased the selectivity, with **11a** formed in 98:2 er, although with a slightly decreased yield of 65% (Figure 2D, entry 4).

Having developed a potentially general platform for enantioselective catalysis via the α,β–unsaturated acyl azolium we examined its viability in four reaction designs – two involving the α,β–unsaturated acyl azolium (i.e. **2c**), one the acyl azolium dienolate (i.e. **8**), and the last the dienyl azolium (i.e. **9**). In all cases conditions lacking additional HMDS (**Conditions A**, Figure

2D, entry 3) or with an additional 1 equivalent of HMDS (**Conditions B**, Figure 2D, entry 4) were used. With most reactions the products were produced with serviceable yields and high enantioselectivity. It would be imagined that dedicated re-optimization of any process would lead to improved outcomes.



entry	NHC•HX	HMDS	Sieves	Yield (%)[a]	er[b]
1	**A1-B4**	*(See Supporting information, all er <85:15)*			
2	**A5•HBF$_4$**	-	-	49	92:8
3	**A5•HBF$_4$**	-	200 mg	**85**	**90:10**
4	**A5•HBF$_4$**	1 equiv.	200 mg	**65**	**98:2**

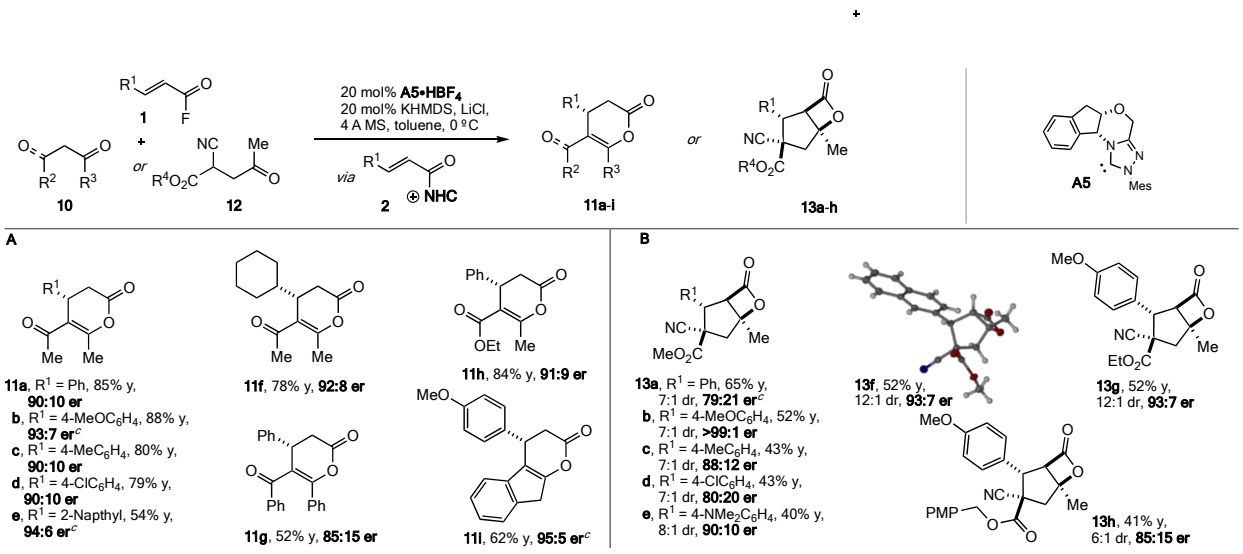
Figure 2. A) Oxidant and base free annulation of acetoacetone **10a** with acyl fluoride **1**. B) Computational modelling of HF reaction with HMDS. C) Reaction of **1a** and **10a** to give **11a** monitored by ^{19}F-NMR. D) Reaction optimization. (a) Isolated yield following flash column chromatography. (b) Enantiomeric ratio determined by HPLC.

The enantioselective synthesis of dihydropyranones was examined first (Table 1A). This reaction was first reported by our group in 2009,[4a] and has subsequently served as a testing ground for new catalysts, or conditions for acyl azolium formation. While HMDS improved selectivity in the optimisation studies the simpler conditions without its addition (**Conditions A**) were used in this study, unless noted. Variation of the cinnamoyl fluoride (**1a-e**) was broadly tolerated with pyranones **11a-e** provided with good enantioselectivity (all >90:10 er). When using electron-rich (**1b**) or more hindered (**1e**) substrates the yield was decreased, which could be addressed somewhat by adding HMDS. Similar outcomes were obtained with the sometimes challenging β–alkyl acyl azolium precursors providing dihydropyranone **11f**, and alternate 1,3-dicarbonyls giving **11g** and **h**. Finally, substrates with decreased acidity, such as 2-indanone could be converted (i.e. to **11i**) with high selectivity and yield using **Conditions B**.

In 2014 we reported a (3 + 2) annulation of the α,β–unsaturated acyl azolium using fluoride induced ring opening of donor-acceptor cyclopropanes.[4d,e] Studies from Studer developed an oxidative approach to related materials,[11] while Biju has developed analogous reactions,[12] and Romo has examined similar annulations with isothiourea catalysts.[13] Rather than directly examine one of these designs we focused on the use of nitrile esters (i.e. **12**) for the synthesis of cyclopentyl β–lactones. Without optimization, using **Conditions A**, the coupling of a range of cinnamoyl fluorides **1** with various nitriles **12** gave eight cyclopentyl β–lactones **13a-e** (Table 1B). The absolute stereochemistry of these materials was determined through single crystal x-ray analysis of **13f** and **13c** and extrapolated for all structures.[14] In contrast to the (3 + 3) annulation, this reaction showed significant sensitivity to the electronics of the acyl azolium. Thus, while cinnamoyl fluoride **1a** and 4-chlorocinnamoyl fluoride **1d** gave the cyclopentyl products with only moderate enantioenrichment (i.e. **13a**, 79:21 and **13d**, 80:20 er) the more electron rich 4-MeO, 4-

Me, and 4-$(Me)_2N$ containing cinnamoyl fluorides gave cyclopentanes **13b**, **c** and **e** with high enantioselectivity (>99:1, 88:12 and 90:10 er respectively) while 2-napthyl containing cyclopentane **13f** formed in 52% yield and 93:7 er. A similar, although less pronounced sensitivity to electronics was observed in our earlier studies on enantioselective (3 + 2) annulations.[4e] Next the ester group was modified allowing ethyl ester containing **13g** to be produced in 93:7 er, while the PMP ester **13h** was formed with 85:15 er.

Table 1. Examples of (3 + 3) and (3 + 2) annulations of the unsaturated acyl azolium.[a,b]

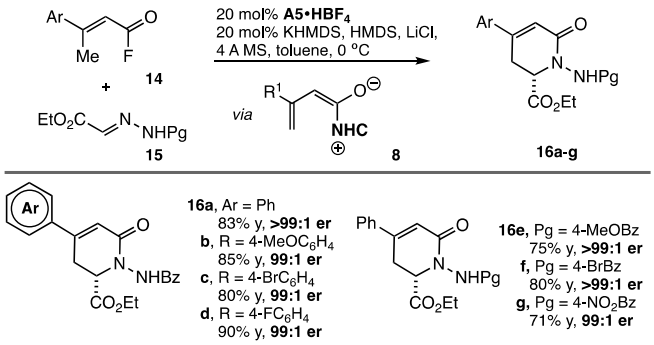


[a] Isolated yield [b] Enantiomeric excess determined by HPLC. [c] **Conditions B** (Figure 2D, entry 4).

In 2013 Chi[15] demonstrated that β–alkyl group on the unsaturated acyl azolium, by the action of additional base, allows access to the acyl azolium dienolate (i.e. Table 2, **8**).[16] To examine the viability of our conditions with this type of reaction design we performed the coupling of β–methyl cinnamoyl fluoride **14** with hydrazone **15** (Table 2). Using the reaction conditions exploited for

the earlier transformations the expected product formed, although the yield was modest. However, with additional HMDS the annulation could be achieved with piperidone **16a** formed in >99:1 er and 83% isolated yield. This outcome could be reproduced with an array of methyl cinnamoyl fluorides **14** and hydrazones **15** coupled in high yield and enantioselectivity (all 99:1 er or greater).

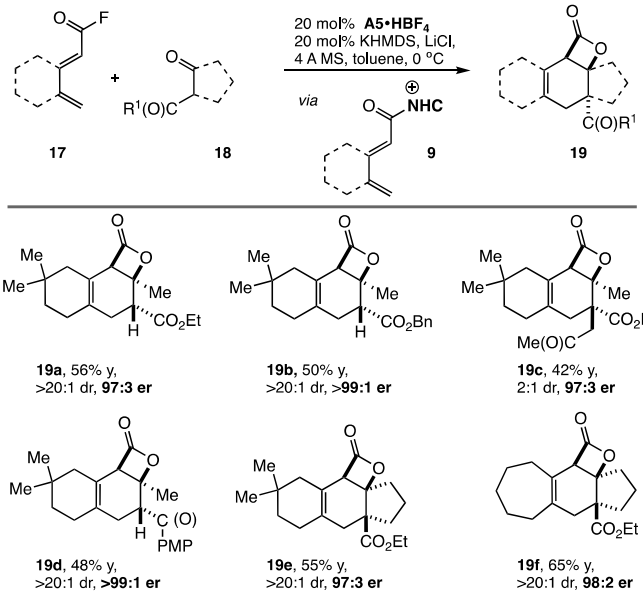
Table 2. Examples of (4 + 2) annulations of the acyl azolium dienolate.[a,b]



[a] Isolated yield [b] Enantiomeric excess determined by HPLC.

Finally we examined the reaction of the dienyl acyl azolium (i.e. **9**, Table 3). This type of species was first reported in 2015,[17] with the first enantioselective design introduced by our group in 2018.[18] Using conditions lacking HMDS an array of tri and tetracyclic products were produced (**19a-f**). Specifically, annulated dienyl acyl fluorides **17** coupled with acyclic ketoesters **18** to give tricycles **19a-d** in greater than 97:3 er (Table 3). In addition, when the coupling was performed with cyclic keto esters the tetracyles **19e** and **f** formed with excellent enantioselectivity (97:3 and 98:2 er respectively) and diastereoselectivity, something not possible using our earlier approach which proceeded with poor enantioselectivity.

Table 3. Examples of annulation of the dienyl acyl azolium.[a,b]



[a] Isolated yield [b] Enantiomeric excess determined by HPLC.

While mechanistic features of each reaction are distinct, there are a number of events that are likely to be common to this approach. Considering the dihydropyranone synthesis (i.e. **11**) the reaction likely commences with the formation of NHC **A5** and HMDS, by deprotonation of the azolium **A5•HBF4** with KHMDS (Figure 3). Substitution of the acyl fluoride by **A5** with resultant fluoride mediated desilylation of HMDS then gives α,β–unsaturated acyl azolium **2d**, TMSF and TMS amide **20**. The later deprotonates 1,3-dicarbonyl **10a** to give enolate **21** which unites with the α,β–unsaturated acyl azolium as described elsewhere.[19] Depending on the presence of additional HMDS subsequent turn-overs either involve desilylation of the HMDS or the silyl amide **22**. In most cases in which the yield is modest the products were accompanied by the primary amide of the acyl fluoride. We believe that this side reaction occurs with sluggish reactions and likely involves either coupling between the acyl azolium **2d** or acyl fluoride **1a** and TMS amide **20** followed by hydrolytic workup.

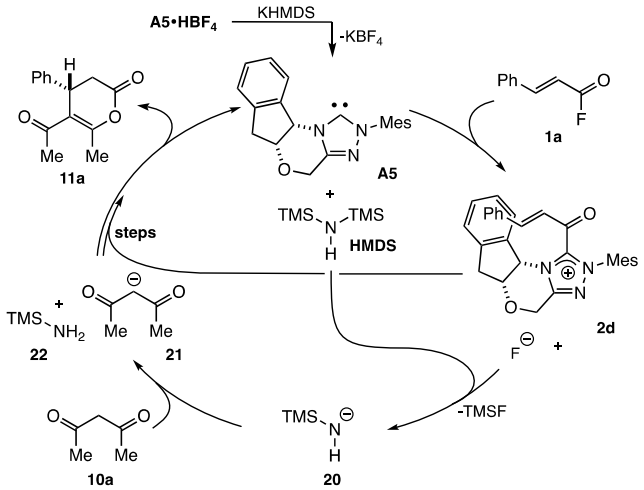


Figure 3. Mechanistic proposal.

Reactions of the α,β–unsaturated acyl azolium have emerged in the last decade as a highly diverse array of complexity generating processes. They are often enantioselective, and can involve a cascade of C–C, C–O and C–N bond forming events. Herein, we report a route to the α,β–unsaturated acyl azolium that avoids commonly exploited exogenous oxidants and/or bases. The conditions are compatible with reaction designs involving both the acyl azolium and acyl azolium enolate. While the designs examined here provide a general indication of the generality of this approach, we believe that the strength of this strategy reside in reaction designs that are not compatible with the intermediacy of the Breslow-intermediate. Studies on this topic are ongoing.

ASSOCIATED CONTENT

Supporting Information. Supporting information documenting methods to prepare all materials, along with appropriate ^{1}H-NMR, ^{13}C-NMR, HPLC traces are contained.

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There are no conflicts to declare

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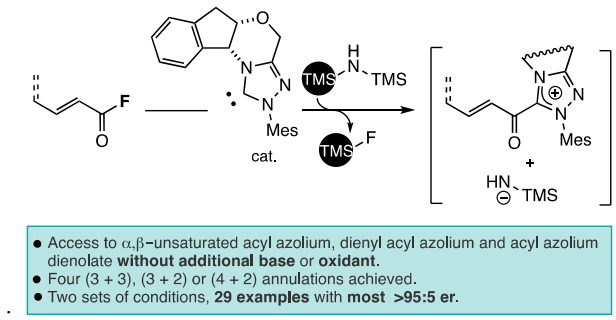
GRAPHICAL ABSTRACT



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