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Enamine/Carbene Cascade Catalysis in the Diastereo- and Enantioselective Synthesis of Functionalized Cyclopentanones

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Abstract

Herein we report an enantioselective synthesis of complex cyclopentanones using aliphatic aldehydes and activated enones. With the combination of a chiral secondary amine and a chiral triazolium catalyst, high diastereoselectivity and excellent enantioselectivity can be achieved. We present evidence of a clear cooperative effect when these two catalysts are present simultaneously in the system.

Introduction

The incorporation of multiple catalytic cycles in a single procedure allows for complex compounds to be easily accessed, a concept that has been termed cascade catalysis.[1–3] By eliminating the need for isolation and purification of intermediates, both time and resources are saved. This is especially important if these intermediates prove unstable upon isolation. While attractive, cascade catalysis provides unique challenges. With the possibility of multiple catalysts present simultaneously, the need for reaction selectivity is important. A solution to this problem is to use catalysts of orthogonal reactivity. Our group has previously reported that secondary amine and *N*-heterocyclic carbene (NHC) catalysts initiate cascade reactions of enals and β-dicarbonyls to form α-hydroxycyclopentanones (Fig 1, a).[4] This reaction proceeds via iminium activation of the enal to induce a conjugate addition by the dicarbonyl followed by an intramolecular benzoin. Importantly the two catalysts work cooperatively, providing higher yields and enantioselectivities compared to a two-step process. Herein, we report the secondary amine/NHC catalyzed cascade reaction of aliphatic aldehydes and activated Michael acceptors to form complex cyclopentanones with a complementary substitution pattern.

Whereas our previous work employed iminium catalysis, we sought to explore the use of enamine catalysis in combination with NHC's in a cascade reaction. Ma has reported a highly diastereo- and enantioselective Michael addition of aliphatic aldehydes into activated enones with the use of a secondary amine catalyst (**3**).[5] We speculated that the aldehyde intermediate formed could undergo an intramolecular benzoin reaction when exposed to an *N*-heterocyclic carbene catalyst (Fig 1, b). This would provide a cyclopentanone product in what may be considered a formal [3+2] cycloaddition. This approach provides complimentary and inaccessible substitution patterns from our previous work.

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†Electronic Supplementary Information (ESI) available: Experimental procedures, spectras, and crystal structues are provided. See DOI: 10.1039/b000000x/

Results and Discussion

Reaction Development

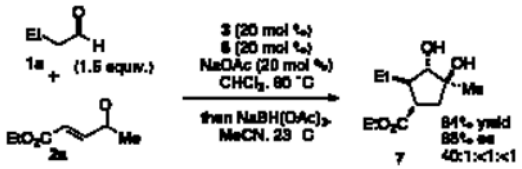
The reaction conditions developed by the Ma group were repeated using the Jorgensen-Hayashi catalyst **3**[7] in methanol at room temperature. After observing the consumption of starting material, achiral triazolium salt **5**[8] and sodium acetate were added to catalyze the benzoin cyclization. These conditions provide no desired product (Table 1, entry 1). When methanol is replaced with chloroform, the desired product is formed in 29% yield and 96% ee but with a 3:1:<1:<1 dr (Table 1, entry 2).[9] Employing a one-step protocol with all reagents present from the outset results in an increase in yield to 35% (entry 3). Increasing the temperature from 23 °C to 60 °C improves the yield to 89% while maintaining high enantioselectivity (96% ee) and a 5:1:<1:<1 diastereomeric ratio. The diastereoselectivity is further improved to 290:15:6:1 when the chiral aminoindanol based triazolium **6**[10,11] is used (entry 5). The use of the antipode of this catalyst, **6′**, results in lower diastereoselectivity (4:1:<1:<1). This is likely a result of a match/mismatch relationship.

Synthetic Scope

With suitable conditions established, a variety of substrates were screened to explore the scope of this new cascade. Aliphatic aldehydes provide the desired products in good yield and high enantio- and diastereoselectivity (Chart 1, **4b–c**). Isovaleraldehyde competitively forms the Stetter product[12] in a 1:1 ratio with cyclopentanone **4d** under standard conditions. This side product can be avoided when the introduction of the triazolium is delayed until after complete formation of the intermediate. Larger aldehydes are also viable but routinely require prolonged reaction times (Chart 1, **4f–g**).

Variation in the enone component was then explored (Chart 2). Esters and tertiary amides are viable under these conditions (Chart 2, **4h–k**).[13] Substitution at the ketone position is also tolerated. *N*-Alkyl ketones provide products in excellent yields while maintaining high stereoselectivity. The isopropyl ketone failed to cyclize under standard conditions. By substituting the bulky triazolium **6** with the smaller achiral catalyst **5**, the intramolecular benzoin was accomplished albeit with a curiously low enantioselectivity (**4o**). Phenyl ketone can also be employed, with diminished diastereoselectivity (**4n**). Diketones may also be used to form products (**4p–q**) with good selectivity despite diminished yield.

With high complexity already built into the cyclopentanone products, functionalization should allow rapid access to even more elaborate products. The addition of sodium triacetoxyborohydride at the end of the reaction permits a diastereoselective reduction of the ketone to 1,2-diol **7**. This action effectively permits the formation of a fourth stereocenter in one pot (Eqn 1).



(1)

Mechanistic Insights

We then explored if there is an advantage between this onestep protocol versus a two-step reaction. Aldehyde **8** was prepared by exposing butyraldehyde and enone **2a** to catalyst **3**,

catalytic acetic acid, and chloroform at room temperature (Scheme 1). After purification, the aldehyde intermediate was isolated in moderate yield with a 2:1 diastereomeric ratio.

Exposure of this intermediate to benzoin conditions provides the cyclized product in comparable yield and enantioselectivity, but with a low diastereomeric ratio (4:1:1:<1). This diastereoselectivity can be improved when the benzoin cyclization is performed with the addition of chiral amine catalyst **3**(10:1:<1:<1 dr).

In our previous work, it was discovered that the amine catalyst is responsible for a retro-Michael reaction, which eroded enantioselectivity in the two-pot reaction. Crossover experiments indicate that this pathway is non-operative in this system.[14] Instead, we propose that the secondary amine catalyst is capable of epimerizing the α-position of the intermediate aldehyde to form an equilibrium between **8** and **8′**. The chiral triazolium **6** prefers cyclization with only one of these diastereomers, and this adduct continues on to the final product. The amine catalyst thus aids in converting the less reactive diastereomerinto its epimer.[15] This hypothesis explains how the amine catalyst can convert aldehyde **8** with low diastereoselectivity to a diastereomerically enriched product.

To support this mechanism, the benzoin cyclization was monitored over time by NMR spectroscopy. When intermediate aldehyde **8** is exposed to catalyst **6**, we see complete consumption of one diastereomer in preference over the other (Fig. 3). When amine catalyst **3** is included in this reaction, consumption of both diastereomers occurs over the course of the reaction, consistent with the hypothesis that amine catalyst **3** serves to interconvert the two diastereomers of **8**.[16,17]

Conclusion

In summary, a one-pot stereoeselective Michael-Benzoin cascade reaction has been developed for the synthesis of complex cyclopentanones. The presence of both the secondary amine and triazolium catalysts is essential for excellent results, indicating a cooperative relationship between the catalysts. This provides a unique and useful method to form complicated cyclopentanes from simple starting materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. Kerr MS, Read de Alaniz J, Rovis T. J Org Chem. 2005; 70:5725. [PubMed: 15989360]
9. Absolute configuration determined by Single Crystal X-ray diffraction of the chiral salt(see SI):

10. (a) Vora HU, Lathrop SP, Reynolds NT, Kerr MS, Read de Alaniz J, Rovis T. Org Synth. 2010; 87:350.(b) Kerr MS, Read de Alaniz J, Rovis T. J Am Chem Soc. 2002; 124:10298. [PubMed: 12197730]

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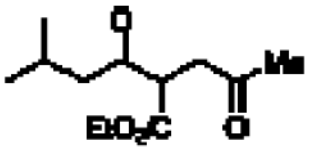
12. Stetter Product formed:



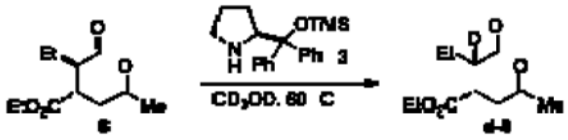
13. Secondary amides and thioesters do not provide desired products.

14. See Supporting Information for crossover experiment results.

15. The second step of this reaction could then be considered analogous to a dynamic kinetic resolution, which has been invoked in several other organocatalyzed transformations: (a) Lee A, Michrowski A, Sulzer-Mosse S, List B. Angew Chem Int Ed. 2011; 50:1707.(b) Hoffman S, Nicoletti M, List B. J Am Chem Soc. 2006; 128:13074. [PubMed: 17017786] (c) Ward DE, Jheengut V, Akinnusi OT. Org Lett. 2005; 7:1181. [PubMed: 15760169]

16. See Supporting Information for spectra from NMR experiments.

17. In addition, when intermediate **8** is exposed to catalyst **3** in deuterated methanol at elevated temperature, complete deuteration is observed at the α-position.



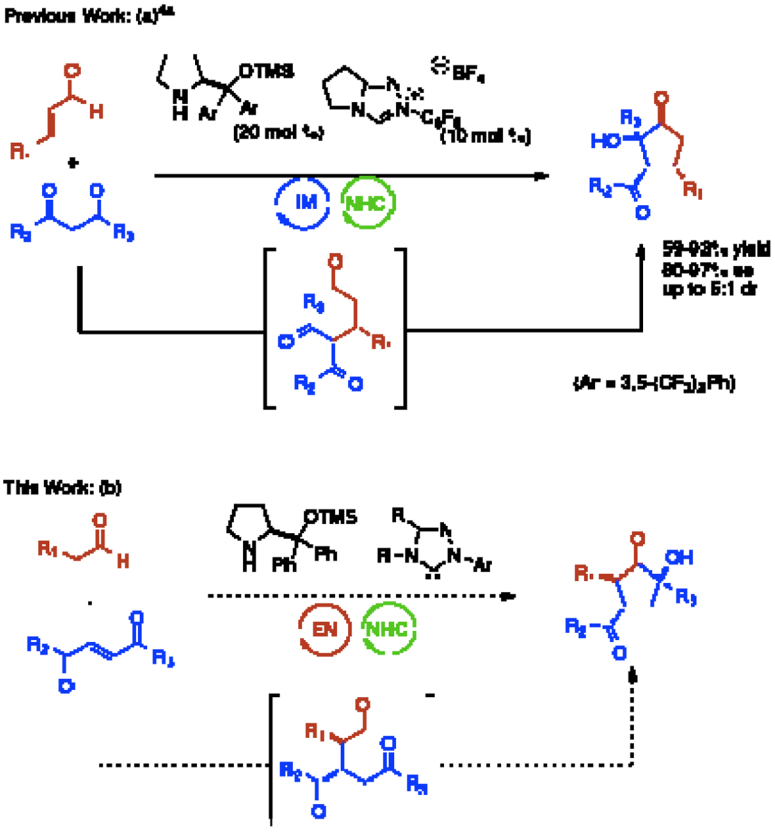


Fig 1.
Secondary amine/NHC cascade reactions[6]

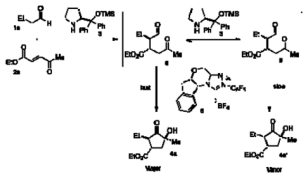


Fig 2.
Proposed Mechanism

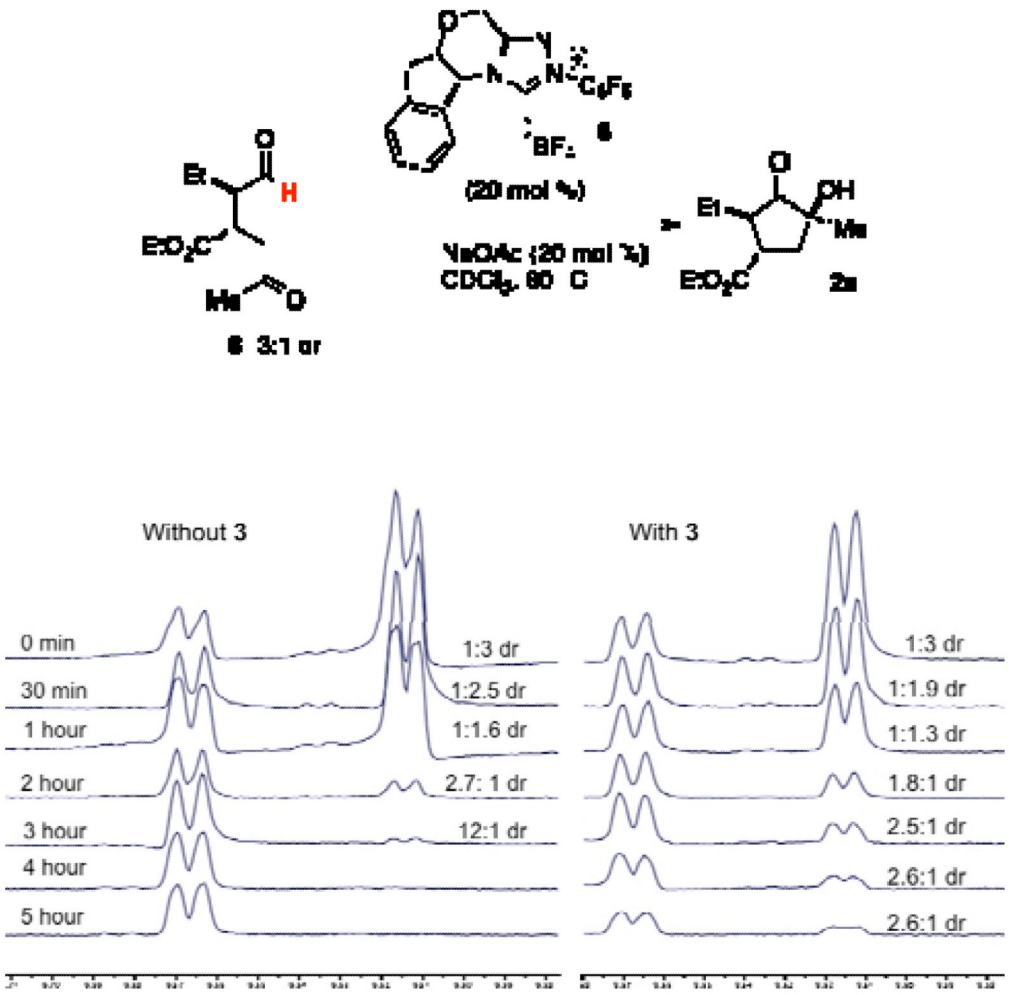
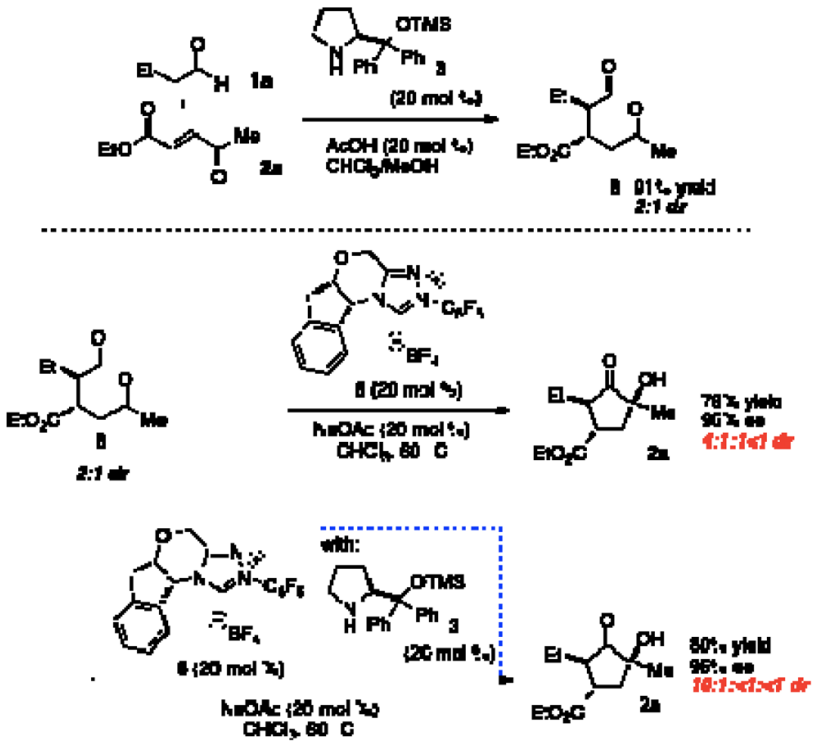


Figure 3.
NMR experiments



Scheme 1.
Two-Pot Reactions

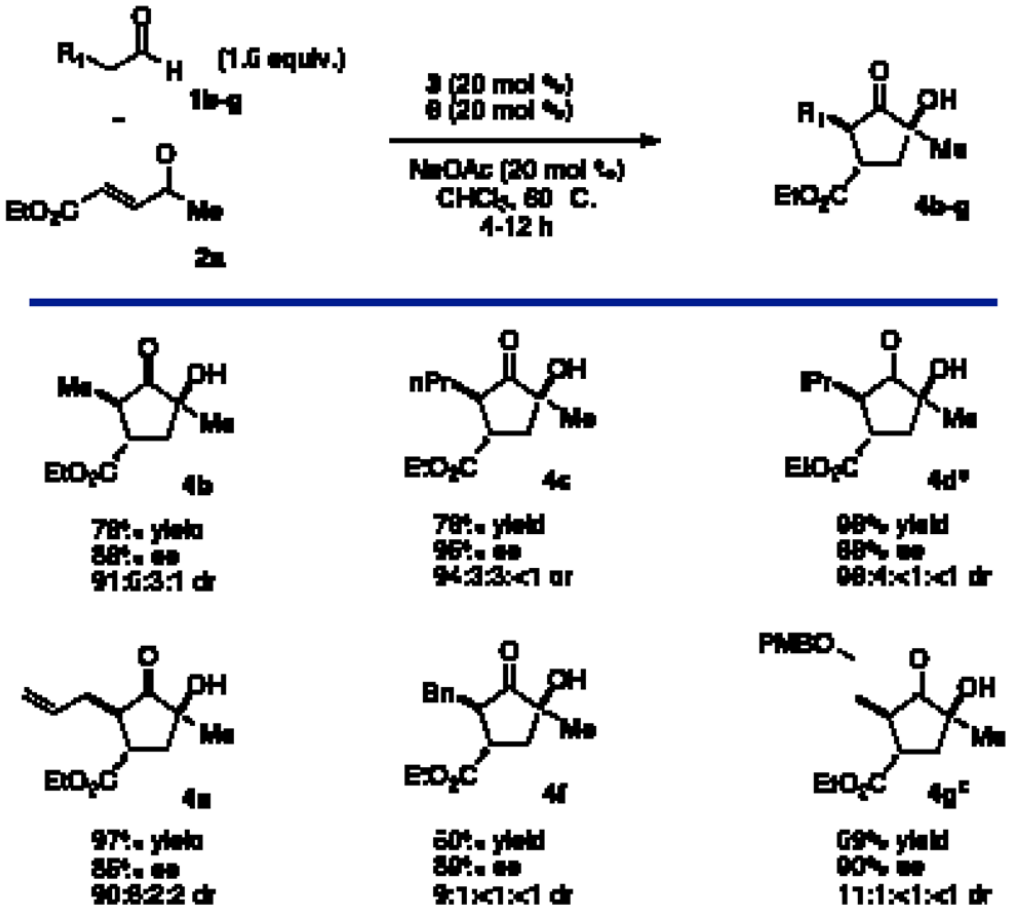


Chart 1.
Aldehyde Scope[a]
[a]See Table 1. [b]Catalyst **6** was added after consumption of starting material. [c]Diastereomeric ratio determined by ^{1}H NMR

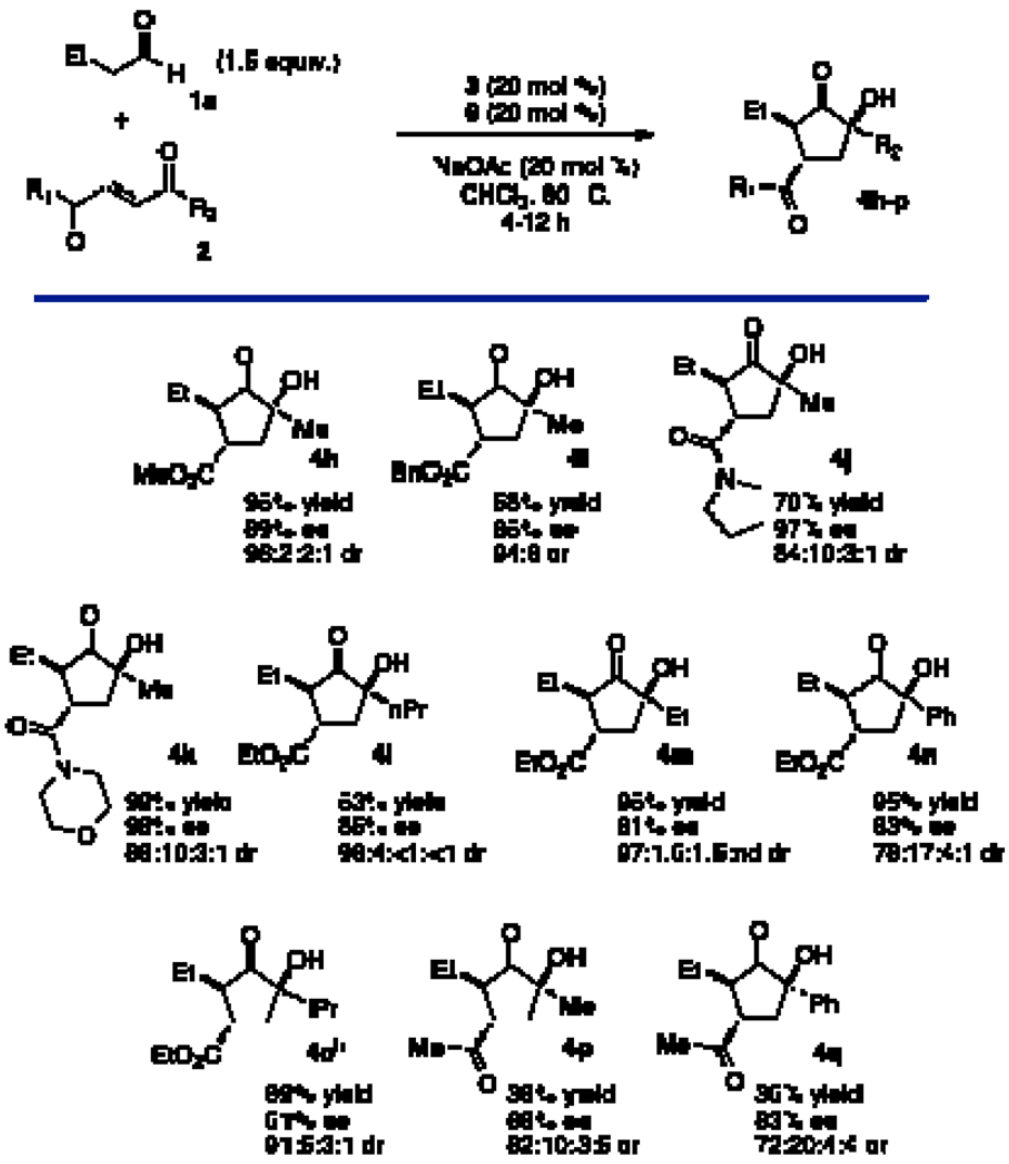
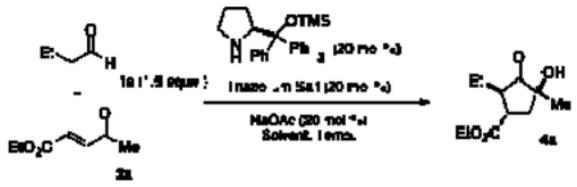


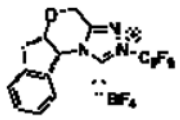
Chart 2.

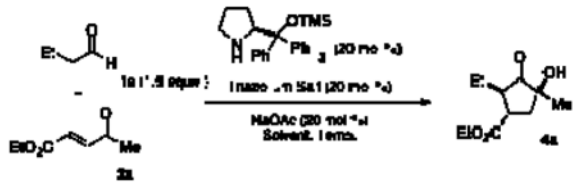
Keto-ester Scope[a]

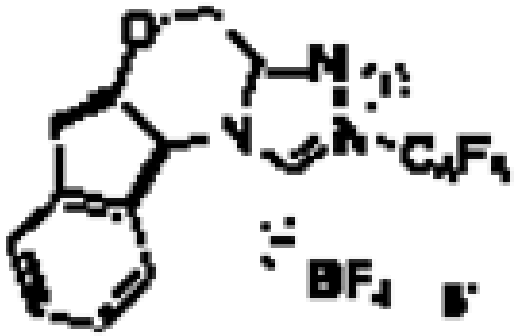
[a]See Table 1. [b]Catalyst **5** was used in place of **6**.

Table 1



	Solvent	Triazolium salt	Temp. (°C)	Yield (%)	ee (%)[b]	*dr*[b]
1[c]	MeOH	 **5**	23	0	--	--
2[c]	$CHCl_3$	**5**	23	29	96	3:1:<1:<1
3[d]	$CHCl_3$	**5**	23	35	96	2:1:<1:<1
4[d]	$CHCl_3$	**5**	60	89	96	5:1:<1:<1
5[d]	$CHCl_3$	 **6**	60	87	95	19:1:<1:<1



	Solvent	Triazolium salt	Temp. (°C)	Yield (%)	ee (%)[b]	*dr*[b]
6[d]	$CHCl_3$		60	59	93	4:1:<1:<1

6′

[a] See supporting information for general procedure.

[b] Enantioselectivity and diastereoselectivity were determined by GC.

[c] 20 mol % Triazolium salt was added after full consumption of **2a**.

[d] 20 mol % Triazolium salt was added at the beginning of the reaction.