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Catalytic Asymmetric Intermolecular Stetter Reaction of Enals with Nitroalkenes: Enhancement of Catalytic Efficiency through Bifunctional Additives

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Supporting Information

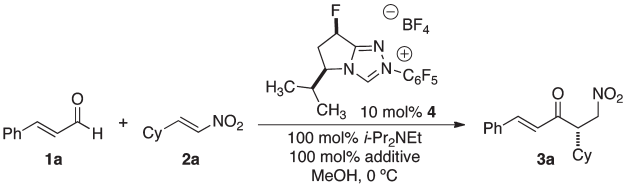
ABSTRACT: An asymmetric intermolecular Stetter reaction of enals with nitroalkenes catalyzed by chiral N-heterocyclic carbenes has been developed. The reaction rate and efficiency are profoundly impacted by the presence of catechol. The reaction proceeds with high selectivities and affords good yields of the Stetter product. Internal redox products were not observed despite of the protic conditions. The impact of catechol has been found to be general, facilitating far lower catalyst loadings than were previously achievable.

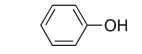
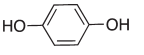
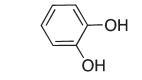
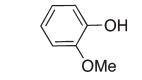
The use of N-heterocyclic carbenes as organocatalysts has led to the development of a variety of enantioselective C−C bond-forming reactions.[1] We recently reported a highly asymmetric intermolecular Stetter reaction[2] of heterocyclic aldehydes and nitroalkenes using novel fluorinated triazolium salt **4** as a precatalyst.[3,4] We found that this reaction requires the presence of a proximal heteroatom for reactivity and were intrigued by its role in both the reactivity and enantioselectivity, given that elucidation could lead to further advancement of this methodology. Because of the invariance in reactivity and enantioselectivity across a range of electronically diverse substrates,[5] it seems unlikely that the heteroatom lone pair acts as a Lewis base, leaving the possibility that its impact is due to sterics.[6] We reasoned that enals would be electronically similar to aryl aldehydes but far less sterically demanding and lacking a proximal Lewis base. To test this hypothesis, cinnamaldehyde (**1a**) and β-cyclohexylnitroalkene (**2a**) were subjected to our established conditions (1.0 equiv of i-Pr_2NEt, MeOH, 0 °C) in the presence of precatalyst **4** (Chart 1, entry 1). Although only a trace amount of product was obtained from this reaction, it was isolated in a promising 93% ee. This experiment demonstrates that a β-heteroatom is not required for high enantioselectivity.

After identifying enals as potential substrates, we began to optimize the reaction in hopes of creating a more efficient process. During previous optimization studies, it was established that protic solvents are required for the desired reactivity. Phenols have previously been shown to be compatible with NHC-catalyzed processes,[7] which led us to investigate them as potential additives in the context of our work. Among those surveyed, bisphenols were the most effective at increasing catalyst turnover. Addition of 1 equiv of phenol to the reaction mixture afforded very little improvement, but addition of 1 equiv of catechol[8] shows a remarkable increase in reactivity and isolated yield (Chart 1, entry 4). We note that products of redox esterification,[9] a common pathway for enals under similar conditions,[7] are not formed in appreciable amounts. We speculated that the special reactivity was due to the proximal nature of the phenolic protons. Indeed, hydroquinone, which contains distal biprotic functionality and is electronically similar to catechol, showed only a slight improvement in yield (Chart 1, entry 3). In order to isolate the effects of electronics from the biprotic functionality, guaiacol was also investigated and found to provide little benefit relative to phenol (Chart 1, entry 5). These experiments strongly suggest the participation of both functional groups in the rate-accelerating event.

Although the origin of its influence on the reactivity is not rigorously understood, we speculate that catechol assists in proton transfer to generate crucial acyl anion equivalent **II**. Under

Chart 1. Effect of Brønsted Acid Additives[a]



entry	additive	time (h)	yield (%)[b]	ee (%)[c]
1	none	8	5	93
2		8	8	93
3		8	15	93
4		*2*	*80*	*93*
5		8	9	93

[a]Reactions were conducted with 1 equiv of **1a** and 1.5 equiv of **2a**. [b]Yields refer to isolated yields after chromatography. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

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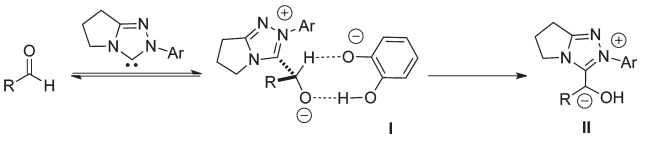
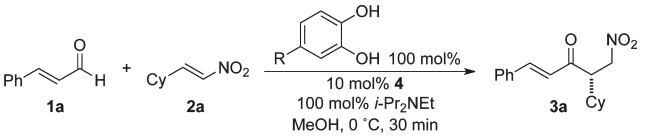


Figure 1. Proposed mode of activation.

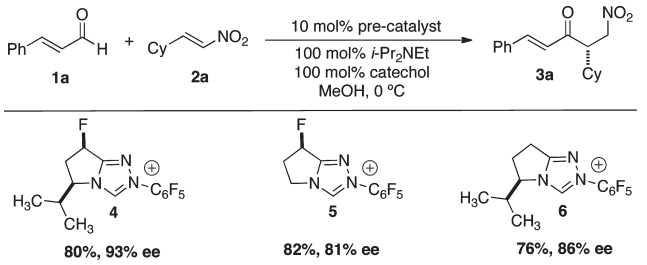
Chart 2. Variation of the Catechol Additive[a,b]



Entry	R	yield (%)[c]	ee(%)[d]
1	*t*-Bu	55	93
2	H	48	93
3	OMe	39	93
4	CO_2Et	40	93
5	CN	36	93

[a]Reactions were conducted with 1 equiv of **1a** and 1.5 equiv of **2a**. [b]Experiments were quenched after 30 min. [c]Yields are isolated yields after chromatography. [d]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Chart 3. Examination of Precatalysts[a,b,c]



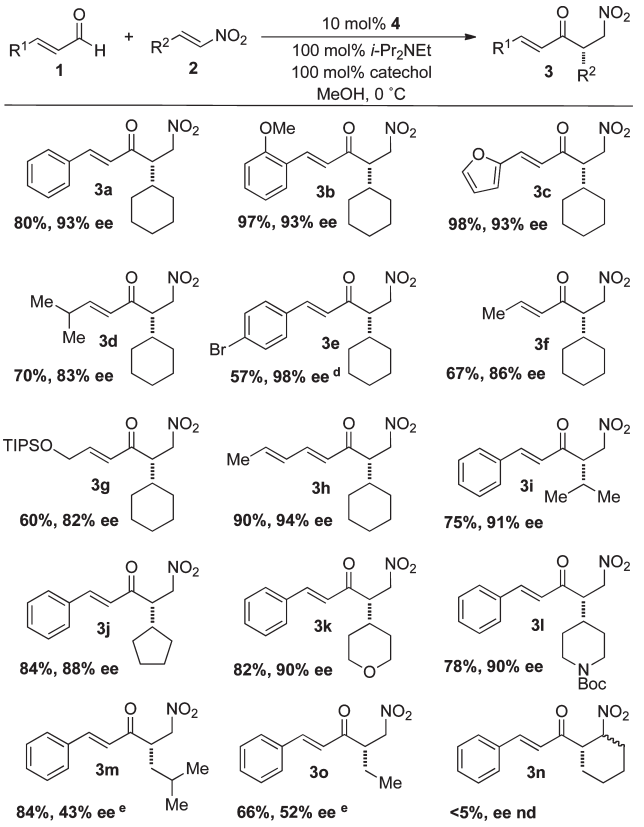
[a,b]See Chart 1. [c]The catalyst counterion (BF_4^-) has been omitted for clarity.

our basic reaction conditions, catechol monoanion (catecholate) is likely the catalytically relevant species. Because direct 1,2-hydrogen shifts are symmetry-forbidden,[10] catecholate could aid in generating the acyl anion by facilitating proton transfer through a synchronous transition state (**I**), reminiscent of the familiar carboxylic acid dimer (Figure 1).

A variety of catechol derivatives were examined to determine their effect on the reactivity (Chart 2). We chose to use catechol as the additive of choice in the remainder of our investigation because of its high reactivity and wide availability.

With the identification of a suitably reactive catalyst system, we began to investigate the effect of the catalyst structure on the enantioselectivity. In our previous studies of the asymmetric intermolecular Stetter reaction, we showed that fluorination of the catalyst backbone has a dramatic impact on the enantioselectivity.[3] To probe the effect of backbone fluorination on the selectivity, we screened both desfluoro analogue **6** and precatalyst **5**, whose chirality is dictated solely by its fluorine substituent. Remarkably, precatalyst **5** displays high enantioselectivity (81% ee) in the absence of any bulky stereodirecting groups (Chart 3). For comparison, desfluoro precatalyst **6** provided the product in 86% ee, only a modest improvement over precatalyst **5**.

Chart 4. Reaction Scope[a,b,c]

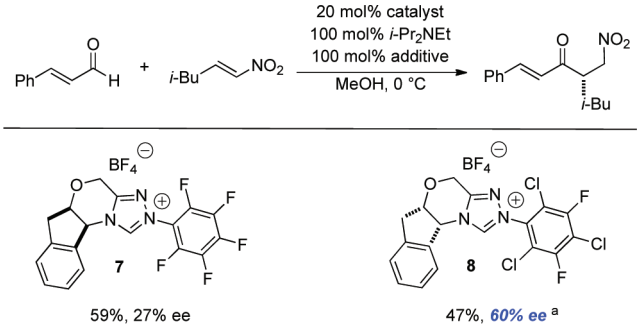


[a]Reactions were conducted with 1 equiv of **1** and 1.5 equiv of **2**. [b]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [c]Absolute stereochemistries were determined by X-ray analysis of **3e** (see the Supporting Information). [d]The product crystallized from the reaction mixture. [e]4-(Ethoxycarbonyl)catechol (Chart 2, entry 4) was used.

With the advent of this efficient dual catalytic system, we investigated the scope of this transformation (Chart 4). Aryl substitution on the enal results in product formation in good yields (57−97%) and excellent enantioselectivities (93−98% ee). Likewise, dienals may be incorporated with uniformly high selectivity, while alkyl substitution on the enal produces somewhat reduced enantioselectivities. Secondary alkyl substitution of the nitroalkene is well-tolerated, providing a variety of carbocyclic and heterocyclic products. Under these conditions, primary-alkyl-substituted nitroalkenes lead mainly to decomposition products; however, the use of a more acidic ester-substituted catechol derivative (Chart 2, entry 4) leads to high yields of the nitroketone product, albeit with diminished enantioselectivity. More sterically demanding electrophiles such as 1-nitrocyclohexene do not participate (Chart 4).[11]

The somewhat disappointing results obtained with primary-alkyl-substituted nitroalkenes prompted us to investigate the effect of including larger electron-deficient *N*-aryl substituents on the catalyst scaffold, in anticipation that these might increase the selectivity. When aminoindanol-derived precatalyst **7** containing a C_6F_5 substituent is subjected to the conditions developed for primary-alkyl nitroalkenes, a modest yield of product **3n** is

Chart 5. Influence of the *N*-Aryl Substituent on the Selectivity



[a]The opposite enantiomer was obtained.

Scheme 1. Effect of Catechol in the Intramolecular Stetter Reaction

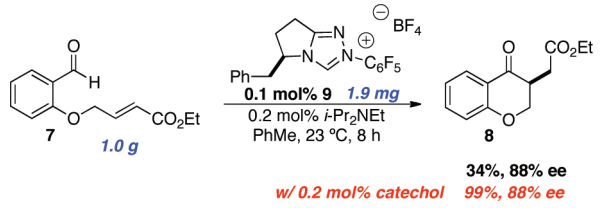
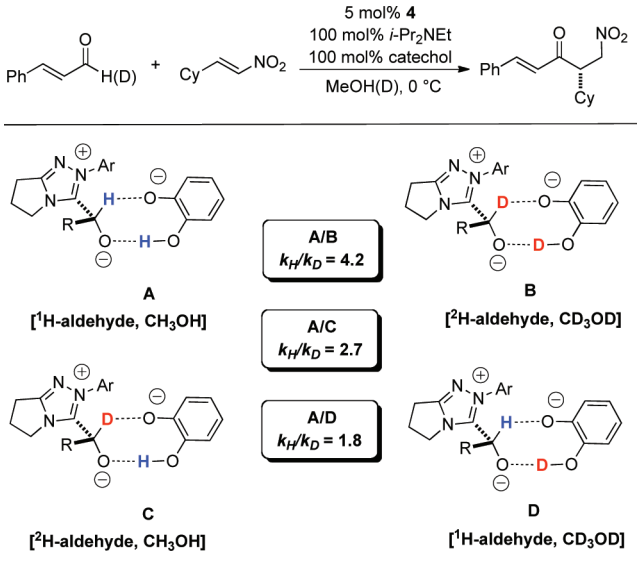


Chart 6. ^{2}H Kinetic Isotope Effect Studies[a]



[a]See the Supporting Information for complete experimental details.

obtained with very low enantioselectivity. We were pleased to find that replacing the C_6F_5 substituent with the larger 2,4,6-Cl_3-3,5-F_2 substituent on the same catalyst scaffold results in a significant improvement in the selectivity. (Chart 5). We anticipate that future catalyst design will lead to a more general solution for difficult substrates.

In an attempt to elucidate further the role of catechol in this transformation, we investigated its effect on the well-studied intramolecular Stetter reaction. A detailed mechanistic study of the intramolecular Stetter reaction has recently provided significant evidence for the conclusion that the turnover-limiting step is initial proton transfer.[12] Exposure of aldehyde **7** to 0.1 mol % triazolium salt **9** and 0.2 mol % i-Pr_2NEt in toluene provides low yield (34%) of the cyclized product (Scheme 1). However, introduction of only 0.2 mol % of catechol to the reaction results in a dramatic increase in reactivity and an excellent isolated yield (99%). Thus, it stands to reason that catechol is intimately involved in facilitating proton transfer in this system, which may be closely related to its action in the intermolecular reaction.

To test this hypothesis, we conducted a ^{2}H kinetic isotope effect study using **1a** and its deuterated isotopologue (CDO) in methanol or methanol-d_4. The value of k_H/k_D was found to be 2.7 when the reaction was conducted in methanol and 4.2 when conducted in methanol-d_4 (Chart 6). These data suggest that initial proton transfer to form acyl anion equivalent **II** is also turnover-limiting in this transformation. Furthermore, we observed a k_H/k_D = 1.8 when ^{1}H-aldehyde **1a** was subjected to identical reaction conditions in methanol-d_4, suggesting the participation of the phenolic proton of catechol in the turnover-limiting step.[13]

In summary, we have developed a highly efficient and enantioselective intermolecular Stetter reaction of enals and nitroalkenes. The incorporation of enals in the asymmetric Stetter reaction not only significantly expands a scope previously limited to heteroaryl aldehydes but also complements the homoenolate reactivity commonly observed in NHC-catalyzed reactions of enals. High selectivity has been achieved through the use of fluorinated triazolium salt precatalysts. Furthermore, we have shown that bifunctional Brønsted acids such as catechol significantly enhance the reactivity and chemical yield in the Stetter reaction, and their mechanism of action was probed through a series of kinetic isotope effect studies, which provides convincing evidence that the turnover-limiting step is initial proton transfer. This observation was crucial in the development of this methodology and may have long-lasting implications for other NHC-catalyzed processes.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, ^{1}H/^{13}C NMR spectra, and crystallographic data (CIF) for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Evidence suggests that the role of the heteroatom is not simply that of a proximal Lewis base, given that both pyridazine carboxaldehyde and furfural participate with equal facility in spite of their very low basicities (see ref 3).

(6) As an estimate of N lone pair versus C−H size, witness the following *A* values: CH_3 = 1.74, NH_2 = 1.40 (see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001; p 174).

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(10) A 1,2-proton shift is a symmetry-forbidden transformation (see: Kemp, D. S. *J. Org. Chem.* **1971**, *36*, 202–204 and references therein). However, it has been calculated to have barriers of ∼29 kcal/mol for thiazolylidine and ∼51 kcal/mol for cyanide in the formation of the acyl anion equivalent from formaldehyde. See: Goldfuss, B.; Schumacher, M. *J. Mol. Model.* **2006**, *12*, 591–595.

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(13) The role of a solvent isotope effect in this reaction cannot be discounted. However, an experimental value of an isotope effect of 3.6 for the hydration of acetaldehyde has been explained by the intervention of three molecules of water in the addition step, ultimately involving the cleavage of O−H (O−D) bonds. A theoretical investigation of the hydration of formaldehyde supports this assertion; to wit, the isotope effect is due not to solvent but to a specific isotope effect (see: Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* **1995**, *117*, 4240–4260 and references therein). It is also noteworthy that the entropically disfavored intervention of three water molecules in this reaction is preferred because of the preference for the eight-membered ring for the proton tranfer events, with the larger O−H−O bond angles it facilitates. We further note that the catecholate also forms an eight-membered ring in our proposed model for shuttling of the proton from C to O.