Published in final edited form as:

J Am Chem Soc. 2011 July 13; 133(27): 10402–10405. doi:10.1021/ja203810b.

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

Daniel A. DiRocco and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Abstract

An asymmetric intermolecular Stetter reaction of enals with nitroalkenes, catalyzed by chiral N-heterocyclic carbenes, has been developed. Reaction rate and efficiency are profoundly impacted by the presence of catechol. The reaction proceeds with high selectivities affording good yields of the Stetter product. Internal redox products are not observed, in spite of the protic conditions. The impact of catechol has found to be general facilitating far lower catalyst loadings than was 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 Recently, we reported a highly asymmetric intermolecular Stetter reaction² of heterocyclic aldehydes and nitroalkenes using novel fluorinated triazolium salt **4** as pre-catalyst.^{3,4} We found that this reaction requires the presence of a proximal heteroatom for reactivity and were intrigued by its role in both reactivity and enantioselectivity, given that elucidation could lead to further advancement of this methodology. Due to the invariance in reactivity and enantioselectivity across a range of electronically diverse substrates,⁵ it seems unlikely that the heteroatom lone pair is acting 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 -cyclohexyl-nitroalkene **2a** were subjected to our established conditions (1.0 equiv. *i*-Pr₂NEt, MeOH, 0 °C) in the presence of pre-catalyst **4** (Chart 1, Entry 1). Although only trace product was obtained from this reaction, it was isolated in a promising 93% ee. This experiment demonstrates that a β -heteroatom is not requisite 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 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, bis-phenols were the most effective at increasing catalyst turnover. Addition of 1 equivalent of phenol to the reaction affords very little improvement, but addition of 1 equivalent of catechol⁸ shows a remarkable increase in reactivity and isolated yield (Chart 1, Entry 4). We note that products of redox esterification⁹, a common pathway of 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 bi-

roviss@lamar.colostate.edu.

Supporting Information Available: Experimental procedures, characterization, ¹H/¹³C NMR spectra; CIF for **3e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

protic functionality and is electronically similar to catechol, shows only a slight improvement in yield (Chart 1, Entry 3). In order to isolate the effects of electronics from the bi-protic functionality, guaiacol was also investigated, which provides 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 reactivity is not rigorously understood, we speculate that catechol assists in proton-transfer to generate crucial acyl anion equivalent **II**. Under our basic reaction conditions, catechol mono-anion (catecholate) is likely the catalytically relevant species. Because direct 1,2-hydrogen shifts are symmetry forbidden,¹⁰ catecholate could aid in generation of 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 reactivity. We chose to use catechol as the additive of choice in the remainder of our investigation due to its high reactivity and wide availability.

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

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 yield (57–97%) and excellent enantioselectivities (93–98% ee). Likewise, dienals can 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 to mainly decomposition products; however, use of a more acidic ester-substituted catechol derivative (Chart 2, Entry 4) leads to high yields of the nitro-ketone 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 larger electron-deficient *N*-aryl substituents on the catalyst scaffold, in anticipation that these might increase selectivity. When amino-indanol derived pre-catalyst **7**, containing the C₆F₅ substituent was subjected to conditions developed for primary-alkyl nitroalkenes, modest yield is obtained of product **3n**, in very low enantioselectivity. We were pleased to find that replacing the C₆F₅ substituent with the larger 2,4,6-Cl₃-3,5-F₂ substituent on the same catalyst scaffold results in significant improvement of selectivity. (Chart 5). We anticipate future catalyst design will lead to a more general solution of difficult substrates.

In an attempt to further elucidate 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 to conclude 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*-Pr₂NEt in toluene provides low yield (34%) of the

cyclized product. However, introduction of only 0.2 mol% of catechol to the reaction results in a dramatic increase in reactivity and 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 ^2H kinetic isotope effect study using cinnamaldehyde **1a** and its deuterated isotopologue (CDO) in methanol or methanol- d_4 . A $k_{\text{H}}/k_{\text{D}}$ of 2.7 was found when the reaction was conducted in methanol and 4.2 when conducted in methanol- d_4 (Chart 6). This data suggests that initial proton transfer to form acyl anion equivalent **II** is also turnover-limiting in this transformation. Furthermore, we observe a $k_{\text{H}}/k_{\text{D}}$ of 1.8 when ^1H -aldehyde **1a** is subjected to identical reaction conditions in methanol- d_4 , suggesting the participation of catechol's phenolic proton in the turnover-limiting step.¹³

In summary, we have developed a highly efficient and enantioselective intermolecular Stetter reaction of enals and nitroalkenes. Not only does the incorporation of enals in the asymmetric Stetter reaction significantly expand a scope previously limited to heteroaryl aldehydes, but it complements the homoenolate reactivity commonly observed with NHC catalyzed reactions of enals. High selectivity has been achieved through the use of fluorinated triazolium salt pre-catalysts. Furthermore, we have shown that bifunctional Brønsted acids, such as catechol, significantly enhance reactivity and chemical yield in the Stetter reaction, and their mechanism of action has been probed through a series of kinetic isotope effect studies which have provided 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 in other NHC catalyzed processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank NIGMS (GM72586) for support, Kevin Oberg and Derek Dalton for X-ray analysis of **3e**, Amgen and Roche for unrestricted support. D.A.D. thanks Roche for an Excellence in Chemistry award.

References

1. For reviews see: (a) Marion N, Díez-González S, Nolan SP. *Angew. Chem. Int. Ed. Engl.* 2007; 46:2988–3000. [PubMed: 17348057] (b) Enders D, Niemeier O, Henseler A. *Chem. Rev.* 2007; 107:5606–5655. [PubMed: 17956132] (c) Moore JL, Rovis T. *Top. Curr. Chem.* 2009; 290:77–144.
2. (a) Stetter H, Schrecke M. *Angew. Chem., Int. Ed. Engl.* 1973; 12:81. (b) Stetter H. *Angew. Chem., Int. Ed. Engl.* 1976; 15:639–647. (c) Stetter H, Kuhlmann H. *Org. React.* 1991; 40:407–496. (d) Christmann M. *Angew. Chem., Int. Ed.* 2005; 44:2632–2634. (e) Rovis T. *Chem. Lett.* 2008; 37:2–7.. For a review of the asymmetric intramolecular Stetter reaction see: Read de Alaniz J, Rovis T. *Synlett.* 2009:1189–1207. [PubMed: 20585467] . For a general review on Lewis base catalysis, see: Denmark SE, Beutner GL. *Angew. Chem. Int. Ed.* 2008; 47:1560–1638.
3. DiRocco DA, Oberg KM, Dalton DM, Rovis T. *J. Am. Chem. Soc.* 2009; 131:10872–10874. [PubMed: 19722669] . For review of fluorine's effect on molecular conformation, see: Hunter L. Beilstein J. *Org. Chem.* 2010 doi:10.3762/bjoc.6.38.
4. For other contributions to the asymmetric intermolecular Stetter reaction, see: (a) Liu Q, Perreault S, Rovis T. *J. Am. Chem. Soc.* 2008; 130:14066–14067. [PubMed: 18834123] (b) Liu Q, Rovis T. *Org. Lett.* 2009; 11:2856–2859. [PubMed: 19507841] (c) Enders D, Han J, Henseler A. *Chem. Commun.* 2008:3989–3991. (d) Enders D, Han J. *Synthesis.* 2008:3864–3868. (e) Jousseume T, Wurz NE, Glorius F. *Angew. Chem. Int. Ed.* 2011; 50:1410–1414.. (f) For an enzyme-catalyzed

- asymmetric Stetter, see: Dresen C, Richter M, Pohl M, Lüdeke S, Müller M. *Angew. Chem. Int. Ed.* 2010; 49:6600–6603.
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 basicity. See reference 3.
6. As an estimate of N-lone pair vs C-H size, witness the following A values: CH₃=1.74, NH₂=1.40. Smith MB, March J. *March's Advanced Organic Chemistry* (5th Ed.). New York: John Wiley & Sons, Inc.; 174.
7. (a) Reynolds NT, Rovis T. *J. Am. Chem. Soc.* 2005; 127:16406–16407. [PubMed: 16305222] (b) Chan A, Scheidt KA. *Org. Lett.* 2005; 7:905–908. [PubMed: 15727471] (c) Sohn SS, Bode JW. *Org. Lett.* 2005; 7:3873–3876. [PubMed: 16119920]
8. Filloux CM, Lathrop SP, Rovis T. *Proc. Nat. Acad. Sci. USA.* 2010; 107:20666–20671. [PubMed: 20639467]
9. (a) Chow KY-K, Bode JW. *J. Am. Chem. Soc.* 2004; 126:8126–8127. [PubMed: 15225048] (b) Reynolds NT, Read de Alaniz J, Rovis T. *J. Am. Chem. Soc.* 2004; 126:9518–9519. [PubMed: 15291537]
10. 1,2-proton shift is a symmetry forbidden transformation (Kemp DS. *J. Org. Chem.* 1971; 36:202–204. and references therein.) but has been calculated to have a ~29 kcal/mol barrier (thiazolylidene) and ~51 kcal/mol barrier (cyanide) in the formation of the acyl anion equivalent from formaldehyde; see: Goldfuss B, Schumacher M. *J. Mol. Model.* 2006; 12:591–595. [PubMed: 16258739]
11. The use of nitrocyclohexene results in the unusual formation of cinnamaldehyde dimethylacetal. For a similar observation in the Stetter reaction see: Parfenov EA, Bekker AR, Kosterova GF. *Zh. Org. Khim.* 1981; 17:885–886.
12. Moore JL, Silvestri AP, Read de Alaniz J, DiRocco DA, Rovis T. *Org. Lett.* 2011; 13:1742–1745. [PubMed: 21355598]
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 not due 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 8-membered ring for the proton transfer 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 the proton from C to O.

Figure 1.
Proposed mode of activation.

Scheme 1.

Effect of catechol in the intramolecular Stetter Reaction.

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

Chart 1.

Effect of Brønsted acid additives a,b,c

^aReactions conducted with 1 equiv of **1a** and 1.5 equiv of **2a**. ^b Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. ^c Yield refers to isolated yields after chromatography.

Entry	R	Yield (%) ^a	ee (%) ^c
1.	<i>n</i> Bu	93	93
2.	H	49	93
3.	OMe	39	93
4.	CO ₂ Et	49	93
5.	CN	36	93

Chart 2.

Variation of the Catechol Additive a,b,c,d

^aReactions conducted with 1 equiv of **1a** and 1.5 equiv of **2a**. ^bExperiments quenched after 30 min. ^cEnantiomeric excess determined by HPLC analysis on a chiral stationary phase. ^dYield refers to isolated yields after chromatography.

80%, 93% ee

82%, 81% ee

76%, 86% ee

Chart 3.

Examination of pre-catalysts a,b,c

^{a,b} See Chart 1. ^c Catalyst counterion (BF_4) omitted for clarity.

Reaction Scope abc

^a Reactions conducted with 1 equiv of **1** and 1.5 equiv of **2**. ^b Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. ^c Absolute stereochemistry determined by X-ray analysis of **3e**; see supporting information. ^d Product crystallized from reaction mixture. ^e 4-(ethoxycarbonyl)catechol (Chart 2, Entry 4) was used.

59%, 27% ee

47%, **60% ee**^a

Chart 5.
Influence of the *N*-aryl Substituent on Selectivity.
^a Opposite enantiomer obtained.

A[¹H-aldehyde, CH₃OH]

A/B
 $k_H/k_D = 4.2$

B[²H-aldehyde, CD₃OD] **C**[²H-aldehyde, CH₃OH]

A/C
 $k_H/k_D = 2.7$

A/D
 $k_H/k_D = 1.8$

D[¹H-aldehyde, CD₃OD]**Chart 6.**²H Kinetic Isotope Effect Studies.^a^a See supporting information for complete experimental details.