Asymmetric Catalysis

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Catalytic Asymmetric Intermolecular Stetter Reactions of Enolizable Aldehydes with Nitrostyrenes: Computational Study Provides Insight into the Success of the Catalyst**

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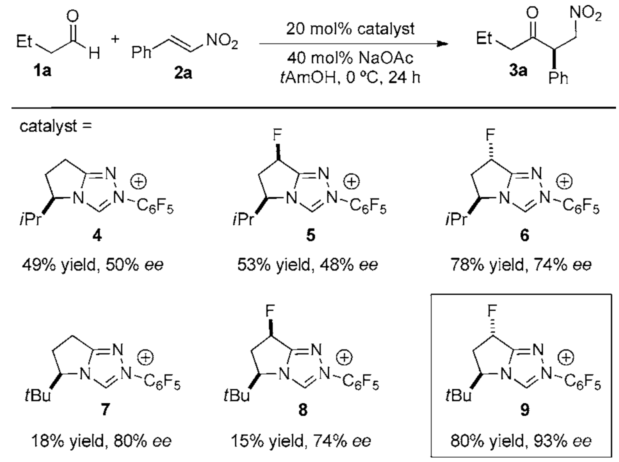
Over the past decade, N-heterocyclic carbenes (NHCs) have been used as catalysts in a variety of C–C bond forming reactions.[1] Our group has been interested in the development of chiral NHCs as catalysts for the asymmetric intramolecular Stetter reaction[2,3] and more recently, the intermolecular variant.[4,5] We recently reported that hetaryl aldehydes and enals react efficiently with nitroalkenes in the Stetter reaction, leading to β-nitro ketones with high enantioselectivity.[4d] Crucial to the success of this method was the development of a fluorinated triazolium salt pre-catalyst that provides significantly enhanced enantioselectivity over *des*-fluoro analogues.[6] Although the new catalyst system greatly expands the scope of this method, these conditions are not amenable to the use of unactivated aliphatic aldehydes. Because of their lower electrophilicity relative to aryl aldehydes, aliphatic aldehydes have rarely been successfully used in the asymmetric intermolecular Stetter reaction.[7,8]

Our initial attempts at rectifying this problem began by evaluating more reactive Michael acceptors, such as β-nitrostyrenes. The unstable nature of the reaction components mandated milder reaction conditions; a brief screen revealed tertiary alcohol solvents and weak inorganic bases as being optimal.[9] Under these conditions, pre-catalyst **5**, which previously demonstrated high reactivity and enantioselectivity for hetaryl aldehydes and enals, affords only modest yield (53 %) with low enantioselectivity (48 %; Scheme 1). Interestingly, this reaction affords the opposite major enantiomer to that observed in our previous work using the same pre-catalyst with aliphatic nitroalkenes.[4d] Surprisingly, *trans*-fluorinated pre-catalyst **6** provides substantial increases in both yield (78 %) and enantioselectivity (74 %). To further increase selectivity we evaluated the more sterically demanding pre-catalyst **7**, derived from *t*-leucine. This pre-catalyst displays low reactivity compared to the valine-derived pre-catalysts (**4**–**6**), but with greatly increased enantioselectivity (80 %). Further evaluation of this scaffold shows the same trends in reactivity and selectivity as the valine-derived series; *trans*-fluorinated pre-catalyst **9** provides drastically better selectivity (93 % *ee*) than both *cis*-fluoro (74 %) and *des*-fluoro (80 %) catalysts.



Scheme 1. Catalyst optimization studies. Reactions conducted with 1.5 equiv **1a** and 1.0 equiv **2a**. Yields shown are of product isolated after chromatography. Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase. BF_4^- counterions omitted for clarity.

Under optimized conditions, the scope of this transformation was evaluated with respect to both the aldehyde and nitrostyrene derivative (Table 1). Using β-nitrostyrene **2a** as the Michael acceptor, a variety of aliphatic aldehydes were examined. Straight-chain aliphatic substitution provides products in high yield (80–87 %) and excellent enantioselectivity (92–93 %), with the exception of acetaldehyde, which gives good yield (71 %), but is only modestly selective (62 % *ee*). β-Branched aldehydes are tolerated and provide excellent enantioselectivity (95 %), albeit in lower yield, while α-branched aldehydes do not participate. A variety of functional groups are well-tolerated, including thio ethers, silyl ethers, alkyl halides, and terminal olefins. Substitution on the aryl ring of the nitroalkene leads to fairly invariant results. *Ortho*-,

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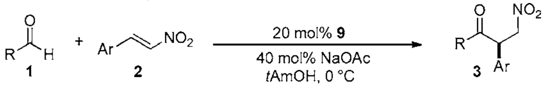
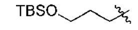
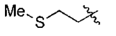
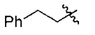
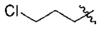
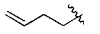
Table 1: Reaction Scope.[a]

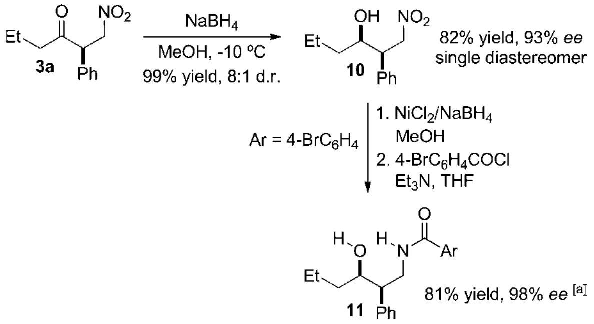


Entry	R	Ar	Yield [%][b]	*ee* [%][c]
1	*n*Pr	Ph	80	93
2	Et	Ph	87	92
3	Me	Ph	71	62
4	*i*Bu	Ph	32	95
5		Ph	68	87
6		Ph	67	92
7		Ph	76	93
8		Ph	83	93
9		Ph	83	93
10	Cy	Ph	< 5	N/A
11	*n*Pr	2-Cl-C_6H_4	70	91
12	*n*Pr	2-F-C_6H_4	75	93
13	*n*Pr	2-MeO-C_6H_4	83	94
14	*n*Pr	3-MeO-C_6H_4	63	91
15	*n*Pr	3-Br-C_6H_4	50	91
16	*n*Pr	4-Cl-C_6H_4	70	92
17	*n*Pr	4-Me-C_6H_4	81	92
18	*n*Pr	4-[B(pin)]-C_6H_4	62	91

[a] Reactions conducted with 1.5 equiv **1** and 1.0 equiv **2** for 24–48 h. [b] Yield of isolated product after chromatography. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

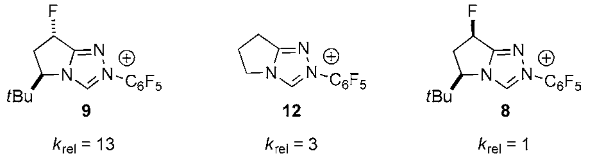
meta-, and *para*-substitutions were examined, providing both fair to good yields (50–83%) and excellent enantioselectivities (91–94%) in all cases. A 2.5 mmol scale experiment was also performed using 10 mol% of **9**, which provided the product in 84% yield and 93% *ee*.

Derivatization of product **3a** was performed to demonstrate the synthetic utility of β-nitro ketone products (Scheme 2). Reduction with $NaBH_4$ leads to the desired nitro alcohol in quantitative yield and 8:1 d.r. The major diastereomer is easily isolated by chromatography, providing 82% of **10** in 93% *ee*. Reduction of the nitro group is accomplished using $NiCl_2/NaBH_4$, which, following a simple workup, is transformed to the corresponding benzamide in 81% yield and 98% *ee*.



Scheme 2. Derivatization of β-nitro ketone products. [a] Absolute and relative configuration determined by X-ray analysis; see the Supporting Information.

We were intrigued by the large differences in both reactivity and enantioselectivity between diastereomeric catalysts **8** and **9**. To further probe this variance, a series of competition experiments was performed between the catalysts, which allowed us to assess their relative rates of product formation.[10] By means of this assessment, we determined that *trans*-fluorinated pre-catalyst **9** is drastically (ca. 13 fold) more active than *cis*-fluorinated pre-catalyst **8**. Even more remarkable is the difference in reactivity between pre-catalyst **9** and achiral catalyst **12**. Pre-catalyst **9** is the most sterically encumbered scaffold that we have examined to date, yet it is still more reactive than achiral pre-catalyst **12**, which lacks a bulky directing group (Scheme 3).



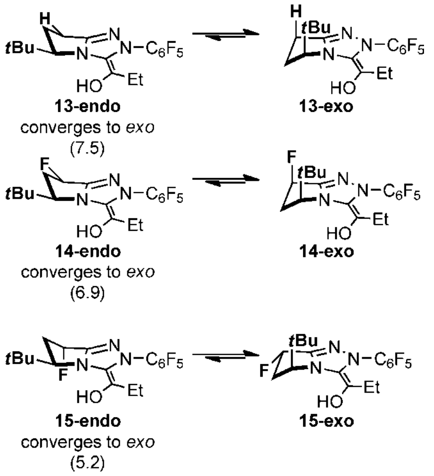
Scheme 3. Influence of catalyst structure on relative rate. See Supporting Information for details. BF_4^- counterions omitted for clarity.

In our initial report on the asymmetric intermolecular Stetter reaction using fluorinated triazolium salt pre-catalyst **5**, we proposed that backbone fluorination of the triazolium salt results in a conformational change owing to the gauche effect.[4c] Our recent DFT study has provided evidence that an attractive electrostatic interaction between the C–F dipole in the catalyst and the developing nitronate in the transition state is the source of increased selectivity.[11] Because of the divergence in both the stereochemical outcome of this reaction as well as the relative stereochemistry of the fluorinated catalyst architecture required for good selectivity, a different effect may be operative in this case.

To further understand the effect of fluorination of the catalyst architecture in this system we undertook a DFT study. Reactions with catalysts **7**–**9** were quantum-mechanically investigated to resolve the origin of selectivity. The focus of our investigation is to determine why the *R* enantiomer of the product is favored, and why *trans*-fluorinated catalyst **9** is more selective than both *cis*-fluorinated catalyst **8** and *des*-fluoro catalyst **7**.

Calculations were performed with Gaussian09.[12] All geometries were optimized using B3LYP/6-31G(d) with the CPCM solvation model[13] for methanol (UAKS radii, methanol, $\varepsilon = 32.6$). Single-point calculations were performed on the B3LYP geometries with M06-2X/6-31+G(d,p), again using the CPCM model for methanol. Aldehyde **1a** was modeled with propionaldehyde. DFT calculations predict good transition state geometries[14] and have been used to study the Stetter and related reactions.[11,15] M06-2X provides more accurate selectivities and thermodynamic values and incorporates dispersion effects.[16] Including the implicit solvation model was important for predicting accurate selectivities.

Catalysts **7**–**9** react with propionaldehyde to form acyl anion equivalents **13**–**15**, respectively (Scheme 4). The



Scheme 4. Relative free energies (M06-2X/6-31 + G(d,p),CPCM-(MeOH)//B3LYP/6-31G(d),CPCM(MeOH) of acyl anion equivalents **13–15**. *Endo* conformations were located by freezing the triazolium ring.

favored conformations of intermediates **13–15** are important for determining the stereocenter that is formed in the product. No minima for the *endo* conformers could be located, as all optimizations beginning from *endo* conformations converge to the *exo* conformations. Optimizations with the triazolium ring frozen in the *endo* conformation predict that these conformations are disfavored by 5.2–7.5 kcal mol^{-1} and are therefore too high in energy to be involved in the reaction. As shown in our previous computational study,[11] the A^{1,3}-like strain involving the alkyl substituent (here *t*Bu) is extremely large in the *endo* conformers of the enol intermediates, and these conformers are not involved in subsequent reactions steps.

Acyl anion equivalents **13–15 exo** attack either the *Si* or *Re* face of the nitrostyrene **2** leading to transition structures **TS1**, **TS3**, **TS5** or **TS2**, **TS4**, **TS6**, respectively (Figure 1). This step determines the stereocenter formed, but is not the rate-determining step.[17] Conformations resulting from rotation about the forming carbon–carbon bond were considered. The optimized geometries for the most favorable transition structures are shown in Figure 1. Unlike previous studies on similar Stetter reactions,[11] **TS1–TS6** do not all follow Seebach's topological rule,[18] which describes a preference for a synclinal orientation of the double bonds of donors and acceptors in Michael-addition transition states.

In agreement with experiment, addition to the *Re* face of the nitrostyrene is favored (**TS2**, **TS4**, **TS6**) and catalyst **9** is computed to be the most selective. A gauche (−) orientation of the double bonds in the *Si* face attack (**TS1** and **TS3**) places the nitro group under the catalyst ring. This is electrostatically favorable for **TS1** and **TS3**. However, for **TS5**, the negative electrostatic interactions between the fluorine, which points down in catalyst **9**, and the nitro group disfavors this conformation. For **TS5** the gauche (+) conformation is favored because it is well solvated owing to its large dipole moment. The *anti* conformation for the *Re*-face attack is favored[19] because of the stabilizing interaction between the hydrogen of the hydroxy group and the carbon α to the nitro group,[20] favorable electrostatic interactions between the alkyl group of the aldehyde and the nitro group, and because it is well solvated. These combined effects are enough to favor the *Re*-face attack over the *Si*-face attack. Also, **TS6** is especially favorable because the negative π cloud of the phenyl ring is near the electropositive catalyst ring and the positive part of the phenyl ring is near the electronegative fluorine. Therefore, **TS6** has the lowest barrier, making catalyst **9** the most selective.

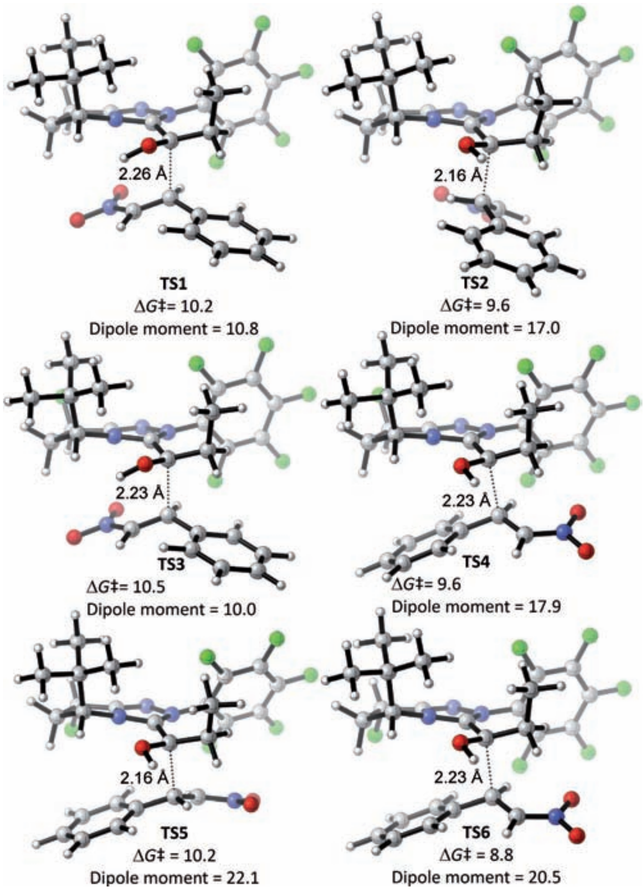


Figure 1. Transition structures **TS1**-**TS6** and energies (M06-2X/6-31 + G(d,p),CPCM(MeOH)//B3LYP/6-31G(d),CPCM(MeOH). The dipole moments are based on Mulliken charges and are given in Debye.

The calculated and experimental enantiomeric excesses are given in Table 2. The calculated values are determined by a Boltzmann distribution of all optimized transition structures.[21] These values correlate well with the experiment but are slightly underestimated.

Table 2: Calculated and experimental enantiomeric excesses.

Catalyst	Calculated[a] % *ee*	Experimental % *ee*
7	62	80
8	51	74
9	80	93

[a] Using M06-2X/6-31 + G(d,p), CPCM(MeOH)//B3LYP/6-31G(d), CPCM(MeOH).

In conclusion, we have identified a novel catalyst, one capable of inducing high levels of enantio-induction in the intermolecular Stetter reaction of aliphatic aldehydes and nitrostyrenes. *Trans* fluorination of the catalyst architecture promotes unparalleled reactivity and enantioselectivity in this transformation, as compared to previously known scaffolds. Computations show that catalyst **9** is the most stereoselective because the *Re*-face attack (**TS6**) is stabilized by favorable electrostatic interactions between the phenyl group and the fluorine on the catalyst backbone. Further computational studies on relative reaction rates and on the selectivities of triazolium catalysts **7**–**9** are underway.

Experimental Section

Triazolium salt **9** (22 mg, 0.05 mmol, 0.2 equiv), β-nitrostyrene (38 mg, 0.25 mmol, 1.0 equiv), sodium acetate (8 mg, 0.10 mmol, 0.4 equiv), and *tert*-amyl alcohol (2 mL, 0.125 M) were added to a dry 4 mL vial with a magnetic stir bar. The vial was cooled to 0 °C in a cooling bath with stirring and purged with argon. Butyraldehyde (34 μL, 0.375 mmol, 1.5 equiv) was added dropwise and the reaction was stirred at 0 °C until TLC indicated consumption of the nitrostyrene (24–48 h), at which point the reaction was concentrated in vacuo. The residue was purified by flash chromatography (20:1, hexanes/ether), which provided the desired β-nitro ketone as a colorless oil.

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[21] A table of all transition structure energies is given in the Supporting Information.