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Catalytic Asymmetric Intermolecular Stetter Reaction of Heterocyclic Aldehydes with Nitroalkenes: Backbone Fluorination Improves Selectivity

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The Stetter reaction utilizes the Umpolung[1] reactivity of aldehydes, the inversion of their normal mode of reactivity, to give rise to acyl-anion equivalents capable of participating in 1,4-conjugate additions with a variety of Michael-acceptors.[2] Following a seminal report by Enders[3] on the asymmetric version, our group has reported extensive investigation on the asymmetric intramolecular Stetter reaction.[4] Although the intramolecular version of this reaction has been rendered highly enantioselective, advances in the asymmetric intermolecular reaction have only recently been reported.[5] Enders and co-workers described an asymmetric intermolecular Stetter using aryl aldehydes with chalcones as Michael-acceptors.[6] Independently and concurrently, we reported the use of glyoxamides in conjuction with alkylidene malonates to afford Stetter products in high yields and high enantiomeric excess.[7]

As part of our efforts to improve this method, we envisioned that nitroalkenes may serve as viable Michael-acceptors in the Stetter reaction based on their high reactivity toward conjugate addition.[8,9] The corresponding β-nitro ketones derived from this transformation are also highly attractive intermediates, which can be derivatized into many synthetically useful compounds due to the versatility of the nitro group.[10]

We began our investigation by reacting the nucleophilic coupling partner picolinaldehyde **1a** with β-substituted nitroalkene **2a** in the presence of triazolium salt **4** and Hünig's base. A brief solvent screen revealed methanol to be optimal, providing the desired β-nitro ketone **3a** in a promising 82% yield and 74% ee (Chart 1).[11] Using a slight excess of nitroalkene at 0 °C provides better yields while ensuring the integrity of the newly formed stereocenter. Under these conditions, catalysts lacking the C_6F_5 *N*-aryl substituent prove inactive while morpholinyl-based catalyst **5** is less effective (Chart 1). These results prompted us to initiate a new exploration of catalyst design in hopes of increasing the enantioselectivity of this transformation.

Since bicyclic triazolium salt **4** gives good yield and enantioselectivity, we hypothesized that increasing the steric environment near the reactive center would improve enantioselectivity without a substantial loss in reactivity. Triazolium salt **6**, derived from L-valine, generates the desired product in 90% yield and 88% ee (Chart 1). Further modification of the steric environment to a larger *tert*-butyl substituent produces only trace amounts of products.

Given the plateauing effects of increasing steric bulk, we turned our attention to manipulating conformation by electronic tuning of the backbone. Inspired by conformational effects induced

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Supporting Information **Available:** Experimental procedures, characterization, $^{1}H/^{13}C$ NMR spectra; CIF files for **6, 8, 9, 10**, and **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

by fluorine substitution on pyrollidine ring-systems,[12] we sought to investigate the role that fluorine substitution would have on our bicyclic triazolium salts.[13]

The use of fluorinated triazolium salt **8** under these conditions shows increased reactivity and enantioselectivity as compared to the non-fluorinated analogue, producing the desired β-nitro ketone in 95% yield and 95% ee (Chart 1). Conversely, fluorinated triazolium salt **9** displays decreased reactivity with no apparent change in enantioselectivity compared to the non-fluorinated analogue **6**.

To better understand these differences, we analyzed the triazolium salts by X-ray crystallography. Triazolium salt **6** unambiguously displays a Cγ-endo ring pucker (Fig. 1), placing the isopropyl group in a lower energy pseudoequatorial position thereby minimizing 1,3-diaxial interactions. In contrast, X-ray analysis of *cis*-fluorinated triazolium salt **8** shows a Cγ-exo ring pucker that cannot be rationalized by steric arguments (Fig. 1). We suggest the switch in conformational preference is due to multiple stereoelectronic effects that overcome the inherent steric bias for the Cγ-endo conformation.[14]

Calculations by Raines *et al* suggest that the exo/endo conformations of 3-fluoroprolines can be stabilized by energies up to 2 kcal/mol due to a gauche effect.[15] The gauche effect arises from the preference of electron-withdrawing substituents to orient themselves gauche to one another. This orientation maximizes σ - σ* hyperconjugative interactions, leading to a lower energy conformer.[16] A Newman projection analysis of the C_3-C_4 bond of the triazolium salt shows clear orbital alignment of the $\sigma^*_{C\text{-}F}$ with an adjacent $\sigma_{C\text{-}H}$ bonding orbital (Fig. 1). Likewise, a stabilizing gauche conformation of the triazolium ring system with the C-F bond is also present in the favored Cγ-exo pucker (Fig. 1). A combination of these interactions is likely the reason for a complete switch in conformational preference.[17]

To gain further insight into this effect, the corresponding *trans*-fluorinated triazolium salt **9** was also analyzed. If the proposed stereoelectronic effects are dependent on the stereochemistry of the fluorine substituent, then the *trans*-fluorinated analogue should favor the Cγ-endo ring pucker, opposite its epimeric partner. Indeed, X-ray analysis confirms a preference for the Cγ-endo conformer, supporting our hypothesis (Fig. 2).

The scope of this transformation was examined using the fluorine-modified triazolium scaffold **8**, which shows remarkable reactivity and enantioselectivity toward a variety of heterocyclic aldehydes and alkyl-substituted nitroalkenes (Chart 2).[18] Five and six-membered heterocyclic aldehydes participate with good to excellent yield and ee. Secondary alkyl-substitution of the nitroalkene provides high yield and excellent ee while primary substitution results in somewhat reduced selectivities. In all cases, the fluorine-modified triazolium salt outperforms the non-fluorinated analogue in terms of enantioselectivity.

It should be noted that the difference in energy between diastereomeric transition states that corresponds to an increase from 86% ee to 96% ee amounts to 2.98 kJ/mol at 0 °C (Chart 2, **3d**), more than one third of the energy required to go from 0% ee to 95% ee (8.03 kJ/mol).[19] We propose the increase in enantioselectivity in our system is due to the conformational change in the bicyclic ring system, which we have fashioned through the use of stereoelectronic effects. This further orients the incoming nitroalkene electrophile to improve enantiofacial discrimination (Fig. 3).

If the above hypothesis is true, it stands to reason that fluorination alone is responsible for conformation in the five-membered ring and may result in a measurable bias in enantiofacial preference as the sole stereocontrol element. With this in mind, we synthesized pre-catalyst **10**. As the atomic radius of fluorine is 1.47 Å, only ~20% larger than hydrogen (1.20 Å), and less than ¾ of the size of a methyl group (2.00 Å), it has been used extensively as a hydrogen

surrogate.[20,21] Discounting the small steric influence of the fluorine atom, chirality should arise from the conformation dictated by stereoelectronic effects alone. Triazolium salt **10** provides moderate enantioselectivity (65% ee, 3.6 kJ/mol) of the desired product when used in the Stetter reaction, and further supports our hypothesis (Fig. 4). X-ray analysis of **10** confirms that the Cγ-exo ring pucker found in **8** is also present.

In conclusion, we have designed a new NHC catalyst that renders the desired intermolecular Stetter reaction of nitroalkenes and heteroarylaldehydes highly efficient and enantioselective through manipulation of stereoelectronic as well as steric effects. We believe the use of stereoelectronic effects, as demonstrated here, will become yet another powerful tool for the development of the next generation of catalysts for asymmetric synthesis. Investigations into the role that the aldehyde-heteroatom plays in reactivity and enantioselectivity are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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been demonstrated to provide improved selectivities in transannular aldols. Chandler CL, List B. J. Am. Chem. Soc 2008;130:6737–6739.6739 [PubMed: 18454521] (c) It has recently been argued that a fluorine substituent improves iminium ion geometry in asymmetric epoxidation of unsaturated aldehydes. Sparr C, Schweizer WB, Senn HM, Gilmour R. Angew. Chem. Int. Ed 2009;48:3065–3068.3068

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18. Benzaldehyde fails to participate under these conditions. The reasons for this are the subject of investigation in our laboratory. 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.
19. Numerical comparison of ee values is problematic. Comparison of er values can be equally problematic. For example, **3d** is formed in 98:2 er with **8** and 93:7 er with **6**, an apparent difference of 5 er points. However, a more instructive comparison here would be 13:1 vs. 49:1 for **3d**.
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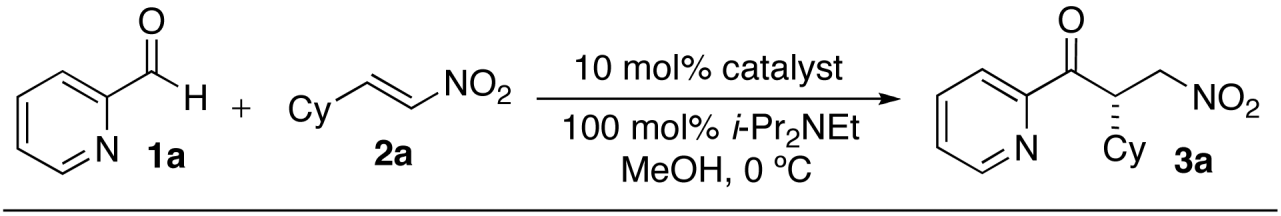

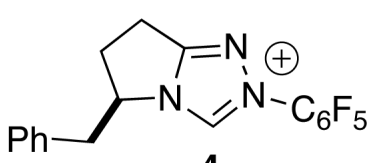
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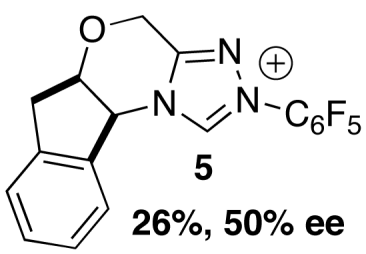
82%, 74% ee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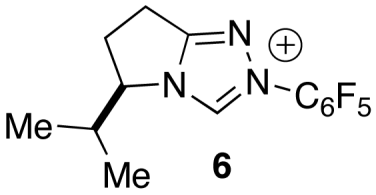
26%, 50% ee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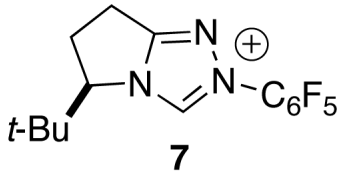
90%, 88% ee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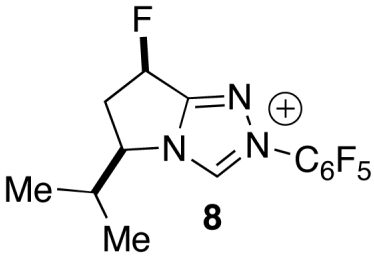
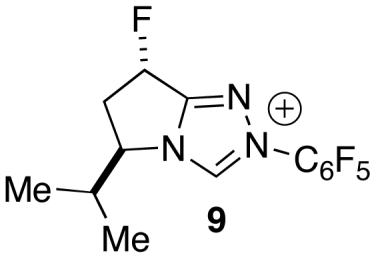
trace, ee nd


8

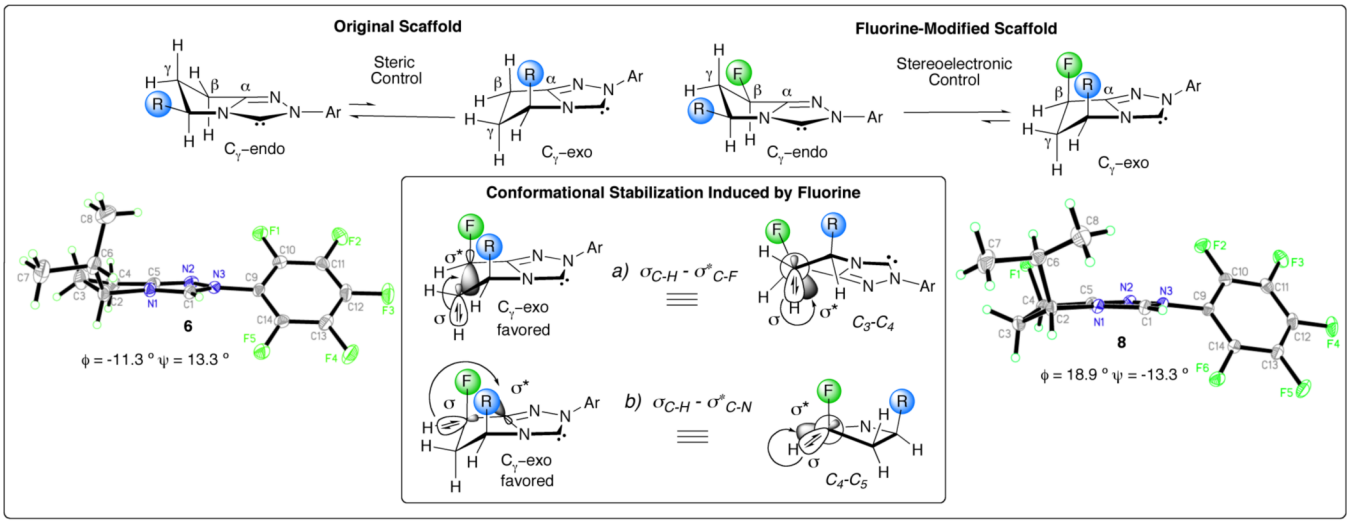
95%, 95% ee


9

22%, 88% ee

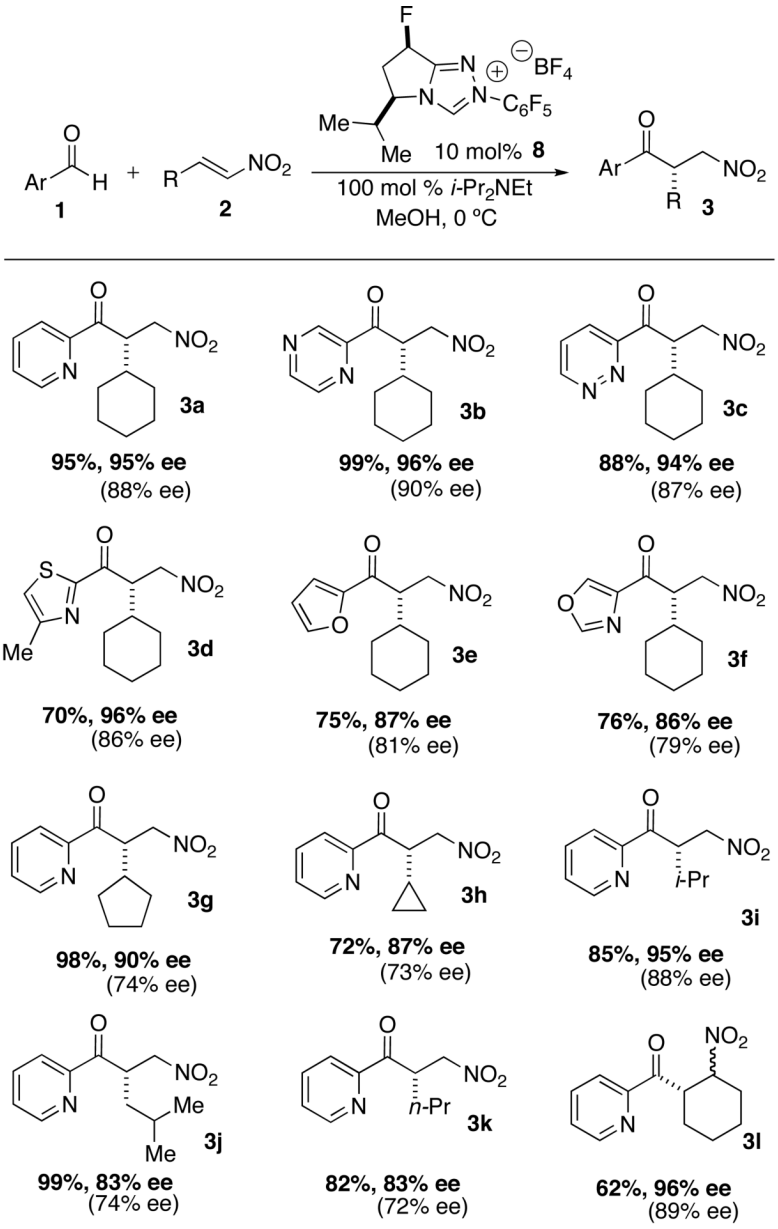
[a] Reactions conducted with 1 equiv of **1a** and 1.5 equiv of **2a** at 0 °C. [b] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. BF_4 counterions omitted for clarity.

Chart 1.
Catalyst Screen [a,b]



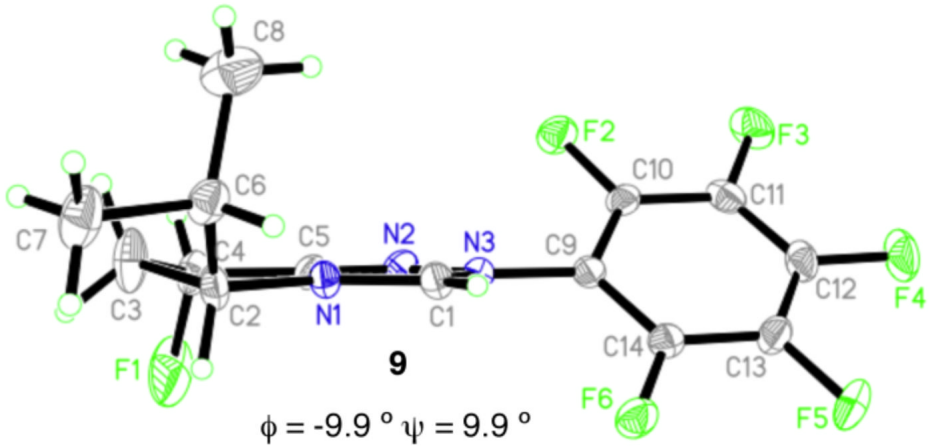
[a] Conformations determined by X-ray analysis; BF_4 counterion omitted for clarity. ϕ and ψ = torsion angles (ϕ = C_5-N_1-C_2-C_3 ψ = N_1-C_5-C_4-C_3)

Figure 1.
Conformational analysis of fluorine-modified and non-modified triazolium salts [a].



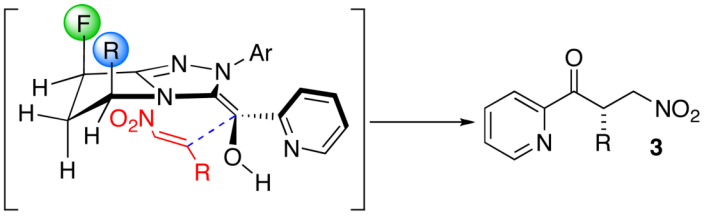
[a] Numbers in parentheses are ee's obtained using pre-catalyst **6**. [b] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

Chart 2.
Reaction Scope [a,b]



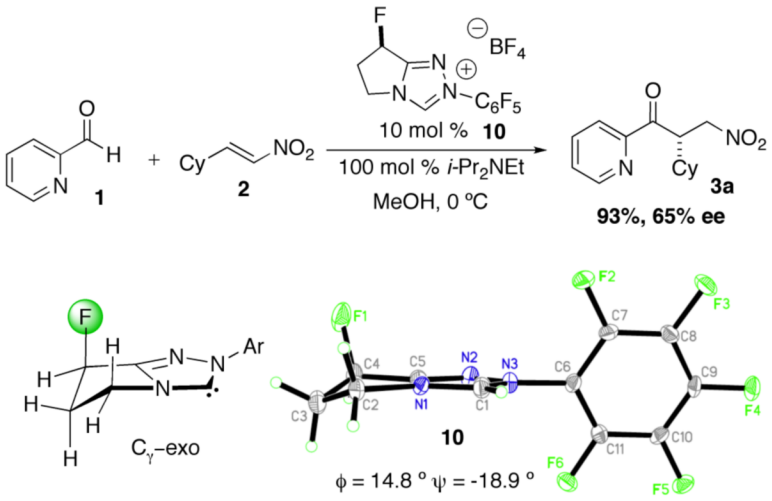
[a] Conformations determined by X-ray analysis; BF_4 counterion omitted for clarity. ϕ and ψ = torsion angles (ϕ = C_5-N_1-C_2-C_3 ψ = N_1-C_5-C_4-C_3)

Figure 2.
X-ray analysis of **9**. [a.]



[a] Absolute stereochemistry determined by X-ray analysis. See supporting information.

Figure 3.
Proposed transition state model [a].



[a] Conformations determined by X-ray analysis; BF_4 counterion omitted for clarity. ϕ and ψ = torsion angles (ϕ = C_5-N_1-C_2-C_3 ψ = N_1-C_5-C_4-C_3)

Figure 4.
Examination of fluorinated triazolium salt **10** [a]