Tunable Divergent Reactivity of Aziridinium Ylides in the Synthesis of Complex Piperidines and Azetidines

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ABSTRACT

Nitrogenated heterocycles comprise the cores of a number of synthetically useful compounds, including pharmaceuticals, bioactive natural products, agrochemicals and other drug-like molecules. The widespread interest in methods to increase the fraction of sp^3 carbon atoms (Fsp^3) of drug-like scaffolds in a stereocontrolled manner, while enabling explorations of novel amine chemical space, inspired our efforts to harness the divergent reactivity of aziridinium ylides for the rapid preparation of new azetidine and piperidine scaffolds. A sequential nitrene-carbene transfer of simple allenes can furnish divergent product outcomes depending on the nature of the carbene precursor or the catalyst identity. Computational studies were employed to shed insight into the major factors that influence the tunable reactivity of the aziridinium ylide intermediates formed in this chemistry.

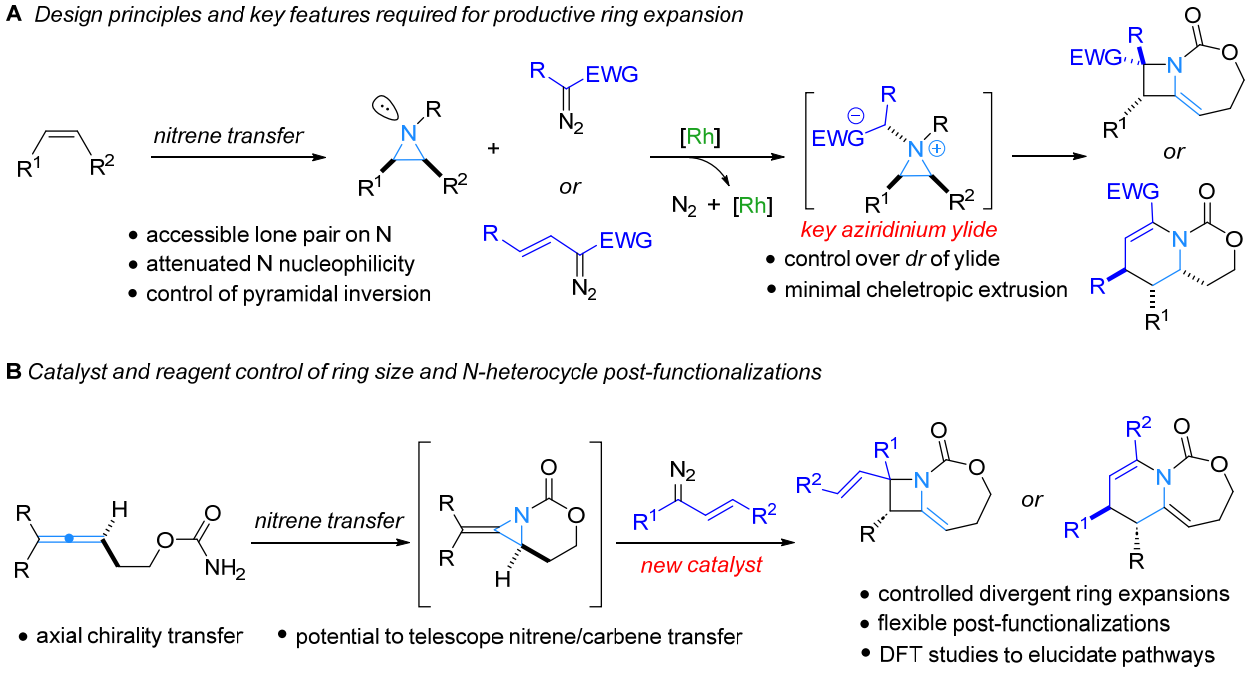
INTRODUCTION

Nitrogenated heterocycles are important motifs that occur in many FDA-approved drugs and they also serve as key building blocks for the construction of natural products, agrochemicals and other bioactive molecules.[1–4] In the pharmaceutical sector alone, over 84% of approved and structurally unique drugs contain at least one nitrogen atom, with 59% of these displaying at least one nitrogen heterocycle.[1] Among this latter group of compounds, piperidines appear in ~55% of all FDA-approved drugs, making versatile and stereocontrolled methods for their synthesis attractive. Their four-membered azetidine counterparts have also shown promise in medicinal chemistry, but strategies for their preparation have been significantly underexplored compared to 5- and 6-membered *N*-heterocycles.[5,6] Given the overall importance of *N*-heterocycles in bioactive molecules, modular methods to rapidly generate diverse libraries of these compounds with high diastereo- and enantiopurity from readily available precursors are highly sought.[1,7–12]

Onium ylides are reactive intermediates that contain a negatively charged carbon atom located adjacent to a positively charged heteroatom.[13] Aziridinium ylides comprise a subset of onium ylides which, in contrast to well-studied ammonium ylides, have been underexplored in terms of their utility for the synthesis of complex heterocycles.[14] The reasons for this lack of utility range from unwanted cheletropic extrusion of the ylide nitrogen to regenerate the original alkene,[15,16] decomposition pathways[17] or the existence of aziridine invertomers that complicate reaction outcomes.[18] However, we were able to successfully achieve ring expansion of simple aziridines[19–30,31–33] to complex *N*-heterocycles via aziridinium ylide intermediates using four key design features: 1) steric accessibility of the nitrogen lone pair, 2) the presence of an ~sp^3 nitrogen that does not bind irreversibly to the catalyst, 3) the ability to form only one ylide stereoisomer, and 4) restricted pyramidal inversion by employing a bicyclic aziridine.[34] Application of these design

principles to carbamate-derived bicyclic aziridines furnished substituted methyleneazetidines and dehydropiperidines (Scheme 1A) through the intermediacy of aziridinium ylides.[35–37]

Despite previous efforts, we have not been able to predictably divert an aziridinium ylide intermediate along multiple pathways to furnish different *N*-heterocycles from the same precursor.[38] The ability to predictably tune the reaction outcome, while concomitantly installing multiple functional handles in the products for further diversification, would comprise a valuable tool to rapidly access new chemical space with potentially valuable bioactivity. In this work, we highlight how reagent or catalyst control of the addition of methyleneaziridines to transition metal-supported vinyl-containing carbenes can be used to control product outcome. Experimental, mechanistic and computational studies are presented to rationalize our findings and inform future reaction and catalyst design.

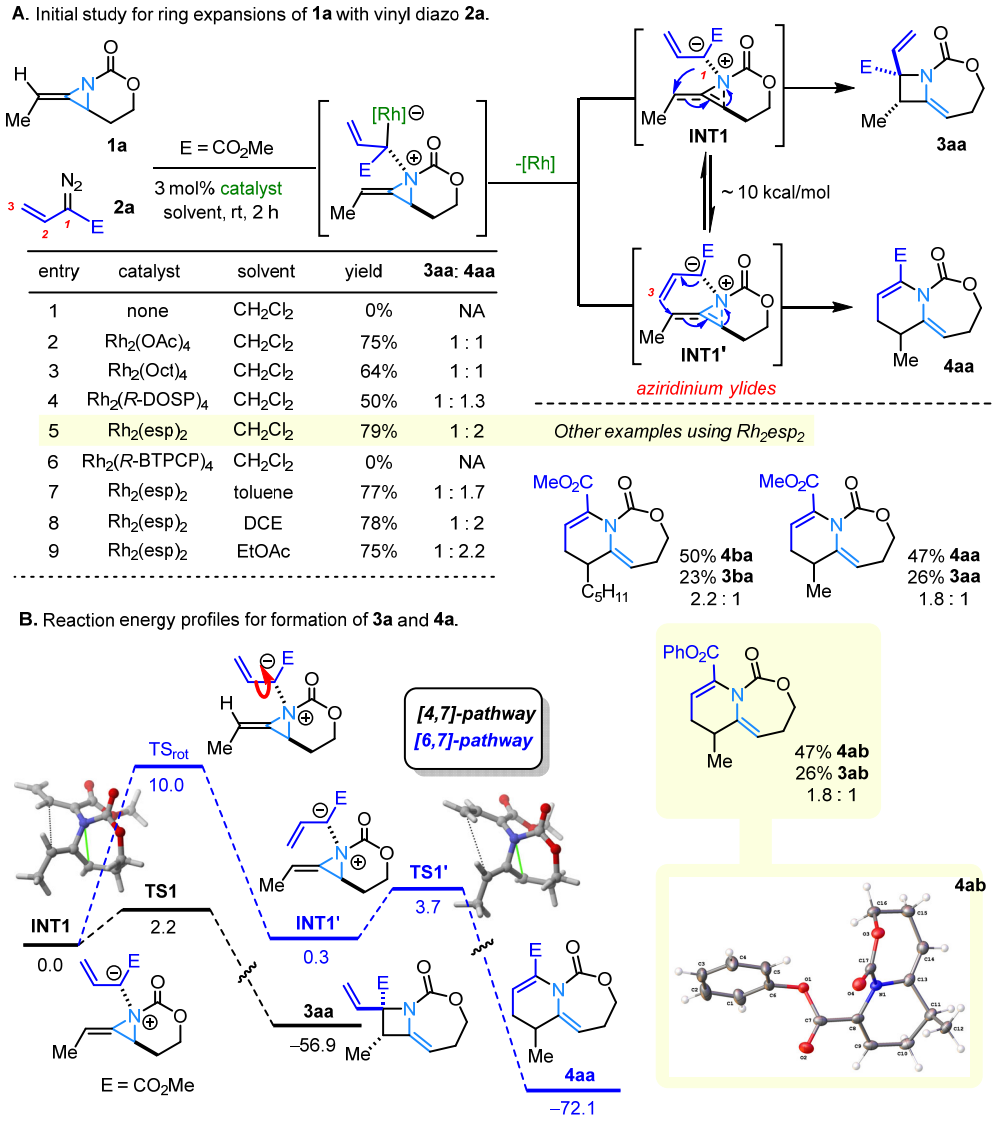


Scheme 1. **A**. Design principles for productive ring expansion of aziridinium ylides. **B**. This work to achieve tunable control over the ring size through both reagent- and catalyst-control.

Results and discussion

Initial explorations of divergent N-heterocycle formation. Studies were initiated by selecting the donor-acceptor vinyl diazoester **2a** to determine if Rh-catalyzed addition of methyleneaziridine[39] **1a** to **2a** would lead to: 1) ring expansion *via* opening of the aziridinium ylide by C1 of **INT1** to form the azetidine **3a** or 2) opening at C3 of **INT1'** to furnish the dehydropiperidine **4a** (Scheme 2A). Somewhat to our surprise, **3a** and **4a** were formed in 1:1 ratio and 75% NMR yield using $Rh_2(OAc)_4$ as the catalyst (Scheme 2A, entry 2). Increasing the size of the bridging carboxylates on the dinuclear Rh complex (entries 3-5) improved the selectivity for **4a** over **3a** to 2:1 using $Rh_2(esp)_2$. However, the increased steric bulk in the Davies catalyst (entry 6, Rh_2(*R*-BTPCP)$_4$, Rh_2-tetrakis[(*R*)-1-(4-bromophenyl)-2,2-diphenylcyclopropane carboxylate) gave no products at rt; heating the reaction gave only dimerization of **2a**. A brief solvent screen for carbene transfer catalyzed by $Rh_2(esp)_2$ was carried out (entries 7-9), with CH_2Cl_2, toluene, 1,2-dichloroethane (DCE) and ethyl acetate are proving to be viable solvents. However, there was no significant change in the ratio of **4a:3a**, suggesting that solvent polarity does not play a key role. Increasing the size of the Me group on **1a** to a C_5H_{11} group (**1b**) in reaction with **2a** also gave ~1:2 mixtures of **3ba** and **4ba**. Increasing the bulk on the ester group of **2a** to a benzoate in **2b** provided the same selectivity for the dehydropiperidine **4ab** over azetidine **3ab** 1.8:1, indicating sterics on the ester do not influence the reaction outcome. A solid-state X-ray crystal structure of **4ab** was obtained to verify its structure, as NMR spectroscopy can often be misleading in terms of assigning product identities.[40]

To better understand the details of this transformation and explore how we might control the selectivity of the ring expansion, Density Functional Theory (DFT) calculations were performed



entry	catalyst	solvent	yield	3aa: 4aa
1	none	CH_2Cl_2	0%	NA
2	$Rh_2(OAc)_4$	CH_2Cl_2	75%	1 : 1
3	$Rh_2(Oct)_4$	CH_2Cl_2	64%	1 : 1
4	Rh_2(*R*-DOSP)$_4$	CH_2Cl_2	50%	1 : 1.3
5	$Rh_2(esp)_2$	CH_2Cl_2	79%	1 : 2
6	Rh_2(*R*-BTPCP)$_4$	CH_2Cl_2	0%	NA
7	$Rh_2(esp)_2$	toluene	77%	1 : 1.7
8	$Rh_2(esp)_2$	DCE	78%	1 : 2
9	$Rh_2(esp)_2$	EtOAc	75%	1 : 2.2

The first letter in the product label refers to aziridine **1***x*, while the second letter refers to the diazoester precursor **2***x*.
The reaction energy profile was computed using $Rh_2(OAc)_4$ as the catalyst.

Scheme 2. **A**. Ring expansion of **1** with **2a** and selected other examples. Standard conditions use slow addition of **2a** (3.5 equiv) over 2 h to 3 mol% Rh_2L_n and **1a** (1 equiv) at rt. ^{1}H NMR yields with a 1,3,5-$(MeO)_3C_6H_3$ internal standard are combined yields of **3aa** and **4aa**. **B**. Computed reaction energy profiles for the formation of **3aa** and **4aa.** Relative free energies (ΔG_{298}, at 298 K) are given in kcal/mol. All data have been computed at the SMD(CH_2Cl_2)B3LYP-D3/def2-SVP level of theory.

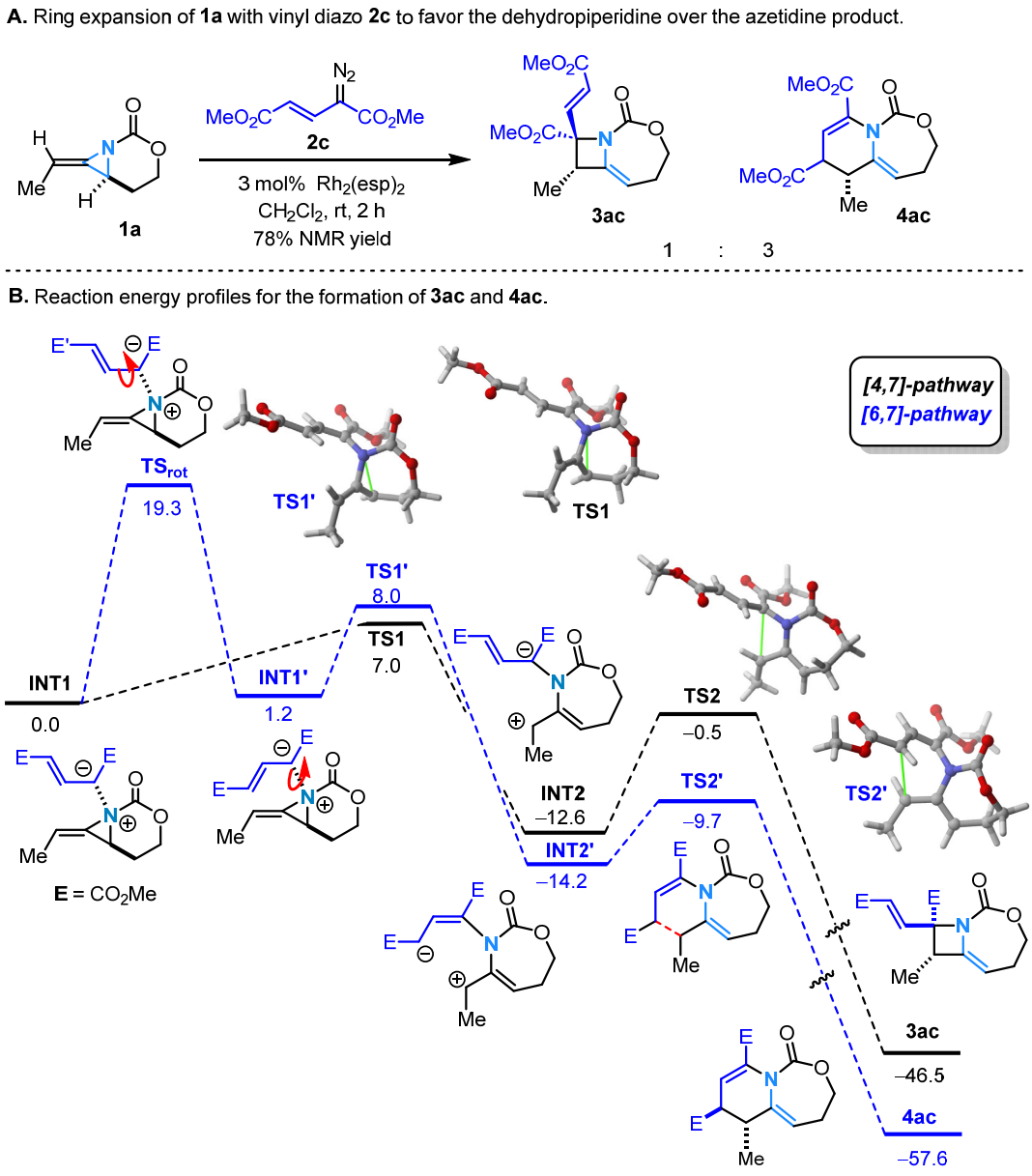
at the dispersion-corrected SMD(CH_2Cl_2)-B3LYP-D3/def2-SVP level (see the Supporting Information for further details). Scheme 2B shows the computed reaction profiles leading to the formation of **3aa** or **4aa** from the corresponding free aziridinium ylides **INT1/INT1'**, which

according to our previous calculations on related systems,[36-38] derives from the nucleophilic addition of the aziridine **1a** to the corresponding Rh_2-carbenoid intermediate. Our results indicate that the barriers associated with the aziridine ring-opening and concomitant four/six-membered ring formation (via **TS1/TS1'**) are rather low (< 5 kcal/mol), with the barrier leading to **3aa** slightly favored ($\Delta\Delta G^{\neq}$ = 1.5 kcal/mol). Despite this, the formation of **4aa** is strongly thermodynamically favored; when coupled with the negligible energy difference between the key ylide intermediates **INT1** and **INT1'** ($\Delta\Delta G$ = 0.3 kcal/mol) and a room-temperature feasible rotational barrier between them ($\Delta\Delta G^{\neq}$ = 10 kcal/mol), results in an equal possibility of formation of both bicyclic products. For these reasons, it is not surprising that no clear selectivity (from 1:1 to 1:2) was observed experimentally.

Approaches to control product outcomes. The brief catalyst screening and computational study in Scheme 2 suggested a few potential approaches for tuning either the carbene precursor or catalyst to achieve better control over the divergent formation of azetidines vs. dehydropiperidines. If **INT1** is the initially formed species, then raising the barrier to rotation between **INT1** and **INT1'** should favor formation of the azetidine. While computations in Scheme 2B did not address the role of catalyst in determining the reaction outcome, $Rh_2(esp)_2$ did increase preference for formation of the dehydropiperidine **4aa**. Other catalysts were briefly explored, including diverse Au, Cu and Fe-based complexes; however, these catalysts required heating to form the metal-supported carbene and led only to the decomposition of **2a**.

We hypothesized that selectivity towards dehydropiperidine formation might be improved by introducing electron-withdrawing groups (e.g. $-CO_2Me$) at the β-carbon of the diazoester precursor (e.g. C3 in **2a**). This should lead to greater delocalization of the negative charge of the ylide on the β carbon, which could increase the preference for formation of the six-membered ring. To test this

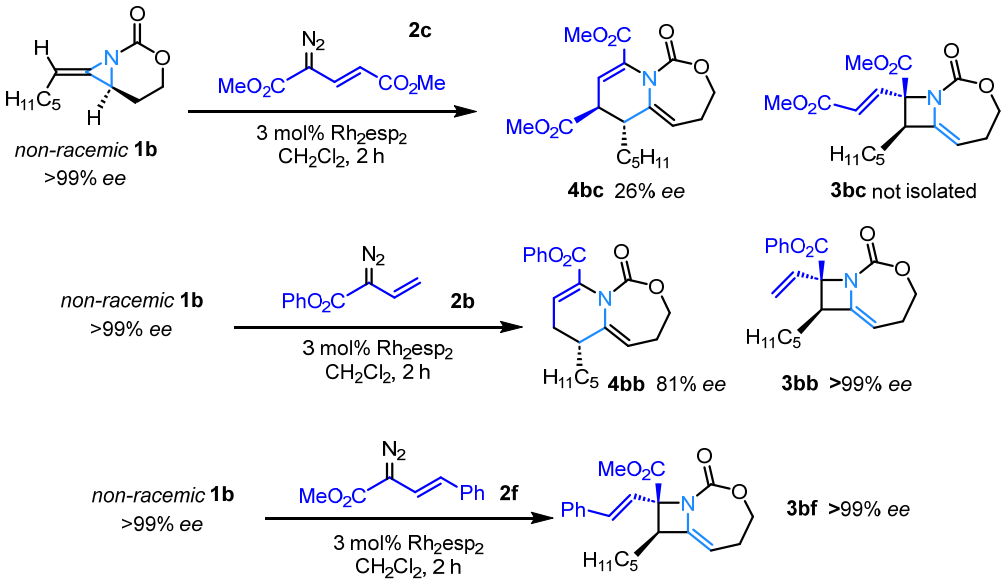
hypothesis, the carbene precursor was altered from **2a** (Scheme 1) to the CO_2Me-containing vinyl diazoester **2c** (Scheme 3A). Indeed, an increase in the **4ac:3ac** selectivity to 3:1 was observed in a 78% NMR yield.



Scheme 3. **A.** Ring expansion of **1a** with **2c**. **B**. Computed reaction energy profiles for the formation of **3ac** and **4ac**. Relative free energies (ΔG_{298}, at 298 K) are given in kcal/mol. All data have been computed at the SMD(CH_2Cl_2)B3LYP-D3/def2-SVP level of theory.

Our DFT calculations from the corresponding ylide **INT1** derived from **2c** (Scheme 3B) revealed the potential for a change in the mechanism as compared to that involving **2a**. First, the rotational barrier between the two key conformers **INT1** and **INT1'** increased to 19.3 kcal/mol, compared to the 10.0 kcal/mol barrier for the unsubstituted diazoester **2a**, but was still low enough for rapid interconversion between **INT1** and **INT'**. However, in marked contrast to the use of carbene precursor **2a**, the presence of the electron-withdrawing group CO_2Me, which is able to greatly stabilize the negative charge of the ylide, renders the process stepwise through the intermediacy of zwitterionic species **INT2/INT2'**. Interestingly, the formation of **INT2'** is thermodynamically favored over **INT2** ($\Delta\Delta G$ = 1.6 kcal/mol) and the subsequent ring-closure leading to **4ac** is both kinetically ($\Delta\Delta G^{\neq}$ = 9.2 kcal/mol) and thermodynamically favored over the formation of **3ac**. Therefore, our calculations indicate a strong bias towards the formation of the dehydropiperidine over the alternative azetidine, which is consistent with the experimental results.

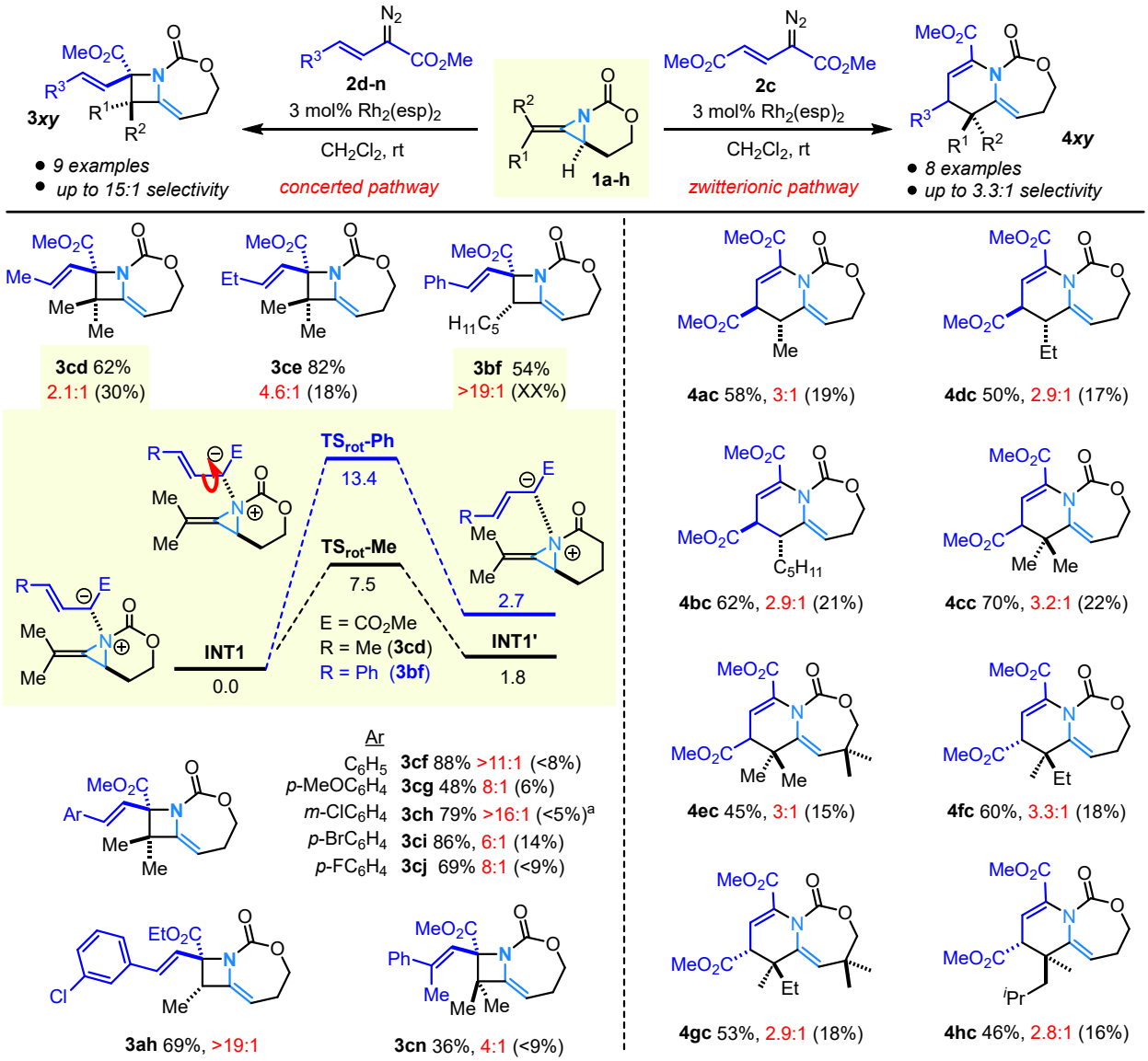
To provide experimental support for these divergent mechanisms dependent on the carbene precursor, a series of stereochemical probe experiments were carried out (Scheme 4).[31] Non-racemic **1b** was obtained in >99% *ee* from the corresponding enantioenriched propargyl alcohol.[35] Treatment of **1b** with **2c** showed that some of the stereochemical information is lost in the ring expansion to **4bc** (26% *ee*), suggesting that a competing stepwise pathway may be operating in the reaction. Unfortunately, **3bc** could not be isolated and the *ee* could not be determined. However, while treatment of non-racemic **1b** with **2b** also gave reduced *ee* in the dehydropiperidine product **4bb** (81% *ee*), interestingly, complete chirality transfer was noted in **3bb** (>99% *ee*). Finally, use of **2f** as the carbene precursor also resulted in complete transfer of chirality to the azetidine **3bf** (>99% *ee*); no formation of the dehydropiperidine was noted. These experiments support the likelihood that the mechanism of the ring expansion differs depending on the carbene precursor.



Scheme 4. Chirality transfer studies to interrogate the mechanism of both pathways.

These experiments also suggest that ring closure to the azetidine occurs faster than the formation of any zwitterionic or other achiral intermediates.

With an improved understanding of how the identity of the carbene precursor impacts the mechanism of the reaction to favor stereodivergent formation of either the azetidine or the dehydropiperidine product, the scope was explored (Scheme 5). First, a series of isomerically pure (*E* vs. *Z*) methyleneaziridines **1a-h** were reacted with diazoesters **2d-n**, where R^3 could be an alkyl, aryl or -CO_2Me group. Based on computations, the lack of the conjugated CO_2Me group directly attached to the C=C alkene of the carbenoid precursor kinetically favors the formation of the azetidine. Treatment of the *gem*-dimethylsubstited methyleneaziridine **1c** with carbene precursors **2d-f** showed that increasing the group on the β carbon from Me (**2d**) to Et (**2e**) to Ph (**2f**) increased the selectivity for formation of the azetidine from 2.1:1 to >15:1, which can be ascribed in part to an increased rotational barrier between the initial ylides and the increased energy difference between them. The inset in the left-hand column of Scheme 5 shows computations on the system



Standard conditions: slow addition of the vinyldiazo (3.5-10 equiv) over 2 h to a mixture of 3 mol% $Rh_2(esp)_2$ and aziridine (1.0 equiv) in CH_2Cl_2 at rt. The yield of the minor product is given in parenthesis after the product ratio. The first letter of the product refers to the aziridine **1** employed, while the second letter is the carbene precursor **2**. [a]The ethyl ester of the diazocarbene precursor was used.

Scheme 5. Aziridine and carbene precursor scope in Rh-catalyzed ring expansions to dehydropiperidines and azetidines. Inset: Computed **INT1/INT1'** interconversion processes for ylides derived from **1c** and **2c** (R^3 = Me) or **2f** (R^3 = Ph). Relative free energies (ΔG_{298}, at 298 K) are given in kcal/mol. All data have been computed at the SMD(CH_2Cl_2)B3LYP-D3/def2-SVP level of theory.

derived from **1c** and **2f** (R^3 = Ph). The computed rotational barrier is 13.4 kcal/mol (blue line) and the corresponding **INT1** is ca. 3 kcal/mol more stable than **INT1'**, whereas for the analogous

species involving **2d** (R^3 = Me), the barrier decreases to only 7.5 kcal/mol (black line) and the **INT1/INT1'** energy difference to 1.8 kcal/mol. These data suggest that the pathway leading to the dehydropiperidine is hampered by the increased bulkiness of the substituent R^3 attached to the terminal carbon of the carbenoid. NMR NOE studies were used to support the assignment of the relative stereochemistry for **3bf** (see Section IX in the Supporting Information for details).

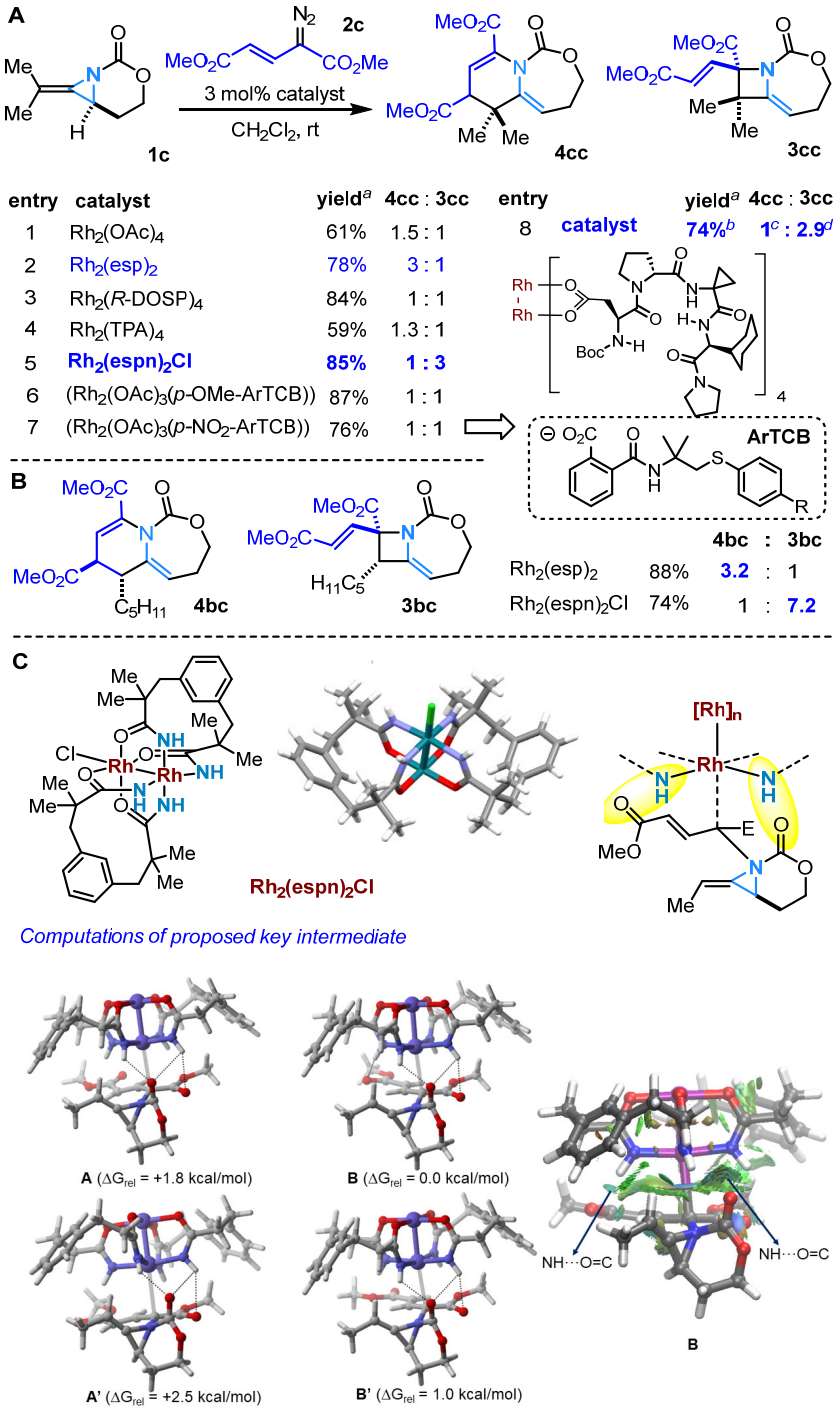
Substitution on the aryl ring was explored in reactions of **1c** with carbene precursors **2f-j**. Substitution on the aryl ring of the carbene precursor had a minimal impact on the ratio of the azetidine:dehydropiperidine, as highlighted in reactions to furnish **3cf-3cj**. Reaction of the monomethyl-substituted aziridine **1a** with **2h** gave azetidine **3ah** in 69% yield and a high selectivity of >19:1, indicating that sterics of the methyleneaziridine is not solely responsible for the preference for the 4-membered ring. We were also pleased to find that disubstitution could be tolerated at the β alkene carbon of the carbene precursor **2n** to give the fully substituted azetidine **3cn** with a 4:1 preference over formation of the dehydropiperidine.

Preferential formation of the dehydropiperidine products, potentially through zwitterionic intermediates, was investigated by reaction of the carbene precursor **2c** with various methyleneaziridines (Scheme 5, right-hand panel). Linear alkyl substituents on the methyleneaziridines **1a**, **1b** and **1d** were well-tolerated and furnished **4ac**, **4bc** and **4dc** in moderate yields and selectivity favoring the dehydropiperidine as the major isomer. Methyleneaziridine **1c** containing *gem*-dimethylsubstitution on the terminal carbon gave 70% yield of **4cc**, indicating that the chemistry can tolerate withstand steric pressure to favor the piperidine in a 3.2:1 ratio over the azetidine. A *gem*-dimethylsubstitution on both the terminal methyleneaziridine carbon and the tether in **1e** also favored **4ec**, albeit in a lower 60% overall yield. Finally, three tetrasubstitued methyleneaziridines **1f-1h** gave dehydropiperidines **4fc**, **4gc** and **4hc** in moderate yields and

selectivities. NMR NOE studies on **4hc** were inconclusive, as NOE correlations were observed between the methyl (1.09 ppm) and the methylene carbon of the isobutyl (1.50 ppm) groups on the dehydropiperidine ring and the adjacent proton (3.0 ppm, see the Supporting Information, Section IX for details).

A more intriguing question was whether we might be able to achieve catalyst control over the size of the ring formation, independent of the identity of the carbene precursor. Reaction of **1c** with **2c** (Scheme 6A) with a series of dinuclear Rh complexes supported by bridging carboxylate ligands and no axial ligand showed the best selectivity for **4cc** over **3cc** using $Rh_2(esp)_2$ at 3:1 (Fig 5A, entry 2), but the others all gave an ~ 1:1 mixture of products (entries 1, 3, 4). We were curious if more drastic changes to the ligand might furnish valuable insights to drive future reaction and catalyst design. We tried two dinuclear Rh catalysts developed by the Darko group, ($Rh_2(OAc)_3$(*p*-OMe-ArTCB) and $Rh_2(OAc)_3$(*p*-NO_2-ArTCB). These catalysts replace one of the -OAc ligands of $Rh_2(OAc)_4$ with a bridging N/S ligand, as shown in Scheme 6A; however, the presence of the N/S bridging ligand with sulfur position as an axial ligand gave no change in the product distribution (entries 6-7).[41]

We were pleased to find that a $Rh_2(espn)_2Cl$ complex (entry 5),[42] where the typical bridging carboxylate ligand has been replaced with a bridging amide ligand, reversed the product distribution in favor of the azetidine **3cc** over the dehydropiperidine **4cc** by a ratio of 3:1. This catalyst control was also observed using **1b** (Scheme 6B), where $Rh_2(esp)_2$ gave a 3.2:1 ratio of piperidine **4bc** over azetidine **3bc**; the selectivity was reversed using $Rh_2(espn)_2Cl$ to 7.2:1 in favor



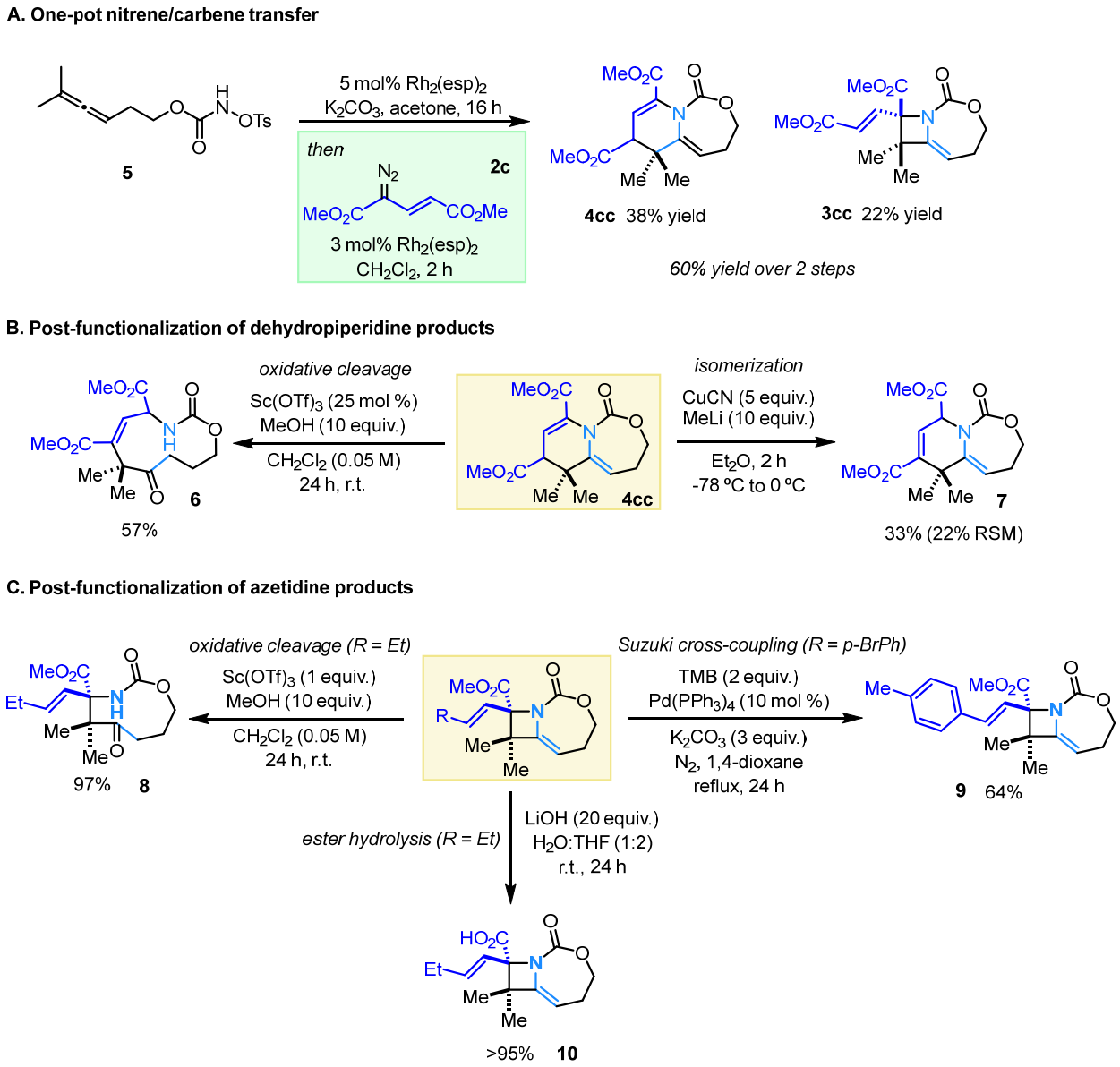
[a] NMR yields using mesityene as the internal standard. [b] Isolated yield. [c] 9% *ee*. [d] 8% *ee*.

Scheme 6. A. Effect of catalyst on ring size. **B**. Catalyst-controlled ring expansion. **C**. Computational support for hydrogen bonding with $Rh_2(espn)_2Cl$.

of **3bc**. We hypothesized that the amide groups of $Rh_2(espn)_2Cl$, which are bound to only one Rh atom of the dinuclear Rh complex (Scheme 6C), engage in hydrogen-bonding with the aziridine substrate. Specifically, we propose that the amides of the catalysts H-bond to both the carbonyl group of the carbamate and the carbonyl of ester from the carbene precursor. Attempts to methylate the amide nitrogen of $Rh_2(espn)_2Cl$ to determine if disrupting hydrogen-bonding changed the reaction outcome were unsuccessful. Thus, we turned to computations (Scheme 6C, bottom) for support. Among the possible metal bound ylides involving aziridine **1a**, the most stable species was computed to be **B**; this is the intermediate that ultimately leads to the experimentally observed formation of the four-member ring upon release of the transition metal fragment. Computations showed that this species is indeed stabilized by several NH···O=C hydrogen bonds. Note that the Rh···C distance is rather long (ca. 2.7 Å), which indicates that the Rh_2 fragment is only weakly bound to the ylide. We also observed catalyst control using a representative example of a dirhodium (II) metallopeptide class of catalysts developed by the Miller group (entry 8).[43] To our delight, we not only saw selectivity for **3cc**, but the first example of enantioselective induction into both **4cc** (9% *ee*) and **3cc** (8% *ee*). Ongoing studies in our group are focused on the elucidation of the details of the enantiodetermining transition state, as well as the development of improved enantioselective catalysts.

One-pot nitrene/carbene transfer and post-functionalization of N-heterocyclic scaffolds. Both the nitrene and carbene transfer steps can be telescoped into a single pot (Scheme 7A) using an *N*-tosyloxycarbamate **5** as the nitrene precursor. Treatment of **5** with $Rh_2(esp)_2$ and K_2CO_3 to achieve the aziridination was followed by treatment with **2c** to give a mixture of **4cc** and **3cc** in 60% yield over the two steps.

Another key design feature of our divergent ring expansion of aziridinium ylides is the ability to flexibly post-functionalize both the azetidine and dehydropiperidine scaffolds under mild conditions to ultimately generate DNA-encoded libraries. As shown in Scheme 7B, dehydropiperidine **4cc** could be oxidatively cleaved to the macrocycle **6** using catalytic $Sc(OTf)_3$



Scheme 7. A. One-pot nitrene/carbene transfer and derivatization of products. **B.** Post-functionalization reactions of dehydropiperidine products. **C.** Post-functionalization reactions of azetidine products.

in MeOH/CH_2Cl_2. The piperidine double bond could also be isomerized to furnish **7**.

In the case of post-functionalizations of the azetidine scaffold, oxidative cleavage of the internal alkene of **3ce** delivered the macrocycle **8** in essentially quantitative yield. Use of **3ci** bearing an aryl bromide successfully underwent Pd-catalyzed cross-coupling to furnish **9** in 64% yield. Finally, hydrolysis of **3ce** using LiOH resulted in **10** in 95% yield; the success of this post-functionalization provides a way forward to prepare large DNA-encoded libraries of compounds from these unusual *N*-heterocyclic scaffolds that may having novel bioactivities.

CONCLUSION

In this paper, we report our investigations employing either substrate or catalyst control to divert the fate of intermediate aziridinium ylides along differing mechanistic pathways to favor formation of highly substituted azetidines or dehydropiperidines. The identity of the carbene precursor can impact whether ring expansion occurs in a concerted fashion to effectively transfer stereochemical information from the substrate to the product, or whether the reaction occurs in a stepwise fashion via formation of zwitterioninc intermediates. Switching from a conventional $Rh_2(esp)_2$ to an amide-supported $Rh_2(espn)_2Cl$ catalyst for the key carbene transfer reverses the preference for a 4- vs. 6-membered *N*-heterocyclic product. Both the azetidines and piperidines are decorated with multiple functional handles to enable divergent elaborations of the products. A combination of computations and mechanistic studies provided support for our experimental observations.

ASSOCIATED CONTENT

Supporting Information. The supporting information contains NMR characterization data for all new compounds, reaction optimization conditions, unsuccessful substrates, computational details and relevant references.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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