Facile Synthesis of Z-Alkenes via Uphill Catalysis

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S *Supporting Information*

ABSTRACT: Catalytic access to thermodynamically less stable Z-alkenes has recently received considerable attention. These approaches have relied upon kinetic control of the reaction to arrive at the thermodynamically less stable geometrical isomer. Herein, we present an orthogonal approach which proceeds via photochemically catalyzed isomerization of the thermodynamic E-alkene to the less stable Z-isomer which occurs via a photochemical pumping mechanism. We consider two potential mechanisms. Importantly, the reaction conditions are mild, tolerant, and operationally simple and will be easily implemented.

Olefins are a fundamental building block for the synthetic community, and many possess biological activity. Not surprisingly, considerable effort has gone into developing methods that can lead to stereodefined alkenes. While methods to access thermodynamically more stable E-alkenes are abundant, corresponding methods to access the less stable Z-alkene are far less common. A number of conceptually diverse strategies have been employed to access Z-alkenes[1] (Figure 1)
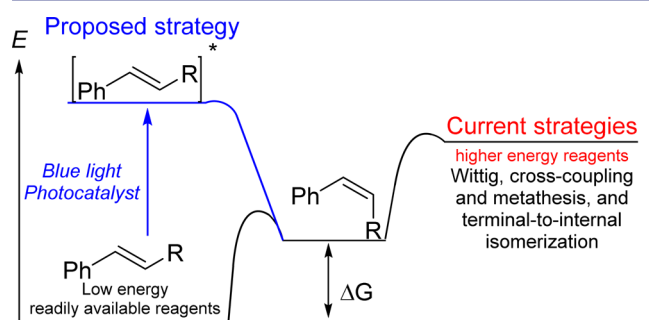
Figure 1. A comparison of the current strategies to access Z-alkenes to our proposed photochemically driven isomerization.

and include semihydrogenation of alkynes,[2] the Wittig reaction,[3] stereospecific cross-coupling reactions,[4] and more recently Z-selective cross-metathesis[5] and terminal-to-internal olefin isomerization.[6] Inherently, all of these strategies rely on kinetic control of the reaction and use higher energy reagents to access the Z-alkene.

A strategy missing from this collection of methods is the photocatalytic E-to-Z isomerization,[7] which does not rely on kinetic control of the reaction to deliver the desired product. Photocatalysis has the ability to "pump" or circumvent the normal thermodynamic constraints of a reaction. In other words, the more energetic product can actually be favored as a

result of the catalysis. From a synthetic perspective, such a process could take advantage of the many existing methods to synthesize the E-alkenes for the synthesis of Z-alkenes which could give it a distinct advantage when compared to other methods. However, challenges to this strategy do exist. For instance, the molecule must not decompose upon irradiation, the thermal back reaction should not take place, and finally a significant rate difference in the catalytic excitation of the E- and Z-isomers must exist. The first issue is mostly overcome by using a photocatalyst which absorbs in the visible region. Solutions for the other issues are less obvious, and herein we present one successful strategy.

Allylamines are an important class of biologically active molecules,[8] and in contrast to the E-isomer, accessing the Z-isomers is particularly challenging. Most commonly, partial hydrogenation, over a poisoned catalyst, of protected propargylamines is employed. This requires starting from the alkyne as well as a protection and deprotection step.[9] Thus, there is a real need for methods that can efficiently deliver Z-allylamines in fewer steps which utilize more accessible starting materials and consequently seemed like a good place to start our investigation.
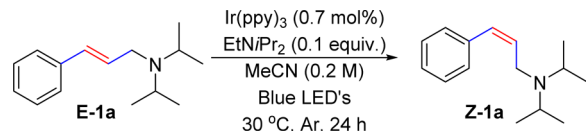
Our initial efforts focused on cinnamyl derived amines (Table 1). The reaction parameters were investigated utilizing **E-1a**. Fortuitously, our initial conditions gave, within the detection limits,[10] almost exclusively the Z-isomer (**Z-1a**). Controls showed that both the photocatalyst fac-tris[2-phenylpyridinato-C²,N] iridium(III), [Ir(ppy)₃], and light were essential (entry 2). Remarkably, the isomerization worked well in a number of solvents (entry 3) with the exception of nitromethane (entry 4) which may be due to efficient quenching of the excited photocatalyst by solvent.[11] Interestingly, the reaction works well over a range of concentrations (entries 5−8). The effect of the external base was probed both by removing it (entry 9) and by substituting it (entry 10−12). While the effect is subtle, EtNiPr₂ does seem to promote the reaction and is easily removed *in vacuo* after reaction completion. Other bases were less effective. The presence of air prevents the isomerization from occurring but does not cause degradation of the starting material (entry 13). Conveniently, the reaction did not display moisture sensitivity (entry 14) adding to the operational simplicity of the method.

Having established the reaction conditions, we next sought to evaluate the scope of the reaction (Table 2). The reaction works well for a number of other methylene carbinamines (**Z-2a, 3a, 4a**), as well as substrates with a methine carbinamine (**Z-5a, 6a, 7a**). Reactions with aryl bromides (**Z-8a, 9a, 10a**)

Table 1. Effects of Reaction Parameters
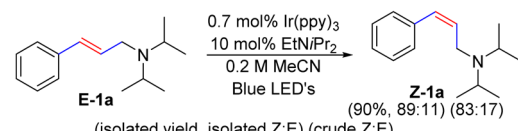
entry	deviation from standard conditions	GC-MS conversions
1	none	>95%
2	no Ir(ppy)₃ or in the dark	0%
3	DMA, THF, Tol, DCM, and DMF	>95%
4	nitromethane	0%
5	0.02 M in substrate	88%
6	0.1 M in substrate	93%
7	1.0 M in substrate	92%
8	2.0 M in substrate	90%
9	no EtNiPr₂, after 20 h	88%
10	0.1 equiv of EtNiPr₂, after 20 h	94%
11	0.1 equiv of DBU, K₂CO₃, Cs₂CO₃, after 20 h	90%
12	0.1 equiv of pyridine, imidazole, after 20 h	84%
13	without degassing	0%
14	with 1 drop of H₂O	>95%

Table 2. Scope of the Photochemical Isomerization

highlight the orthogonality of this chemistry to other late transition metal chemistry (i.e., Pd-catalyzed cross-couplings). Substitution is well tolerated at the 4-position (**Z-11a**, **13a**), 3-position (**Z-12a**), and the 2-position (**Z-14a**). Furthermore, the reaction tolerates secondary aliphatic amines (**Z-15a**, **16a**) and aromatic amines (**Z-17a**). The reaction tolerates amides (**Z-18a**) giving better than 99:1 Z/E after chromatography. Additionally, acid labile silyl ether (**Z-19a**), which would be difficult to maintain during a partial hydrogenation under acidic conditions, is a particularly good substrate. Finally, several common N-protecting groups were evaluated. Tosyl (**Z-20a**) protected, N-acyl (**Z-21a**), and even acid sensitive N-Boc protected amines (**Z-22a**) worked well. It is noteworthy that the reactions are remarkably clean with essentially no other chemistry occurring under these conditions and, in most cases, the lower isolated yields are simply the result of the partial resolution of the alkenes by chromatography.

Having explored the scope we next began to consider the mechanism. Given the uphill nature of the reaction in the ground state as well as the need for the photocatalyst and light, we believed it was unlikely that the reaction could be proceeding by a purely thermal process. Rather, the reaction must be driven by light. Given that substrates do not absorb light in the visible region as well as the need for the photocatalyst, a direct photochemical isomerization is unlikely. Instead, the selectivity of the reaction must result primarily from a difference in rates of the photoquenching event of the photocatalyst by the E- and Z-isomers.

With E- and Z-isomers in hand, we were able to investigate this question by performing photoquenching studies with both isomers. In this study, the Ir(ppy)₃ is excited by the absorption of photons at the appropriate wavelength (370 nm) to facilitate a metal ligand charge transfer-excited state which emits at 520 nm. Quenching of the excited photocatalyst can be observed by monitoring the disappearance of the emissive wavelength (520 nm). From the slope of the line generated by plotting of $I°/I$ (I = emission intensity) vs concentration of the quencher, we can glean information regarding the rate of the quenching event. The slope of the lines in this Stern−Volmer plot is proportional to the rate of the quenching event.[12] Indeed, we found that **E-**

19a (>99:1, E/Z) quenches the emission of the excited catalyst with a slope of 0.0915 while **Z-19a** (3:97, E/Z) quenches the excited state of the catalyst with a slope of 0.012. These results suggest that the E-isomer quenches the photoexcited state with a relative rate 8-fold greater than that of the Z-isomer,[13] confirming our suspicions and suggesting that the geometrical isomers quench the photocatalyst at significantly different rates (Figure 2).

Having established that the difference in the rate of quenching of the photoexcited catalyst by the two isomers is responsible for the buildup of the Z-isomer, we wanted to understand the nature of the quenching event. Two conceivable mechanisms that lead to photoquenching of the Ir(ppy)₃* catalyst are outlined below (Figure 3). In the first (eq 1), reductive quenching by electron transfer from the amine to the excited photocatalyst[14] gives radical cation **E-23a**. Upon amine oxidation, the αC−H becomes significantly more acidic[15] and could be reversibly deprotonated by an exogenous base to give allylic radical **E-23b**. Radical **E-23b** is expected to have a diminished barrier toward cis−trans isomerization[16] and would lead to **Z-23b**. **Z-23b** would undergo protonation and back
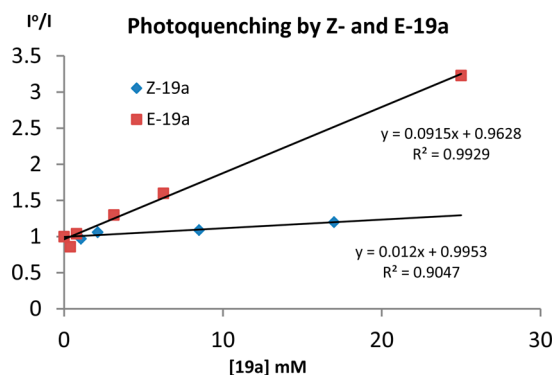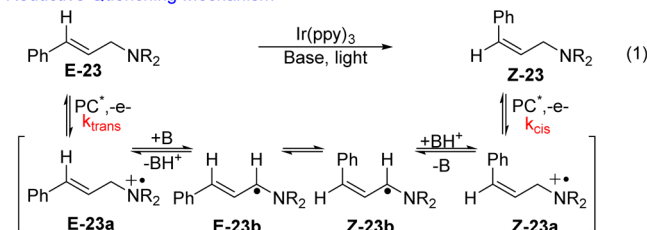
Figure 2. A Stern–Volmer photoquenching plot of *E*-19a and *Z*-19a.

Figure 3. Two possible mechanisms.

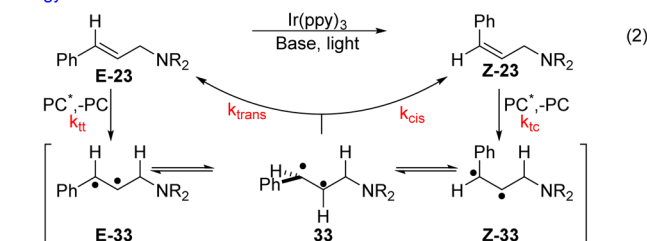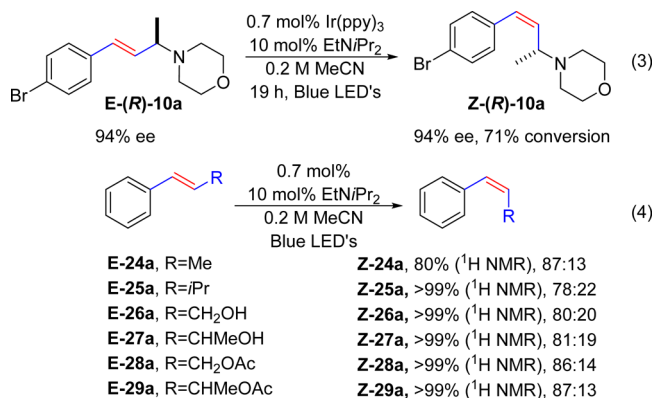Scheme 1. Mechanistically Insightful Reactions; Stereochemical Probe and Reaction of Simple Styrene Derivative

electron transfer to afford **Z-23**, which quenches the excited photocatalyst more slowly than **E-23**, resulting in buildup of **Z-23**.

We next considered an energy transfer (ET) mechanism in which enerergy transfer from the photoexcited catalyst leads to a biradical intermediate (**E-23**, eq 2), which is expected to rapidly lead to intermediate **33**[12] which has the critical geometry in which a 90° rotation about the C–C has occurred.[17] **33** can undergo intersystem crossing to give either **E-23** or **Z-23**. A buildup of **Z-23** would result from a greater k_{tt} value.[18] Interestingly, in contrast to what we observe, Yoon reported a related triplet sensitized [2 + 2] of cinnamyl ethers in which he observed rapid *E/Z* isomerization. One intriguing potential explanation is the difference in emissive energy of the different photocatalysts used.[19] Specifically, the catalyst used by Yoon has greater emissive energy (470 nm, 61 kcal/mol) than the Ir(ppy)$_3$ catalyst (520 nm in MeCN, 55 kcal/mol).

Given that radical inversion of sp^3 hybridized carbons is rapid (i.e., **E/Z-23b**, Figure 3),[20] we expected that if the reductive quenching mechanism were operative, any stereochemical information at a carbinamine stereocenter would be lost. Thus, we synthesized a chiral, nonracemic alkene **E-(R)-10a** (Scheme 1) and subjected it to the reaction conditions. Upon photocatalytic *E*, *Z*-isomerization, no racemization was detected, indicating that the reductive quenching mechanism is not likely operative and suggesting direct ET as the operative mechanism.

If the direct ET mechanism is operative, then it would be reasonable to assume that the amine may not be a necessary structural component. Thus, we subjected several nonamine containing styrenes, including hydrocarbons, alcohols, and acetates (**E-24a**−**29a**) to the reaction conditions. Indeed, all of the substrates undergo isomerization to give **Z-24a**−**29a** in *Z*/*E* ratios ranging from 87:13 to 78:22, further supporting the direct ET mechanism and suggesting a much broader scope for this reaction should be possible.

In conclusion, we have demonstrated a novel approach to access thermodynamically less stable alkenes directly from the more stable and easily synthesized *E*-alkenes in synthetically useful ratios and yields. Importantly, the starting alkenes are readily available and the photocatalyst is both highly efficient and commercially available. The reaction is remarkably clean and allows for the incorporation of a number of functional groups and maintains adjacent stereocenters in the substrates. Our preliminary mechanistic experiments indicate that the reaction proceeds by selective triplet sensitization of the *E*-alkene, suggesting that the reaction should be general to the styrenyl motif. This reaction serves as a rare example of uphill catalysis, which arguably is an underutilized strategy in the catalysis field, and provides useful insight into this underexploited strategy.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Complete experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(8) The fungicidal drugs Lamisil and Naftin are both allylamines.

(9) For access to Z-1,2-disubstituted allylamines a semi-hydrogenation approach is taken using propargylic N-phthalamides or ammonium salts using Lindlar's catalyst, which necessitates use of the alkyne and the added complications of using the phthalamide protecting group or running the reaction under acidic conditions; for an example, see: Tomassy, B.; Zwierzak, A. *Synth. Commun.* **1998**, *28*, 1201.

(10) No special measures were taken to increase the sensitivity of the GCMS towards our samples or to quantify these results but rather were used to illuminate the relevant trends.

(11) Currently, it is not clear why nitromethane prevents the isomerization, given that its redox potentials $\pm$ 2.4 V vs NHE suggest it is unlikely to oxidatively or reductively quench the photocatalyst. Furthermore, the lowest lying electronic transition is $\sim$3.4 eV which is significantly above the 2.5 eV energy of the excited photocatalyst. (a) Voorhies, J. D.; Schurdak, E. J. *Anal. Chem.* **1962**, *34*, 939. (b) Arenas, J. F.; Otero, J. C.; Peláez, D.; Soto, J. *J. Chem. Phys.* **2003**, *119*, 7814.

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(18) Technically, a buildup of **Z-23** should be expressed as **Z-23**/**E-23** = $(k_{tt}*k_{cis})/(k_{tc}*k_{trans})$. We have experimentally observed a 93:7 photostationary state. Our photoquenching studies indicated a 7.6-fold rate difference, which amounts to an 88:12 product ratio. This difference is relatively small but could be attributed to the less than geometrically pure nature of the alkene (97:3, Z/E) which would make the Z-alkene appear to quench with a greater rate due to the presence of the E-alkene. Alternatively, it could reflect the rates of ISC (k_{cis} and k_{trans}), but more likely the difference is a result of a combination of these two factors. For now we assume these relative rates to be near

unity and thus the overall equilibrium to be primarily a reflection of the rate of quenching. This is consistent with the findings of Hammond, which suggest that the rates of intersystem crossing (k_{trans} and k_{cis}) approach unity for the isomerization of 1,3-dienes and stillbenes by high energy sensitizers; see: Hammond, G. S.; Saltiel, J.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, V.; Dalton, C. *J. Am. Chem. Soc.* **1964**, *86*, 3197.

(19) One intriguing potential explanation for the difference in the observed reactivity of our system and that of Yoon's is the emissive energy of the different photocatalysts. The photocatalyst used by Yoon Ir(dF(CF$_3$)ppy)$_2$dtbbpy$^+$ has an emission wavelength (470 nm) (61 kcal/mol) while *fac*-Ir(ppy)$_3$ has a peak emission at 520 nm in MeCN (55 kcal/mol): Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329.

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