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$Sc(OTf)_3$-Catalyzed Transfer Diazenylation of 1,3-Dicarbonyls with Triazenes via N−N Bond Cleavage

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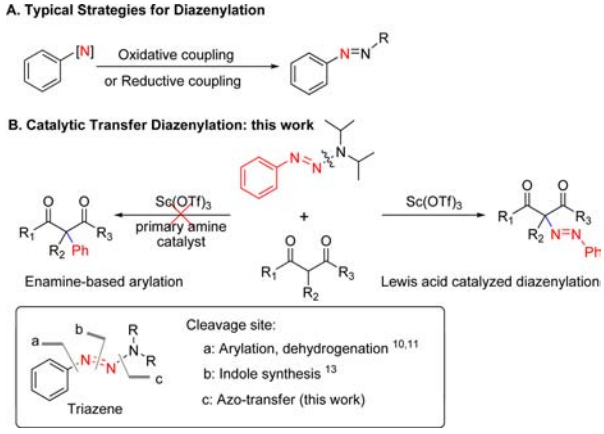
Supporting Information

ABSTRACT: A new and efficient method for diazenylation reactions was developed with a $Sc(OTf)_3$-catalyzed nitrogen−nitrogen bond cleavage process with triazenes. The transfer diazenylation reactions accommodate a diverse range of active methylene substrates including simple ketones to give aliphatic azo compounds that are of significant potential as azo prodrugs in high yields under mild conditions.

Azo derivatives are commonly utilized in both laboratories and industry as indicators, radical reaction initiators, azo ligands of metal complexes, dyes and pigments, therapeutic agents, modern material sciences, and food additives.[1,2] Reflecting on the development of azo syntheses, classic and general methods in the formation of nitrogen−nitrogen double bonds include electrophilic azo coupling reactions of diazonium salts, Mills coupling of anilines with aromatic nitroso and nitro compounds, and Wallach rearrangements of azoxy derivatives.[3] Recent advances in the synthesis of azo compounds mainly involve catalytic reductive aromatic nitro derivatives,[4] oxidation of anilines,[5] as well as dehydrogenation of arylhydrazines[6] (Scheme 1, A). Development of a chemoselective diazenylation strategy is still in high demand in order to address remaining issues such as excess use of explosive diazonium salts, harsh reaction conditions, and invariably accompanying oxidant or reductant waste. In this regard, the synthesis of aliphatic azo compounds is particularly challenging due to the lack of functional group tolerance of most of the available synthetic procedures as well as the inherent instability of the aliphatic azo moiety. Recently, aliphatic azo compounds with the general structures ArN=*N*-alkyl have been developed as prodrugs with promising antibiotic and anti-inflammatory activity,[7] addressing significant demands for economic and selective synthetic protocols. Herein, we present a conceptually distinctive azo-transfer reaction in which an aryl azo moiety can be directly transferred from aryl triazene and installed chemoselectively onto aliphatic carbons under rather mild conditions.

Scheme 1. Synthetic Strategies for Azo Derivatives



Aryl triazenes ($ArN{=}NNR_1R_2$), are a class of compounds with intriguing structural and chemical properties and a long history dating back to 1875.[8,9] Recent pursuit of chemoselective methodology has sparked new interest in the chemistry of aryltriazenes. Accordingly, aryltriazenes have been explored as precursors of phenylium cations or radicals in arylation and dehydrogenation reactions.[10,11] The triazene moiety can also be utilized as a directing group in C−H functionalization[12] as well as in oxidative indole synthesis[13] (Scheme 1, B). Though typically regarded as masked diazonium ions, aryl triazenes have seldom been employed in diazenylation reactions. In a single instance, intramolecular coupling of triazene with alkyne has been reported to give cinnolines under either thermal[14] or Pd-catalytic conditions.[15,16] Intermolecular azo-transfer with aryl triazenes has surprisingly not been reported so far.

Initially, we sought to develop an asymmetric α-arylation reaction using aryl triazenes as phenyl precursors under enamine catalysis; however, no α-arylation product was detected in our initial experiments with our previously developed chiral primary amines.[17] Instead, we found Lewis acid $Sc(OTf)_3$ can promote transfer diazenylation with aryl

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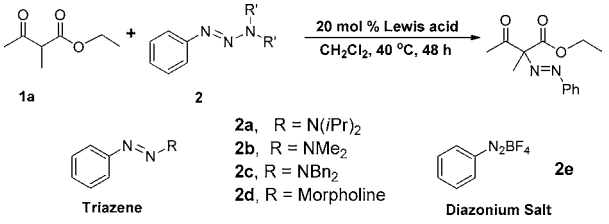
triazene via efficient N−N cleavage, which enables chemoselective aryl diazenylation of β-dicarbonyls beyond the reach otherwise[18] (Scheme 1, B), and this diazenylation reaction was hence further explored.

Our investigation began with the phenyl diazenylation of 2-methyl acetoacetate **1a**, and the representative results are summarized in Table 1. To our gratification, we found that

Table 1. Optimization for Phenyl Diazenylation Reaction of 2-Methyl Acetoacetate[a]



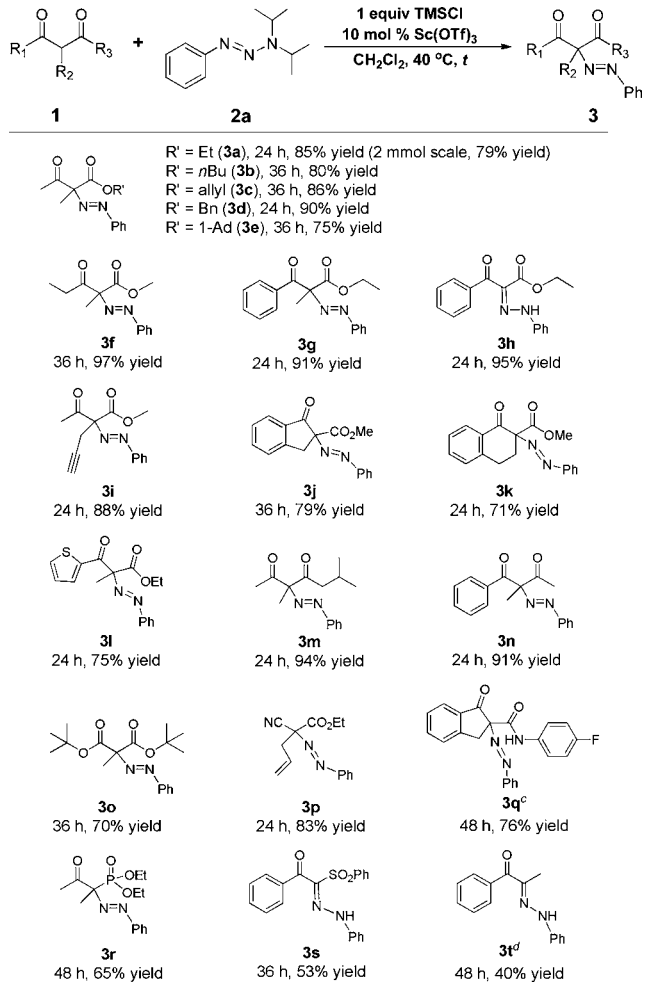
entry	Lewis acid	reagent	solvent	time (h)	yield[b] (%)
1	$Sc(OTf)_3$	**2a**	CH_2Cl_2	48	75
2	$Sc(OTf)_3$	**2b**	CH_2Cl_2	48	48
3	$Sc(OTf)_3$	**2c**	CH_2Cl_2	48	66
4	$Sc(OTf)_3$	**2d**	CH_2Cl_2	48	69
5	$Sc(OTf)_3$	**2e**	CH_2Cl_2	24	N.D.
6[c]	$Sc(OTf)_3$	**2a**	EtOH	48	trace
7[c]	$Sc(OTf)_3$	**2a**	DMSO	48	N.D.
8[c]	$Sc(OTf)_3$	**2a**	CH_3CN	48	39
9[d]	$Sc(OTf)_3$	**2a**	hexane	48	43
10	$Sc(OTf)_3$	**2a**	ether	48	69
11[e]	$BF_3{\cdot}Et_2O$ (2 equiv)	**2a**	CH_2Cl_2	3	31
12	$FeCl_3$	**2a**	CH_2Cl_2	48	46
13	$Bi(OTf)_3$	**2a**	CH_2Cl_2	48	32
14	$CuBr_2$	**2a**	CH_2Cl_2	48	N. D.
15	$Hf(OTf)_4$	**2a**	CH_2Cl_2	48	72
16	$Sc(OTf)_3$ (10 mol %)	**2a**	CH_2Cl_2	48	50
17[f]	$Sc(OTf)_3$ (10 mol %)	**2a**	CH_2Cl_2	24	54
18[g,h]	$Sc(OTf)_3$ (10 mol %)	**2a**	CH_2Cl_2	24	85
19[g,h]	none	**2a**	CH_2Cl_2	24	<10

[a]General conditions: **1a** (0.1 mmol), **2** (0.1 mmol), and Lewis acid (20 mol %) at 40 °C in the solvent (0.4 mL) under Ar. [b]Isolated yield. [c]80 °C. [d]60 °C. [e]At room temperature. [f]CH_3COCl (0.1 mmol) as the additive. [g]TMSCl (0.1 mmol) as the additive. [h]**1a** (0.12 mmol). N.D. = no product was observed by TLC.

Lewis acids were viable catalysts for the diazenylation reactions. Among various Lewis acids screened (Table 1, entries 1 and 11−15), $Sc(OTf)_3$ was eventually identified as an optimal Lewis acid for this reaction (Table 1, entry 1). The expected diazenylation adduct (**3a**) can be obtained in 75% yield. The nature of the terminal tertiary amine substituent of triazenes was then tested, with similar results for methyl, isopropyl, benzyl, and cyclic morpholine groups (Table 1, entries 2−4). Surprisingly, the use of the common diazonium salt **2e** led to no desired product (Table 1, entry 5), highlighting the chemoselective nature of aryl triazenes. Solvent effects have also been examined, and the reactions were found to work poorly in other solvents such as EtOH, DMSO, CH_3CN, hexane, and ether (Table 1, entries 6−10). The choice of acidic additives significantly influenced the yield (Table 1, entries 16−18), especially to those inert and bulky substrates, with TMSCl proving to be the optimal reaction additive, presumably due to the capture of the liberating diisopropylamine in the catalytic system (Table 1, entry 18, 85% yield over 24 h). It was noteworthy that, in the absence of $Sc(OTf)_3$, almost no diazenylation product **3a** was obtained (Table 1, entry 19). Therefore, it can be concluded that the optimized reaction should be performed under the catalysis of 10 mol % of $Sc(OTf)_3$ in the presence of 1.0 equiv of TMSCl in CH_2Cl_2.

The substrate scope with 1,3-dicarbonyls was next explored (Scheme 2). The diazenylation all occurred at the α-position as

Scheme 2. Scope of Intermolecular Diazenylation of Active Methylene Compounds and Triazophenyl Reagent[a,b]



[a]General conditions: **1** (0.12 mmol), **2** (0.1 mmol), TMSCl (0.1 mmol), and $Sc(OTf)_3$ (10 mol %) at 40 °C in the CH_2Cl_2 (0.4 mL) under Ar. [b]Isolated yield. [c]2 equiv of **1** and 2 equiv of TMSCl. [d]3 equiv of ketone in 80 °C.

expected. The C−N bond formation proceeded in consistently high yield for many acetoacetate derivatives in which the ester moiety (R_3) ranges in size from the ethyl group to the steric adamantyl group (**3a**−**e**). The reaction also worked on a larger scale (2 mmol) with comparable 79% yield (**3a**). The influence of R_1 and R_2 groups of 1,3-dicarbonyls was also investigated. With ethyl ketone (R_1 = Et) and phenyl ketone (R_1 = Ph), the corresponding products **3f** and **3g** were obtained in excellent yield. When unsubstituted ethyl benzoylacetate **1h** was used as the reactant, the product was isolated in 95% yield as a major keto isomer (keto/enol ≈ 7:1). The cyclic 1,3-ketoester methyl 2-carboxylate indanone (**1j**) and tetralone (**1k**) also proceeded

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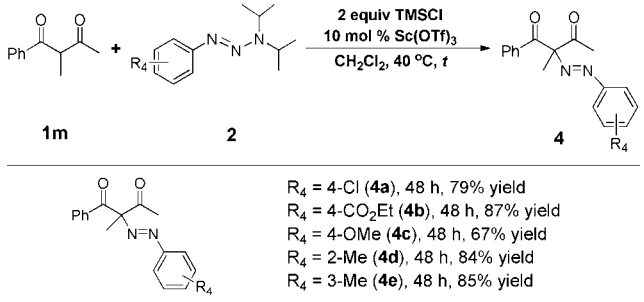
well, giving the products in moderate yields. Pleasingly, propargyl (**1i**) and heterocyclic (**1l**) substituents were well-tolerated to give the desired adducts in 88% and 75% yields, respectively. β-Diketones possess a more acidic C−H bond and a higher enol/keto- ratio than β-keto esters,[19] and this type of substrate worked extremely well to give the diazenylation adducts in 94% and 91% yield (**3m** and **3n**). Moreover, a variety of active methylene compounds, such as the substituted malonic ester (**1o**), ethyl cyanacetate (**1p**), β-keto amide (**1q**), β-keto phosphonate (**1r**), and α-(phenylsulfonyl)acetophenone (**1s**), were well compatible with the reaction conditions. In particular, the reaction also worked for aryl ketones such as propiophenone **1t**, furnishing the α-azo adduct in 40% yield. Other simple ketones such as cyclohexanone and 3-pentanone have also been examined in the reactions, showing unfortunately rather poor reactivity, likely a result of their low α-acidity.

Furthermore, the scope of aromatic triazo reagents has also been examined (Scheme 3). The phenyl ring moiety can be

Scheme 3. Scope of Intermolecular Diazenylation of β-Diketones and Aromatic Triazenes[a,b]

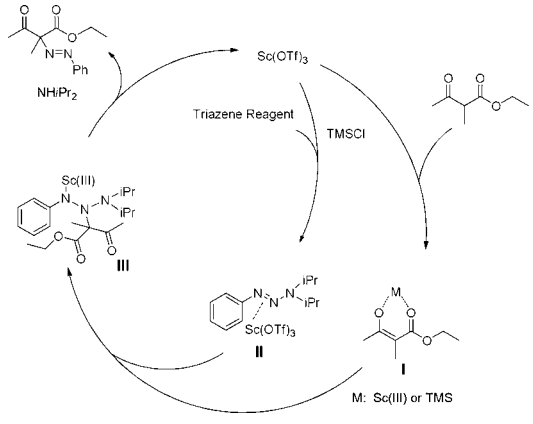


[a]General conditions: **1m** (0.1 mmol), **2** (0.2 mmol), TMSCl (0.2 mmol), and $Sc(OTf)_3$ (10 mol %) at 40 °C in the CH_2Cl_2 (0.4 mL) under Ar. [b]Isolated yield.

ortho-, *meta*-, or *para*-substituted, which can bear an electron-donating or an electron-withdrawing group, including a halide or ester group. The desired aromatic azo products can be obtained in generally good yields.

In light of the above results and previous reports, a plausible mechanism is described in Scheme 4. The β-ketoester is activated usually through coordination to the Sc(III) center in a bidentate fashion by both of the carbonyl groups. Meanwhile,

Scheme 4. Proposed Mechanism

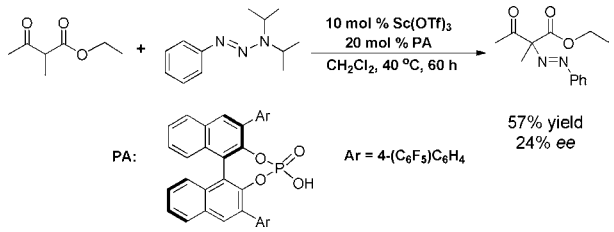


the silyl enol ether of an alkenyl β-keto ester might exist in view of the effect to enhance the equilibrium of the enol/keto ratio, since its generation in situ from the reaction of an alkenyl β-keto ester and a silyl chloride has been well demonstrated.[20]

The reaction is initialize via the coordination of the pendent triazene reagent to $Sc(OTf)_3$ on the nitrogen−nitrogen double bond. The marked affinity of the trimethylsilyl group toward terminal nitrogen lone pair and the weak nucleophilic nature of chloride ions restrain the nucleophilic attack to furnish aryl halides in the present of TMSCl.[21] Afterward, conjugate addition of the active β-keto ester and triazene compound via the intermediate III[15,22] occurs to generate the desired product and $HN(i\text{-}Pr)_2$, and the latter might be trapped by TMSCl or HCl to enhance the catalytic turnovers.

Taking the requirement for β-keto ester activation using Lewis acids into consideration, we hypothesized that the unique binary acid system developed by our group[23] might catalyze this new and enantioselective C−N bond formation. Indeed, we discovered that the desired aromatic azo compound was obtained in 57% yield and 24% ee in $Sc(OTf)_3$/polyfluoro chiral phosphoric acid without further optimizations (Scheme 5).

Scheme 5. Initial Attempt on a Catalytic Asymmetric Version[a]



[a]The reaction was conducted on 0.05 mmol scale in 0.4 mL of CH_2Cl_2 at 40 °C under Ar.

In summary, we have developed a $Sc(OTf)_3$-catalyzed diazenylation reaction of active methylene compounds with triazenes via N−N cleavage. This simple transfer diazenylation method was shown to tolerate a range of substrates to afford aliphatic azo compounds that are beyond reach with other methods. Further studies are currently underway to develop a catalytic asymmetric version.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^1H NMR, ^{13}C NMR, and HPLC spectra for new products. 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.

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