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Catalytic Racemization of Activated Organic Azides

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Abstract

The first detailed description of the catalytic racemization of activated benzylic and allylic azides under mild conditions is reported. A kinetic analysis of the observed racemization indicates a first-order dependence on azide, a first-order dependence on catalyst, and that the rate of racemization correlates to σ^+ . A variety of azides with varying substitution patterns undergo facile racemization, and catalyst selection can tune this process.

Graphical Abstract

Synthetic methods that provide direct access to enantioenriched products are highly desired. A powerful platform for enantioselective synthesis is dynamic kinetic resolution (DKR).^{1–6} DKR is especially powerful because racemic starting materials can be converted to enantioenriched products in both high yield and high selectivity. This surmounts the 50% maximum theoretical yield barrier inherent to kinetic resolution.⁷ A mechanism for rapid racemization is crucial for DKR, which has limited this process to substrates containing easily racemizeable stereocenters. Common DKR substrates include carbonyl containing molecules with an α -stereocenter.^{8–10} Alternatively, chiral secondary alcohols can be racemized via an oxidation/reduction sequence.³ While other mechanisms of racemization are known,^{1,2,11} the applications of DKR remain limited. Identifying new mechanisms of facile racemization for new substrate classes could potentially open unexplored avenues for the development of methods predicated on DKR. Azides are particularly interesting substrates because they are chiral amine equivalents, and chiral amines are an essential motif in many drugs and drug candidates.

Recently, our group has become interested in using organic azides as amine surrogates for DKR.^{12–14} We hypothesized that the Winstein rearrangement^{15–17} could serve as a suitable racemization pathway. An initial example afforded tertiary azides in high er.¹² These promising results led us to ask fundamental questions regarding the mechanism of the allylic azide rearrangement. Under most conditions, the rearrangement occurred via a [3,3]

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sigmatropic pathway and no racemization was observed (Scheme 1a).¹⁸ A second solvolysis pathway led to azide racemization, which proceeded slowly in methanol at 100 °C (Scheme 1b).¹⁸ While this was exciting, racemization was slow, required elevated temperatures, and resulted in significant decomposition of the azide through methanolysis. Therefore, these conditions could not be readily adapted to DKR. Nevertheless, the observed racemization prompted a search for a suitable racemization catalyst.

We sought to identify a catalyst for azide racemization that would (i) significantly increase the rate of racemization, (ii) proceed without significant decomposition of the azide, and (iii) broaden the scope of azides that could be efficiently racemized. This report provides the first detailed account documenting the catalytic racemization of organic azides. Several catalysts for racemization are described that proceed with an exceptional rate enhancement relative to the solvolysis pathway (Scheme 1b vs 1c). This process is broad in scope and is tunable based on catalyst selection.

We began this study with allylic azide **1a** (Table 1). Prior work indicated that this azide is configurationally stable in nonpolar solvents at 100 °C for >1 week.¹⁸ Catalysts were examined in dichloromethane at 50 °C so that any observed racemization could be attributed to the catalyst. Azide **1a** (>99:1 er) was exposed to 10 mol % of various possible catalysts for 24 h, and the reaction was monitored by chiral HPLC. Initially, transition metal catalysts were investigated (entries 1–4). As part of a report on an allylic substitution reactions, Trost and co-workers suggested that the presence of palladium may accelerate the allylic azide rearrangement.¹⁹ Exposure of azide **1a** to Pd(0) sources led to minimal racemization (entries 1–2). Exposure to a more electrophilic Pd(II) salt led to considerable racemization along with significant azide decomposition (entry 3). Based on Liu's observation,²⁰ Lewis acidic salts were investigated (entries 5 and 6). Several of these catalysts resulted in racemization along with appreciable decomposition of azide **1a** (entries 4–6 and Supporting Information). Gratifyingly, Zn(OTf)₂ led to full racemization with minimal azide decomposition (entry 6). Triflamide, as a Brønsted acid catalyst, was found to be minimally effective (entry 7). A report by Toste and coworkers suggested that cationic gold salts may cause partial racemization of some azides.²¹ Catalyst 1 was chosen as a representative gold(I) complex. Exposure of azide **1a** to 10 mol % of this catalyst led to complete racemization with minimal decomposition of the azide. Based on these results, Zn(OTf)₂ and gold catalyst 1 were selected for further study.

A secondary screen was conducted to determine whether Zn(OTf)₂ or catalyst 1 was more efficient (Table 1, entries 9 and 10). Racemization was slow with Zn(OTf)₂ at room temperature (entry 9). However, full racemization occurred with gold catalyst 1 at room temperature over 24 h (entry 10). This indicated a greater rate of acceleration with the gold(I) catalyst relative to Zn(OTf)₂. A more detailed kinetic analysis indicated that catalyst 1 is capable of full racemization within 10 min at room temperature. This is considerably faster than the uncatalyzed solvolysis conditions, which proceeded at 100 °C in methanol

Supporting Information

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Experimental procedures and data (PDF)

over several hours (Scheme 1b). This clearly indicates a remarkable acceleration of the racemization rate to a level that could conceivably be compatible with DKR applications.

Other cationic gold(I) complexes were investigated (Table 1, entries 11–14). These results indicate that other gold(I) complexes with noncoordinating counterions are suitable for racemization. Significantly, minimal azide decomposition was observed even with rapid racemization. Decreasing the catalyst loading slowed racemization (entry 15 and SI); however, activity could be restored by increasing the temperature and concentration (entry 16). As a control experiment, AgSbF₆ was used as the catalyst (entry 17), which led to both racemization and significant azide decomposition. We proceeded to study catalyst 4 because it is readily available and fully soluble, provided rapid racemization at room temperature, and caused minimal azide decomposition.

With a catalyst identified, we were interested in illuminating the mechanism of racemization. Using the method of initial rates,²² the reaction was found to be first-order in both azide and gold catalyst. To gain more insight, a series of substituted azides were synthesized (Figure 1, **1a–1e**). For each azide, the initial rate of racemization was measured using chiral HPLC analysis. The rate of racemization correlated to the Hammett parameter σ^+ (Figure 1, $R^2 = 0.97$, $\rho = -5.9$), indicating buildup of positive charge in the transition state. The large negative ρ value is consistent with formation of a carbocation intermediate.²³ Based on the known binding mode of a similar gold complex to adamantyl azide²⁴ and the kinetic analysis, a mechanism is proposed (Scheme 2). The gold catalyst likely binds the azide (step (i)), ionizes the azide (step (ii)), recombines with the carbocation (step (iii)), and dissociates (step (iv)).

Other organic azides could be racemized under these gold catalyzed conditions (Table 2). In order to tease apart subtle differences in the rate of racemization, the following experiments were conducted under dilute conditions (5 mM). As expected based on the Hammett correlation, a tertiary allylic azide underwent rapid racemization (entry 1). A doubly benzylic and tertiary azide racemized and gradually decomposed to the corresponding styrene, which was independently verified (entry 2). Other tertiary benzylic azides demonstrated a range of activity based on the substituents (entries 3–5). Diaryl secondary azides reached a 50:50 er within 6 h (entries 6 and 7). These results are particularly exciting because they demonstrate that this process is not restricted to allylic azides and is operable on a much broader class of compounds. Less activated azides also reacted, albeit at a decreased rate under these dilute conditions (entries 8 and 9). Other activated secondary azides were stable under these conditions (entries 10–12).

With several suitable catalysts identified in the initial screen, we hypothesized that the catalyst and substrate combination could be fine-tuned to (i) increase the reactivity of less activated azides or (ii) prevent decomposition for the most activated azides. For model substrate **1a**, the use of a decreased AgPF₆ loading resulted in racemization with less decomposition (Table 3, entry 1). Furthermore, the reactivity of the silver salt could be tuned by the addition of ligand (entry 2). Secondary azides **11** and **13** were stable to catalyst 4, but treatment with AgPF₆ resulted in near-complete racemization in under 5 h at room temperature (entries 3 and 5). Racemization could be further accelerated by mildly heating

the reaction (entry 4). Racemization of azide **10** was sluggish under the initially optimized conditions, but increasing the temperature and concentration resulted in moderate racemization in 5 h (entry 6). Highly active substrates can be efficiently racemized under more mild conditions with Zn(OTf)₂ (entries 7–8). While azide **2** began to decompose using catalyst 4, Zn(OTf)₂ resulted in minimal decomposition (entry 8).

Herein we disclose the catalytic racemization of activated organic azides. The rate of the reaction is correlated to the Hammett constant σ^+ , implicating the involvement of a carbocation intermediate. The reactivity can be modulated by the choice of catalyst. Investigations into utilizing this racemization for a downstream functionalization are currently underway.

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Figure 1. Plot of $\log(k/k_0)$ vs σ^+ for substituent effects on the racemization of azides **1a–1e** using catalyst **4**. Rates were measured in duplicate, replicates shown.

Prior work:

This work: Catalytic Racemization

Scheme 1.
Mechanisms of Azide Rearrangement and Racemization

Scheme 2.
Proposed Mechanism for Azide Racemization

Table 1.

Initial Screen for Racemization Catalyst

entry	catalyst	temp	er ^a	% azide remaining ^b
1	Pd(PPh ₃) ₄	50 °C	81:19	68
2	Pd ₂ (dba) ₃	50 °C	98:2	89
3	PdCl ₂ (NPh) ₂	50 °C	64:36	76
4	(cod) ₂ RhOTf	50 °C	59:41	23
5	Cu(OTf) ₂	50 °C	60:40	61
6	Zn(OTf) ₂	50 °C	50:50	86
7	Tf ₂ NH	50 °C	82:18	65
8	catalyst 1	50 °C	50:50	82
9	Zn(OTf) ₂	rt	82:18	94
10	catalyst 1	rt	50:50	88
11 ^c	Ph ₃ PAuSbF ₆	rt	50:50	84
12 ^c	catalyst 2	rt	52:48	75
13 ^c	catalyst 3	rt	78:22	85
14 ^c	catalyst 4	rt	57:43	97
15 ^{c,d}	catalyst 4	rt	98:2	99
16 ^e	catalyst 4	50 °C	60:40	99
17	AgSbF ₆	rt	50:50	72

^a Measured using chiral HPLC analysis.^b Determined by calibrated HPLC analysis using 1,1-di-*tert*-butylbiphenyl as a standard. Reactions were run in duplicate, and the average yield and er values are reported. Room temperature = rt.^c Reaction time of 10 min.^d Reaction with 1 mol % catalyst.

^eReaction with 1 mol % catalyst at 0.1 M [N₃] and at 3 h.

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Table 2.

Scope of Azides That Can Be Racemized

$ \begin{array}{c} \text{N}_3 \\ \\ \text{R}^1\text{C} - \text{R}^2 - \text{R}^3 \\ \xrightarrow[\text{CH}_2\text{Cl}_2, \text{rt}]{\begin{array}{c} 5 \text{ mM } [\text{N}_3] \\ 10 \text{ mol } \% \text{ catalyst } 4 \end{array}} \\ \text{N}_3 \\ \\ \text{R}^1\text{C} - \text{R}^2 - \text{R}^3 \end{array} $				
% azide remaining ^a , er ^b				
entry	azide	1 h	6h	24h
1 ^c	2	90% 50:50	81% 51:49	77% 51:49
2 ^d	3	86% 74:26	71% 56:44	--
3 ^e	4	84% 83:17	86% 55:45	79% 50:50
4 ^f	5	97% 98:2	93% 92:8	90% 88:12
5	6	98% 97:3	95% 91:9	93% 81:19
6	7	97% 57:43	95% 50:50	94% 50:50
7	8	99% 50:50	96% 50:50	96% 50:50
8	9	93% 84:16	92% 80:20	92% 70:30

% azide remaining ^a , er ^b				
entry	azide	1 h	6h	24h
9	10	99% >99:1	99% 97:3	97% 93:7
10 ^e	11	96% >99:1	96% >99:1	96% >99:1
11 ^e	12	99% >99:1	99% >99:1	99% >99:1
12	13 Ar = 4-CF ₃ -C ₆ H ₄	--	--	98% 98:2

^aDetermined by HPLC analysis using 1,1-di-*tert*-butylbiphenyl as a standard. Reactions were run in duplicate, and the average yield and er values are reported.

^bMeasured using chiral HPLC analysis.

^cTime points are 1, 5, and 10 min.

^dTime points are 1 and 3.5 h.

^eYield determined by GC analysis.

^fTime points are 1, 3.5, and 6 h. Room temperature = rt, PMP = *para*-methoxyphenyl.

Table 3.

Alternate Catalysts for Racemization

% azide remaining ^a , er ^b					
entry	azide	catalyst	temp	1 h	5 h
1 ^{c,d}	 1a	AgPF ₆	rt	94% 63:37	93% 57:43
2 ^c	Ar = 4-CH ₃ -C ₆ H ₄	AgPF ₆ /PPh ₃	rt	92% 64:36	89% 59:41
3	 11	AgPF ₆	rt	94% 67:23	95% 52:48
4	 11	AgPF ₆	50 °C	92% 51:49	92% 50:50
5 ^e	 13 Ar = 4-CF ₃ -C ₆ H ₄	AgPF ₆	rt	91% 52:48	88% 51:49
6	 10	Cat. 4	50 °C	90% 78:22	88% 68:32
7 ^e	 8	Zn(OTf) ₂	50 °C	>99% 85:15,	>99% 51:49
8 ^e	 2	Zn(OTf) ₂	rt	97% 71:29	95% 51:49

^aDetermined by HPLC analysis using 1,1-di-*tert*-butylbiphenyl as a standard. Reactions were run in duplicate, and the average yield and er values are reported.

^bMeasured using chiral HPLC analysis.

^cTime points are 10 min and 1 h at 6 mM [N₃].

^dReaction with 3 mol % catalyst loading.

^eTime points are 1 and 3 h. Room temperature = rt.

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