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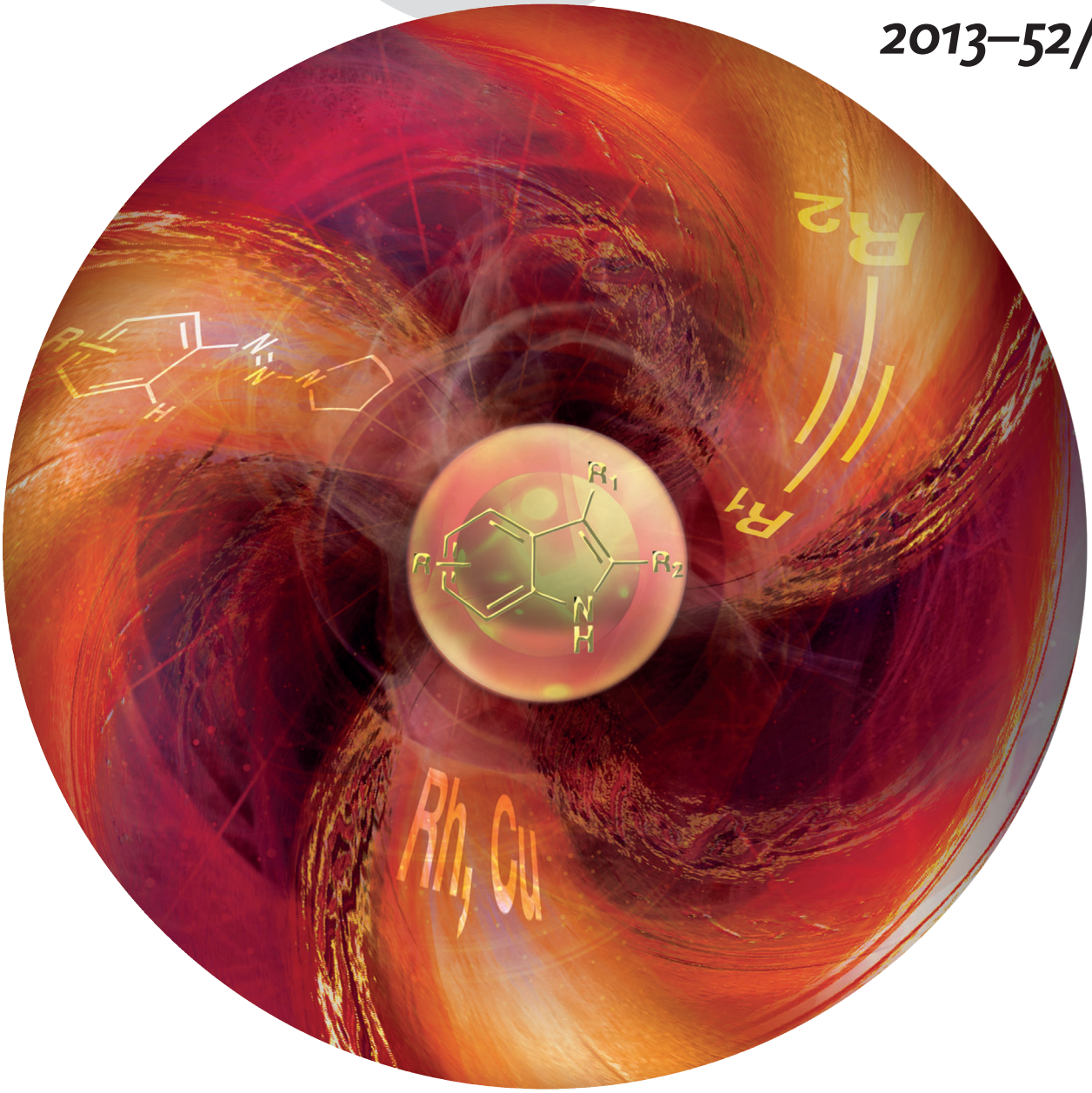

Directed C–H annulation reactions ...

... provide a straightforward solution to the synthesis of substituted indoles. In their Communication on page 5795 ff., Y. Huang and co-workers describe a general protocol for the synthesis of unprotected indoles. By using a cleavable triazene as the directing group, C–H annulation with a wide scope of alkynes was accomplished with excellent regioselectivity for both aryl,alkyl and alkyl,alkyl disubstituted acetylenes.

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Synthetic Methods

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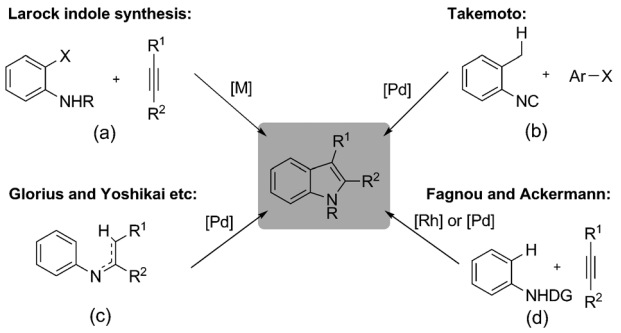
General and Efficient Synthesis of Indoles through Triazene-Directed C–H Annulation**

*Chengming Wang, Huan Sun, Yan Fang, and Yong Huang**

Indole is one of the most abundant and important class of heterocycles found in natural products, pharmaceuticals, and other functional molecules.[1] Despite more than 100 years of efforts and numerous methods developed, organic chemists continue to search for more straightforward and economical ways to make various substituted indoles.[2] Among them, transition-metal-catalyzed aniline–alkyne cyclizations emerged as the most widely adopted protocols (Scheme 1 a).[1h,2b,c,e,3] However, preactivation of substrates by halogenation or alkynylation was required, which often is not trivial. Advantageous over these methods is that the direct C–H activation and functionalization bypasses the need for preactivated reaction partners and also tolerates a much wider substrate scope with controlled regioselectivity.[4] Recently, several indole syntheses using C–H activation were developed.

Takemoto and co-workers reported an isocyanide insertion and benzylic C–H activation strategy to access certain substituted indoles (Scheme 1 b).[5] However, both reaction substrates need to be preactivated. Cross-dehydrogenative coupling (CDC) reactions were explored as an alternative to the popular Larock indole synthesis (Scheme 1 a).[6] Glorius and co-workers reported palladium(II)-catalyzed oxidative cyclization reaction of N-aryl enamines derived from anilines and β-dicarbonyl compounds to afford the corresponding indoles (Scheme 1 c).[6b,c] The research groups of Jiao,[6d] Cacchi,[6e] Zhao,[6f] and Liang[6g] explored different metals and oxidants for the parallel CDC reactions. Yoshikai and co-workers recently reported significantly improved reaction conditions and substrate scope.[6h]



Scheme 1. Transition-metal-catalyzed indole synthesis. DG = directing group.

Directed intermolecular C–H annulation represents a straightforward and attractive strategy to access indoles.[7] Fagnou and co-workers reported an NHAc-directed dehydrogenative cyclization between internal alkynes and arenes catalyzed by rhodium (Scheme 1 d).[7a–c] A method employing Ru and other NH protecting groups was later reported by Ackermann and others.[7d,f] Owing to the static nature of these directing groups (DGs), only protected indoles could be accessed. Further functionalization of the indole NH would require an additional deprotection step. The direct access to unprotected indoles by using this strategy remains a challenging task. In addition, regioselectivity is a major issue, since asymmetrically substituted internal alkynes often gave a mixture of region isomers.[5c] Herein, we report the first general protocol to synthesize unprotected indoles through directed C–H annulation between arenes and alkynes by using a triazene as the DG. Excellent regioselectivity was achieved for both aryl–alkyl and alkyl–alkyl internal alkynes.

Our recent work on removable directing groups (DG) for C–H activation and functionalization led to the discovery of triazenes as a class of highly efficient and manipulable DGs for oxidative Heck coupling reactions (Scheme 2 a).[8] Inspired by the report by Yamane and Zhu on cinnoline synthesis using *ortho*-iodo triazenyl arenes and alkynes (Scheme 2 b),[9] we attempted to develop a directed C–H activation route to cinnoline. To our surprise, no desired cinnoline product was observed despite intensive condition search. Instead, the corresponding unprotected indole was isolated (Scheme 2 c). It prompted us to investigate this unprecedented transformation.

Our initial study was carried out by examining triazenyl arene **1e** and diphenylacetylene **2a** in the presence of $[\{RhCp^*Cl_2\}_2]$ and $Cu(OAc)_2 \cdot H_2O$ in MeOH under argon atmosphere. The indole product **3e** was isolated in 20% yield (Table 1, entry 3). Other catalysts did not promote this reaction (for comprehensive reaction investigations, see the Supporting Information). Solvents proved to be critical and only MeOH promoted this reaction (Table 1, entry 6–8). A stoichiometric amount of copper oxidant was essential, and catalytic noncoordinating counter ion silver salts could further improve the yields. The use of a triazene bearing

[*] C. Wang, H. Sun, Y. Fang, Prof. Dr. Y. Huang
Key Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University, Shenzhen Graduate School Shenzhen (China)
E-mail: huangyong@pkusz.edu.cn
Homepage: http://scbb.szpku.edu.cn/huang

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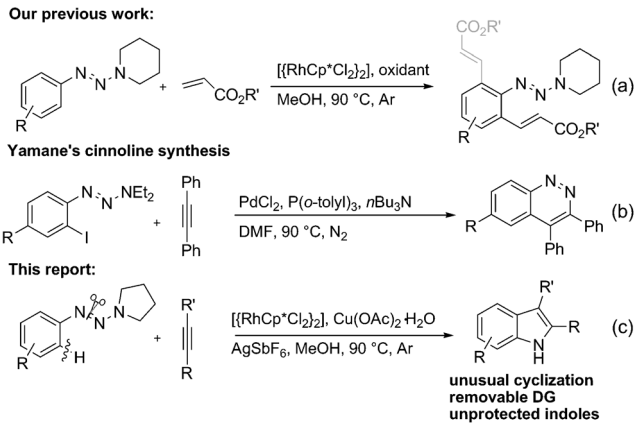
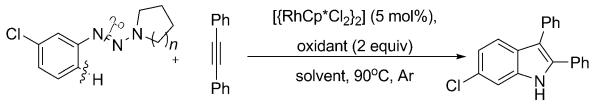


Scheme 2. Indole synthesis through triazene-directed C–H annulation. Cp* = pentamethylcyclopentadienyl.

a five-membered pyrrolidine led to significant conversion enhancement, and the product was isolated in 90% yield (Table 1, entry 9). Triazenes containing other cyclic or acylic side chains gave inferior results. Eventually the following conditions were chosen for examination of the reaction scope: $[\{RhCp^*Cl_2\}_2]$ (5 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv) in methanol under argon at 90°C (oil-bath temperature).

Various triazenyl arenes and alkynes were examined under standard conditions (Scheme 3). Aromatic substrates with a broad substitution pattern and of different electronic nature were tolerated, and indoles bearing substitutions at 5-, 6-, and/or 7-positions were synthesized in good to excellent yields. In reactions with arenes having strong electron-donating substituents major side reactions occurred, resulting in compromised yields. Halogens did not interfere with this transition-metal-catalyzed process (**3a**–**c**, **3e**,**f**). The relatively low yield observed for *ortho*-iodo triazenyl benzene was likely due to low reactivity (steric reasons), as the starting material partially remained after 24 h (**3h**). Aryl–aryl, aryl–alkyl, and alkyl-alkyl disubstituted acetylenes were all well-tolerated, thereby further broadening the substrate scope. In particular,

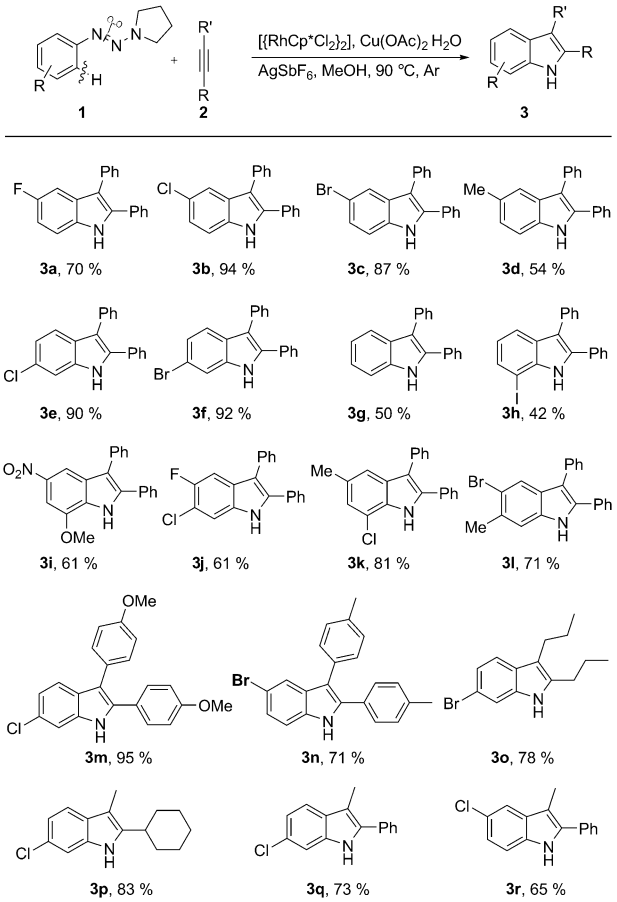
Table 1: Conditions screening.[a]



1e 1 equiv — **2a** 1.1 equiv — **3e**

Entry	Solvent	Oxidant	Additive	Yield [%][b]
1	MeOH	$CuCl_2$	–	–
2	MeOH	$Cu(OTf)_2$	–	–
3	MeOH	$Cu(OAc)_2{\cdot}H_2O$	–	20
4	MeOH	–	–	< 5
5	MeOH	$Cu(OAc)_2{\cdot}H_2O$	AgOAc	35
6	MeOH	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	67
7	DMF	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	–
8	CH_3CN	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	–
9[c]	**MeOH**	**$Cu(OAc)_2{\cdot}H_2O$**	$AgSbF_6$	**90**

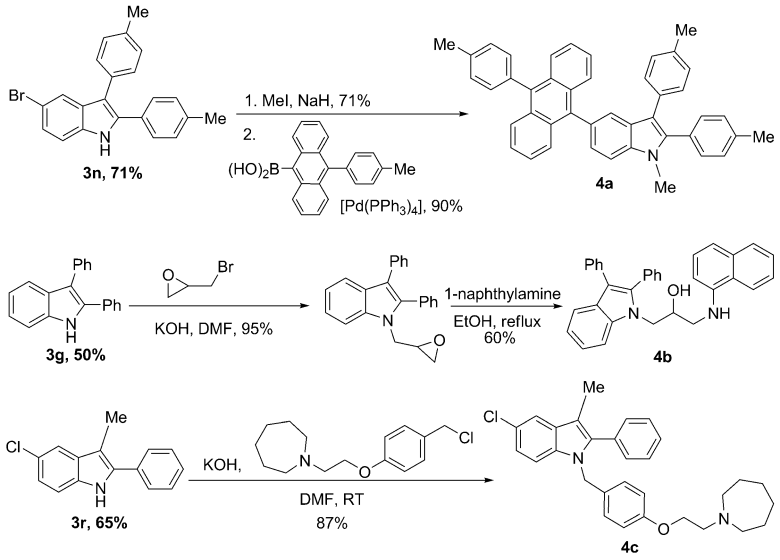
[a] $n = 2$ for all entries, except entry 9 ($n = 1$). [b] Yields of isolated products. [c] 2 equivalents of alkyne were used.



Scheme 3. Substrate scope. Reactions were carried out on a 0.3 mmol scale. Yields of isolated products are given.

asymmetric alkynes afforded excellent regioselectivity (**3p**–**3r**). For various alkyl phenyl acetylenes, only one regioisomer was obtained (**3q**–**r**). Significantly, excellent steric differentiation (regioisomeric ratio > 10:1) was accomplished for alkyl–alkyl acetylenes (**3p**). This result represented a major advantage over the protocol reported by Fagnou and co-workers. The authors explored a detour strategy to address this selectivity issue: by using sp^2–sp^3 disubstituted acetylene followed by hydrogenation.[7c] Reactions involving terminal alkynes were compromised by side reactions such as alkyne dimerization.

This method allowed quick access to a number of functional molecules (Scheme 4). Product **3n** was converted to a popular organic light-emitting device **4a** with improvements in turn-on voltage, efficiency, and color-purity characteristics in two steps: methylation and subsequent Suzuki coupling.[10] A indole N-substituted aminohydroxypropane **4b**, which structurally resembles a potent BACE1 inhibitor for the potential treatment of Alzheimer's disease, was synthesized from **3g** by following a standard alkylation–epoxidation opening sequence in 60% yield.[11] In addition, product **3r** obtained from an asymmetric internal alkyne was alkylated to produce **4c**, an analogue of bazedoxifene.[12] These three examples of our triazene-directed C–H annulation method demonstrated clear advantages over the use of other DGs, for



Scheme 4. Demonstration of product utilities.

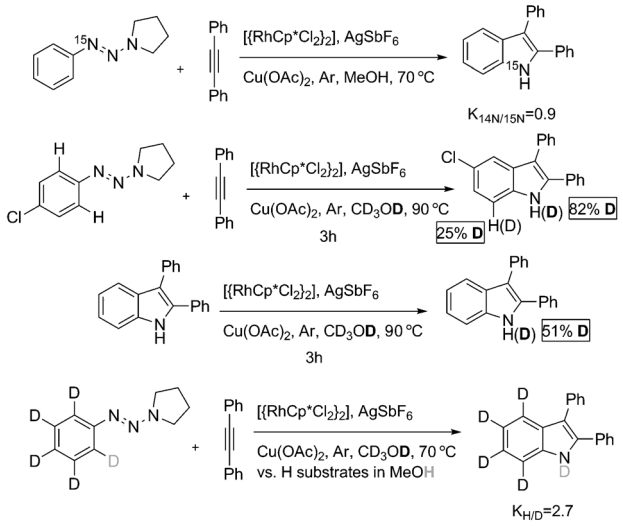
which an independent deprotection step to reveal the indole NH group would be required.

To probe the reaction mechanism, isotope experiments were carried out (Scheme 5). Experiments with a ^{15}N substrate confirmed that the indole nitrogen came from the triazene nitrogen directly attached to the aromatic ring. A mild inverse nitrogen kinetic isotope effect was observed in a competition experiment ($K_{14N/15N} = 0.9$), indicating the N–N cleavage was not the rate-limiting step. Interestingly, the ^{15}N substrate afforded significantly higher yields than the corresponding ^{14}N compound (80% vs. 50%). The C–H activation step was reversible as indicated by the 25% H/D scrambling in the product.[7b,e–f,13] The H/D exchange of the unreacted *ortho*-C-H proton complicated the KIE measurement for the C–H insertion step. Separate experiments using a pentadeuterated substrate were carried out to independently assess the rates of reaction for *ortho*-C-H vs. C-D. A measurement of $K_{H/D} = 2.7$ indicated that the C–H activation was the rate-determining step. Subjecting the indole product to the standard conditions resulted in fast NH proton exchange.

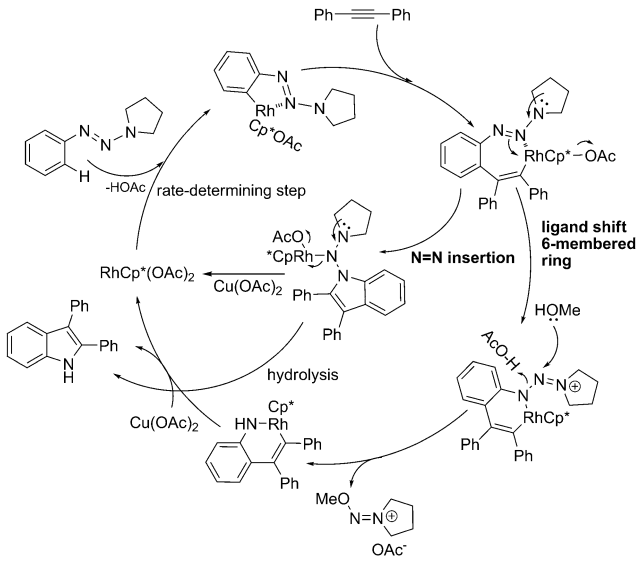
Based on these facts and literature precedence,[7b] we propose an Rh^{3+}–Rh^{+}–Rh^{3+} catalytic cycle triggered by an N-ligand shift (Scheme 6). First, an active Rh^{3+} acetate species is generated from $[\{RhCp^*Cl_2\}_2]$, $AgSbF_6$, and copper acetate. This is followed by a reversible C–H bond insertion directed by the middle nitrogen atom of the triazene moiety.

The resulting 7-membered metallacycle, presumably quite unstable, quickly rearranges to a more stable six-membered Rh complex. Reductive elimination releases the indole product. Alternatively, N=N insertion to Rh–C, followed by subsequent reduction and hydrolysis would also generate the desired heterocycle. It is not clear whether the appending diazonium residue undergoes solvolysis prior to or after reductive elimination. The crucial N_1–N_2 bond cleavage may be promoted by HOAc generated from the C–H activation. The lack of reaction in the absence of an external oxidant (Table 1, entry 4) indicated that triazene did not act as an internal oxidant for this tranformation, which would naturally lead to the cinnoline product.[14]

In summary, we have developed a general synthesis of unprotected indoles through a triazene-directed C–H annulation using alkynes. This reaction is proposed to undergo a 1,2-rhodium shift ring contraction or an N=N insertion mechanism. A broad scope of substrates was well tolerated. Excellent regioselectivity was achieved by asymmetrically substituted alkynes, which found immediate synthetic applications. Further exploration of the synthetic utilities of this chemistry and in-depth mechanistic study are currently in progress and will be reported in due course.



Scheme 5. Reactions using isotope-labeled substrates.



Scheme 6. Proposed mechanism of the triazene-directed NH indole synthesis.

Experimental Section

[{Cp*RhCl$_2$}$_2$] (9.3 mg, 0.0015 mmol, 5 mol%), triazene **1** (0.3 mmol, 1.0 equiv), Cu(OAc)$_2$·H$_2$O (120 mg, 0.6 mmol, 2.0 equiv), and $AgSbF_6$ (22 mg, 0.060 mmol, 0.2 equiv) were subsequently weighed into an oven-dried Schlenk tube. The reaction vessel was capped and evacuated/flushed with argon three times. A solution of alkyne (0.6 mmol, 2.5 equiv) in methanol (3.0 mL) was added through the side arm by using a syringe. The reaction was stirred under an argon balloon at 90 °C, and the progress of the reaction was monitored by TLC. Upon complete consumption of **1**, the mixture was cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation and the residue was purified by silica gel flash chromatography using petroleum ether/EtOAc (50:1 to 10:1) to afford the indole product **3**.

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Keywords: C–H activation · indole · N–N cleavage · rhodium · triazene

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