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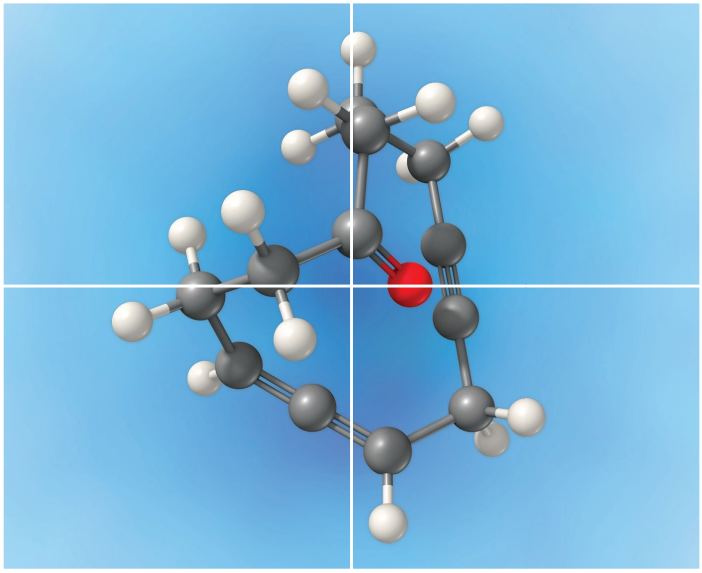

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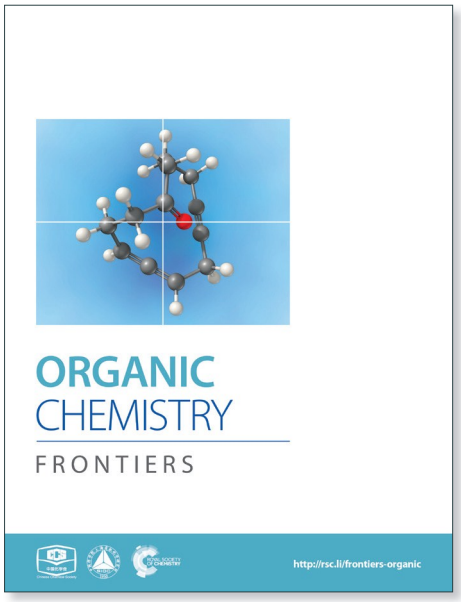

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RESEARCH ARTICLE

Manganese(II)-catalyzed modular synthesis of isoquinolines from vinyl isocyanides and hydrazines †

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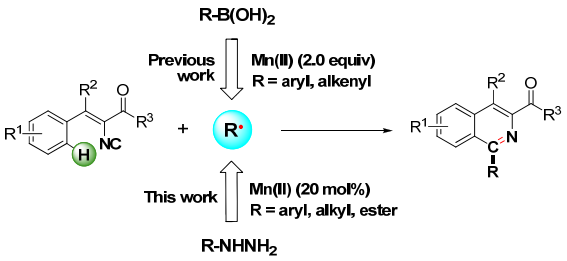
An efficient manganese(II)-catalyzed oxidative radical cascade reaction was developed for the modular synthesis of multi-substituted isoquinolines from easily accessible vinyl isocyanides and hydrazines. Pyrrolo[1,2-*a*]quinoxalines and phenanthridines could also be afforded efficiently by this method and a wide range of alkyl, (hetero)aryl and alkoxycarbonyl substitutions could be easily introduced.

Isoquinolines represent one of the most important molecules in pharmaceutical and agrochemical industries due to their biological and pharmacological activities as therapeutic agents in medicinal chemistry[1,2] and natural products,[3] and for this reason the practical synthesis of the core skeleton is of considerable interests in organic synthsis.[4,5] Followed by the early established traditional reactions such as Bischler–Napieralski, Pomeranz–Fritsch and Pictet–Spengler,[4] many synthetic methods have been developed recently to construct isoquinoline frameworks.[5] Among them, one of the most common synthetic strategies was attributed to C–H bond activation through transition metal catalyzed cyclization of alkynes with amines,[5c] aryl hydrazones,[5b] aryl imines,[5a,d,h–j] azides,[5f] benzamidines,[5g] or oximes.[5e] However, the reaction products are usually less substituted or lack of diversity and the use of noble metals (Pd, Rh, Ru) would limit their applications in synthetic chemistry although these reactions had overcome many drawbacks from previously reported reactions such as using strong acidic conditions and elevated temperature.

Manganese salts, which exist widely in nature, are ideal catalysts or promotors in organic synthesis due to their inexpensiveness, chemical stabilities and special reactivity properties.[6] However, as a first-row transition metal, manganese has been less studied except for some well-known oxidants like high-valent species $KMnO_4$ and MnO_2. Recently, promising and wide applications of manganese reagents have been explored based on their existance with various valents of manganese. For example, Wang and co-workers reported a $MnBr(CO)_5$ catalyzed dehydrogenative annulation of imines and alkynes,[7] which suggested that Mn(I) could be an efficient catalyst to replace noble metals such as palladium or rhodium in the field of C–H bond activation. More typically, Mn(III) salts are recognized as efficient promotors in radical reactions due to their property of oxidation tendency.[8] In this context, the use of stoichiometric amounts of manganese reagents in some reactions will limit their application, and result in the unwanted production of quantities of waste metals in the meanwhile. Although Mn(II)-catalyzed reactions have been developed in the cross coupling reactions[9a-c] and asymmetic oxidations,[9d,e] it's still rare to act as a radical initiator catalytically in comparison with the use of stoichiometric amount of manganese in radical reactions.[9f,g] Therefore, from the viewpoint of sustainable development, green chemistry and the fact that an efficient catalytic turnover remains to be challenging, the development of manganese-catalyzed reactions, especially using the cheaper Mn(II) salts, will be highly desirable and of great value.

Isocyanides are uniquely versatile C1 building blocks and have been widely applied in the synthesis of various complicated compounds.[10] They are not only capable of reacting with nucleophiles and electrophiles, but also be served as effective radical acceptors. Although 2-isocyanobiphenyls have been fully reported for the synthesis of phenanthridines with various radical precursors through the somophilic isocyanide insertion reaction,[8a,11] the chemistry of vinyl isocyanides remains largely unexplored and less examples have been demonstrated to construct the useful isoquinolines from them.[12] An elegent example was reported by a visible light-promoted annulation in the catalysis of noble iridium.[12a] Recently, we have demonstrated the feasible synthesis of isoquinolines through Mn(II)/O_2-promoted vinyl isocyanides insertion with organoboronic acids (Scheme 1),[13] however, two equivalents of manganese was necessary to accelerate the reaction and limited substrates could be applied as no desired 2-alkyl substituted products could be obtained from corresponding alkyl boronic acids. In continuation of our recent research interests on the isocyanide chemistry,[13-15] herein, we disclose an oxidative radical cascade reaction which, to the best of our knowledge, represents the first example of Mn(II)-catalyzed protocol for the synthesis of multi-substituted isoquinolines from easily accessible vinyl isocyanides and various hydrazines,[16] whereby the formation of two C–C bonds was involved in one step (Scheme 1). For the given approach, various functional groups including aryl, alkyl, alkoxycarbonyl and acyl could be introduced efficiently from hydrazines onto the C1-position of isoquinolines in good to excellent yields.

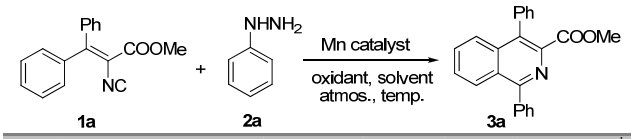


Scheme 1 Mn(II)-catalyzed radical cascade reaction of vinyl isocyanides.

At the outset of this investigation, we commenced our study by exploring the catalytic reaction of vinyl isocyanide **1a** with phenylhydrazine **2a** in the presence of manganese(II) acetate tetrahydrate in DMF using TBPB as an oxidant under nitrogen atmosphere at 70 °C. Intriguingly, the desired product **3a** was isolated in 31% yield after reacted for 23 h (Table 1, entry 1).

Various solvents were examined next, which resulted in that CH_3CN was the most suitable solvent in this catalytic system (entries 2–6). Other oxidants such as TBHP and DTBP also worked in the reaction and afforded **3a** in relatively lower yield compared with TBPB (entries 7 and 8). No much better results were observed with reaction temperature increased or decreased (entries 9 and 10), and nitrogen atmosphere was preferred after the screening of atmosphere (entries 11 and 12). Extensive optimization studies of the amount of $Mn(OAc)_2{\cdot}4H_2O$ (entries 13 and 14), phenyl hydrazine (entries 15 and 16) and TBPB (entry 17) as well as other manganese catalysts (entries 18–20) suggested that the use of 20 mol% of $Mn(OAc)_2{\cdot}4H_2O$ and TBPB in CH_3CN solvent at 70 °C under nitrogen atmosphere turned out to be the best choice and afforded the target product **3a** in 82% yield (entry 6). Low yield of **3a** (30%) was afforded in the absence of Mn(II) catalyst, which indicated that manganese catalyst was crucial for this cyclization reaction (entry 21).

Table 1 Optimizations of the reaction conditions[a]

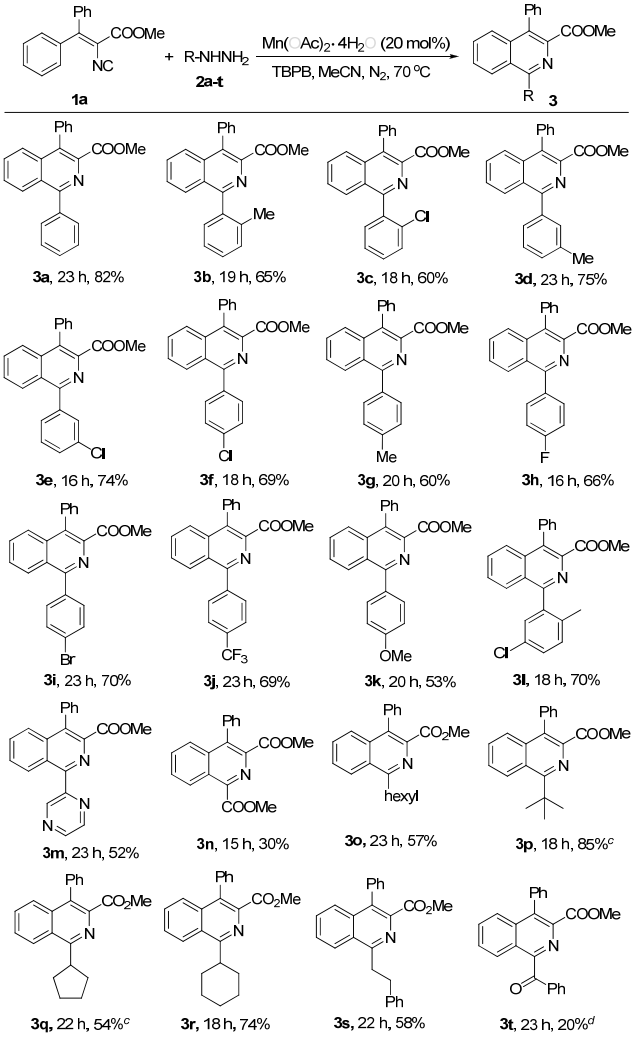


Entry	Catalyst (mol%)	Solvent	Oxidant	Atmos.	Temp. (°C)	Yield[b] (%)
1	$Mn(OAc)_2{\cdot}4H_2O$ (20)	DMF	TBPB	N_2	70	31
2	$Mn(OAc)_2{\cdot}4H_2O$ (20)	THF	TBPB	N_2	70	38
3	$Mn(OAc)_2{\cdot}4H_2O$ (20)	EtOH	TBPB	N_2	70	24
4	$Mn(OAc)_2{\cdot}4H_2O$ (20)	Toluene	TBPB	N_2	70	42
5	$Mn(OAc)_2{\cdot}4H_2O$ (20)	PhCN	TBPB	N_2	70	40
6	**$Mn(OAc)_2{\cdot}4H_2O$** (20)	**CH_3CN**	TBPB	**N_2**	**70**	**82**
7	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBHP	N_2	70	52
8	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	DTBP	N_2	70	18
9	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	N_2	80	74
10	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	N_2	60	77
11	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	Air	70	56
12	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	O_2	70	63
13	$Mn(OAc)_2{\cdot}4H_2O$ (15)	CH_3CN	TBPB	N_2	70	65
14	$Mn(OAc)_2{\cdot}4H_2O$ (10)	CH_3CN	TBPB	N_2	70	63
15	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	N_2	70	53[c]
16	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	N_2	70	57[d]
17	$Mn(OAc)_2{\cdot}4H_2O$ (20)	CH_3CN	TBPB	N_2	70	77[e]
18	$Mn(OAc)_3{\cdot}2H_2O$ (20)	CH_3CN	TBPB	N_2	70	66
19	$Mn(acac)_3$ (20)	CH_3CN	TBPB	N_2	70	72
20	$Mn(acac)_2$ (20)	CH_3CN	TBPB	N_2	70	65
21	-	CH_3CN	TBPB	N_2	70	30

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (1.6 mmol), catalyst (20 mol%), oxidant (2.4 mmol) in solvent (3.0 mL), performed in a nitrogen-purged tube at 70 °C, 23 h. TBHP = *tert*-Butyl hydroperoxide. TBPB = *tert*-Butyl peroxybenzoate. DTBP = Di-*tert*-butyl peroxide. [b] Isolated yield. [c] **2a** (0.8 mmol) was used. [d] **2a** (1.2 mmol) was used. [e] TBPB (1.6 mmol) was used.

With the optimized reaction conditions established, the scope of hydrazine substrates was next examined. Gratifyingly, the catalytic reaction proceeded smoothly with products afforded in moderate to good yields no matter the electron-donating (**3b**, **3d**, **3g**, **3k**) or electron-withdrawing groups (**3c**, **3e**–**3f**, **3h**–**3j**) were on the aryl ring of C1-position of products. Substrates bearing *ortho*- (**3b**–**3c**), *meta*- (**3d**–**3e**), *para*- (**3f**–**3k**) groups or with multi-substitutions (**3l**) all proceeded well. Furthermore, halo-subustituted phenylhydrazines (**3c**, **3e**–**3f**, **3h**–**3i**, **3l**) also accomplished the reactions smoothly with the halo-atoms still remained in the isoquinolines, which implied as the key intermediates for further transformation of these products in the classic cross coupling reactions. To our delight, hydrazines with heterocyclic substituent (**3m**) or ester group (**3n**) were also proved to be suitable components to react with isocyanide **1a** under the optimized conditions. It should be noted that 1-alkyl substituted isoquinolines (**3o**–**3s**) could be obtained in moderate to good yields, which would significantly expand the application scope of the reaction and provide a good complement and improvement to our previous work, where only aryl and limited alkenyl boronic acids could be used.[13] Additionally, alkyl hydrazines worked smoothly, not only for those with linear (**3o**, **3s)** or tertiary carbon center (**3p**), but also with cycloalkyl groups (**3q**–**3r**). 1-Phenethyl quinoline (**3s)** was achieved in 58% yield, however, no desired benzyl substituted isoquinoline product could be isolated from benzylhydrazine, while the corresponding benzoyl substituted product (**3t**) was isolated in 20% yield instead. The reason may be due to the rapid oxidation of generated 1-benzyl isoquinoline to the unusual 1-benzoyl product under the

Table 2 Scope of hydrazines[a,b]

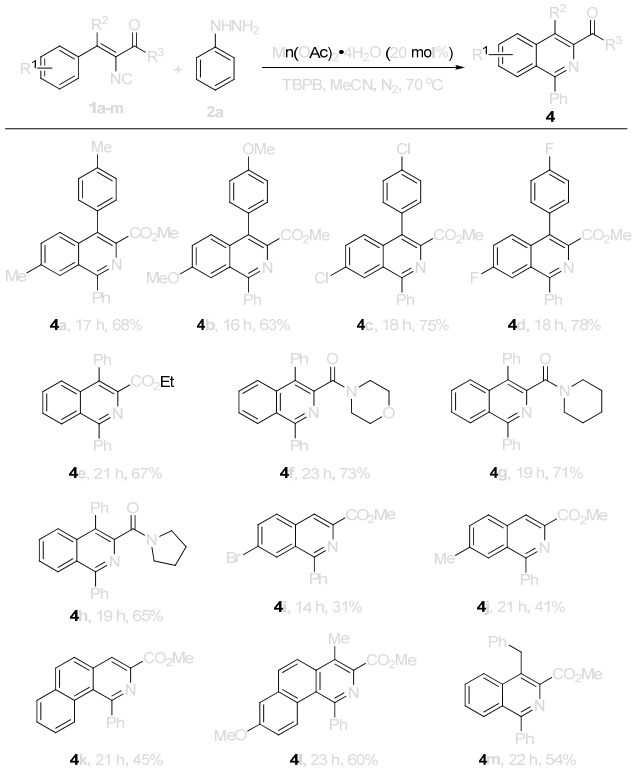


[a] Reaction conditions: the reaction was carried out with **1a** (0.4 mmol), **2a**–**t** (1.6 mmol), $Mn(OAc)_2{\cdot}4H_2O$ (0.08 mmol) and TBPB (2.4 mmol) in CH_3CN (3.0 mL) at 70 °C under nitrogen atmosphere. [b] Isolated yield. [c] *tert*-butylhydrazine hydrochloride or cyclopentylhydrazine hydrochloride was used in the presence of $NaHCO_3$ (5.0 equiv). [d] Benzylhydrazine was used as the substrate.

reaction conditions,[17a] while currently we can not rule out the possibility through the oxidative transformation of instable benzyl radical to corresponding benzoyl radical during the reaction.[17b-e]

To further study the generality and scope of this reaction, a variety of substituted vinyl isocyanides were investigated with phenyl hydrazine. As illustrated in Table 3, substrates with ester (**1a**–**1e**, **1i**–**1m**) and amide (**1f**–**1h**) substituents would proceed efficiently to afford the corresponding isoquinolines in moderate to good yields. Notably, vinyl isocyanides derived from diaryl ketones (**4a**–**4h**), alkyl aryl ketones (**4l**–**4m**) and aryl aldehydes (**4i**–**4k**) all proceeded smoothly under the optimized conditions to obtain the corresponding products, regardless of their different electronic properties and substitution positions. Furthermore, the product type was not limited to isoquinolines, the fused rings such as benzo[*h*]isoquinoline derivatives could also be produced successfully (**4k** and **4l**).

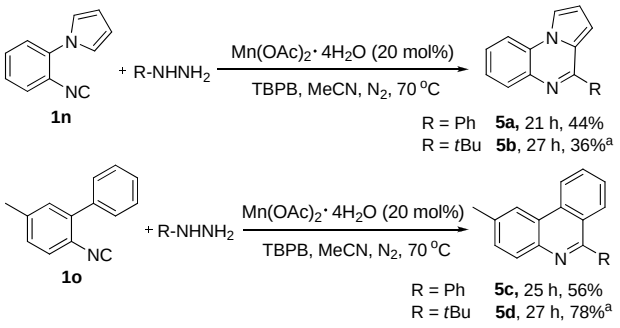
Table 3 Scope of vinyl isocyanides[a,b]



[a] Reaction conditions: the reaction was carried out with **1a**–**m** (0.4 mmol), **2a** (1.6 mmol), $Mn(OAc)_2{\cdot}4H_2O$ (0.08 mmol) and TBPB (2.4 mmol), in CH_3CN (3.0 mL) at 70 °C under nitrogen atmosphere. [b] Isolated yield.

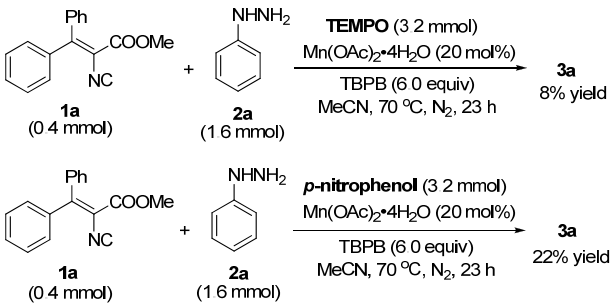
This newly established protocol was not limited to vinyl isocyanides, the substrate scope could also be extended further to include aryl isocyanides providing direct access to corresponding pyrrolo[1,2-*a*]quinoxalines (**5a**–**5b**) and phenanthridines products (**5c**–**5d**) in moderate to good yields (Scheme 2), which will further illustrate the broad substrate scope and product diversity of this reaction.

To understand the mechanism of this Mn(II)-catalyzed cyclization reaction, preliminary mechanistic investigation was carried out, as shown in Scheme 3. The reaction afforded **3a** in only 8% yield with the addition of 2,2,6,6-tetramethyl-piperidine-1-oxy (TEMPO) under the standard conditions, and the addition of *p*-nitrophenol would sluggish the reaction and decrease the product yield to 22%, which implied the reaction may experience a single electron transfer pathway.



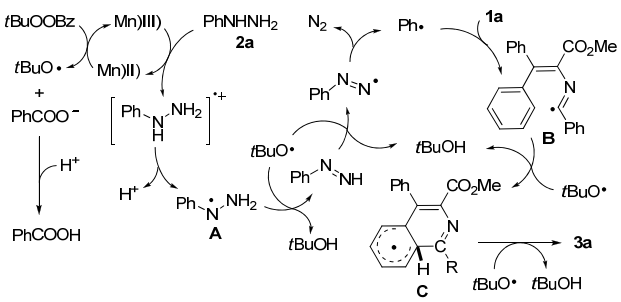
[a] tBuNHNH$_2\cdot$HCl was used in the presence of $NaHCO_3$ (5.0 equiv)

Scheme 2 Construction of other heterocyclic skeletons.



Scheme 3 Prevention reaction by radical inhibitors.

On the basis of above-mentioned experimental observations, a plausible mechanism was proposed for this radical cascade reaction (Scheme 4). Initially, *tert*-butoxy radical was generated from Mn(II) and TBPB by a single electron transfer process, together with the formation of Mn(III) and benzoate anion.[18] The given Mn(III) was then reacted with phenylhydrazine **2a** to afford the phenylhydrazine radical **A** through sequential single electron transfer and proton transfer steps, and the Mn(II) catalyst was regenerated to complete the catalytic cycle. With the assistance of *tert*-butoxy radical, the phenyl radical was formed through stepwise hydrogen abstractions with concomitant release of nitrogen gas.[19] The produced phenyl radical then underwent intermolecular addition to isocyanide **1a** to form the imidoyl radical **B**, which subsequently gave the cyclohexadienyl type radical **C** by a intramolecular attack of the imidoyl radical on the



Scheme 4 Plausible mechanism for synthesis of **3a** from **1a**.

aromatic ring. Finally, the isoquinoline **3a** could be afforded by another hydrogen abstraction from intermediate **C** in the presence of *tert*-butoxy radical with the release of *t*BuOH.

In conclusion, we have developed a manganese(II)-catalyzed cascade radical reaction from easily accessible vinyl isocyanides and hydrazines. This approach offers a unique strategy and alternative route for convenient preparation of pharmacologically interesting isoquinolines in moderate to good yields with wide substrate scope, good functionality tolerance and efficient synthesis modularity. The present manganese catalyst system was also successfully applied to the synthesis of valuable pyrrolo[1,2-*a*]quinoxalines and phenanthridines and a wide range of alkyl, (hetero)aryl and alkoxycarbonyl substitutions could be easily introduced by this method. Further insight into applications of this catalytic system are now undergoing in our laborotary.

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† Electronic Supplementary Information (ESI) available: General experimental procedures, characterization data and copies of the ^{1}H, ^{13}C and ^{19}F NMR spectra for all compounds. See DOI: 10.1039/x0xx00000x/

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