OL Organic Letters

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Au(I) Catalyzed Synthesis of Densely Substituted Pyrazolines and Dihydropyridines via Sequential Aza-Enyne Metathesis/6π-Electrocyclization

Kenji Sugimoto,* Shuto Kosuge, Takae Sugita, Yuka Miura, Kiyoshi Tsuge, and Yuji Matsuya*

Cite This: *Org. Lett.* 2021, 23, 3981−3985 Read Online

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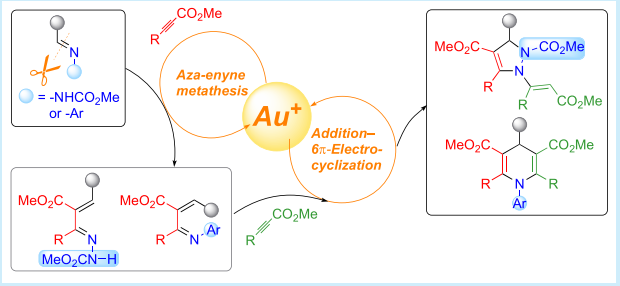
ABSTRACT: A gold(I) autotandem catalysis protocol is reported for the de novo synthesis of densely substituted pyrazolines and dihydropyridines from the corresponding imine derivatives in a highly regioselective fashion via a one-pot aza-enyne metathesis/6π-electrocyclization sequence. The substituents on the nitrogen atom of the imine perfectly control the reaction pathways from the pivotal 1-azabutadiene intermediate; thus, carbazates were converted into pyrazolines via 6π-electrocyclization of α,β-unsaturated hydrazones, while aryl imines provided dihydropyridines via 6π-electrocyclization of 3-azahexatrienes.



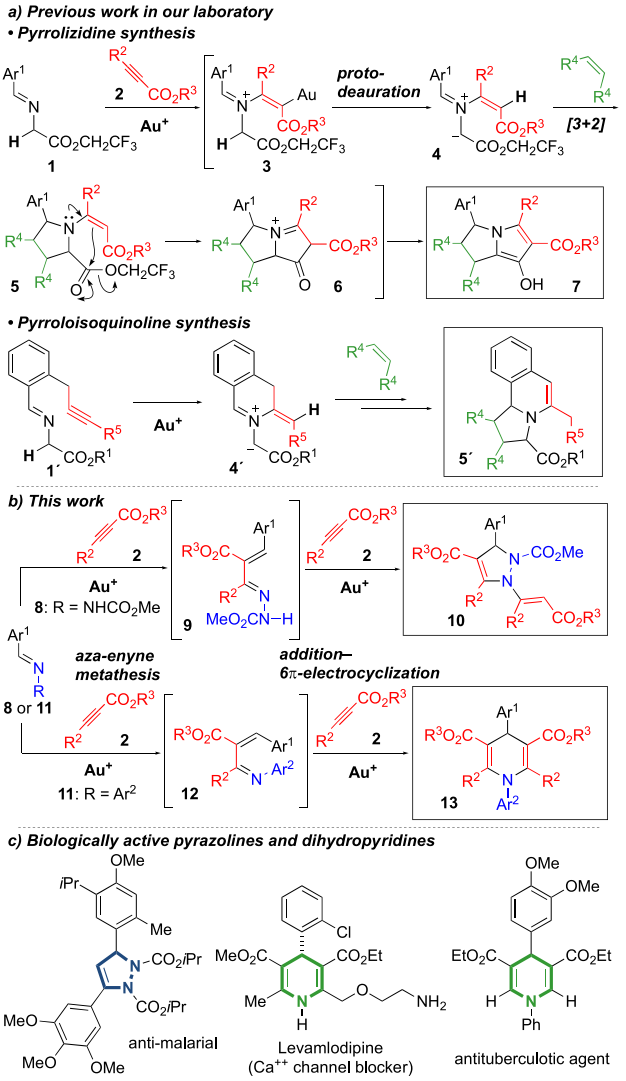
One-pot processes involving several transformations are regarded as highly practical and efficient for the concise construction of complex molecules[1] from the viewpoint of atom-[2] and step-economy.[3] Furthermore, one-pot processes that entail catalytic systems are recognized as being particularly efficient. Specifically, multiple catalytic transformations occurring in a single flask have recently been classified within tandem catalysis by Fogg and dos Santos.[4] Among them, autotandem catalysis is defined as an approach comprising mechanistically distinct multistep chemical transformations using a single catalyst.[5] Owing to the advantages of this approach, including ease of experimental operation and catalyst efficiency, autotandem catalysis is regarded as one of the most powerful and advanced synthetic tools. However, the optimization of reaction conditions for the chemoselective activation of several reactants in the appropriate order is highly challenging. Thus, the development of novel autotandem catalysts has received considerable attention in the field of synthetic organic chemistry.[6]

Our research group has developed a one-pot method for the construction of fused nitrogen heterocycles as well as novel gold-catalyzed cascade reactions yielding pyrrolizidines[7] and pyrroloisoquinolines[8] from imine derivatives (Scheme 1a). Pyrrolizidine **7** was accessed via enamine cyclization of pyrolidine **5**, generated from iminoester **1** and propiolate **2** by cycloaddition of azomethine ylide **4** in the presence of a cationic gold catalyst. The protocol was likewise applicable to an intramolecular variant, and pyrroloisoquinoline skeleton **5′** was satisfactorily constructed from alkynyl iminoester **1′**. These fused nitrogen heterocycles are important core structures of a variety of bioactive alkaloids. In the course of further investigations on the analogous imine derivatives, we discovered an unprecedented, one-pot, de novo pathway leading to densely substituted pyrazolines **10** or highly congested 1,4-dihydropyridines **13** (Scheme 1b), which are important synthetic pharmaceutical motifs (Scheme 1c).[9] The pathway involves gold autotandem catalysis, which includes aza-enyne metathesis[10] and an addition−6π-electrocyclization[11,12] sequence occurring via intermediate 1-azabutadienes **9** or **12**, respectively. Notably, the reaction course was completely regulated by the imine structure, that is, carbazates **8** yielded pyrazolines **10** and arylimines **11** yielded dihydropyridines **13**. Herein, we describe the details of this Au(I) autotandem catalyzed one-pot, de novo heterocycle formation[13,14] and the control thereof by substituents on the imine nitrogen atom.

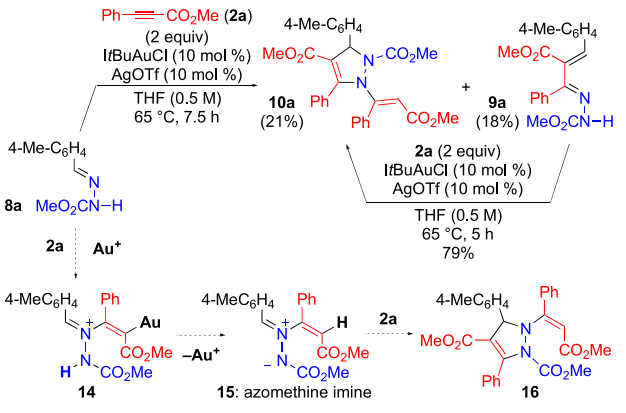
Our investigation commenced with the reaction of carbazate **8a** as the imine derivative with propiolate **2a** in the presence of a cationic gold catalyst (Scheme 2). When the reaction was conducted using the I*t*BuAuCl/AgOTf catalytic system, the desired pyrazoline product (21%) was obtained along with a considerable amount of side product. The pyrazoline product was initially presumed to be the structure **16**, which would be formed through the azomethine imine intermediate **15** via a pathway analogous to that shown in Scheme 1a. However, X-ray analysis revealed that the true structure of the pyrazoline was an isomer of **16**, depicted as **10a**. Furthermore, the side

Received: April 7, 2021
Published: May 12, 2021

Scheme 1. Au-Catalyzed De Novo Synthesis of Heterocycles

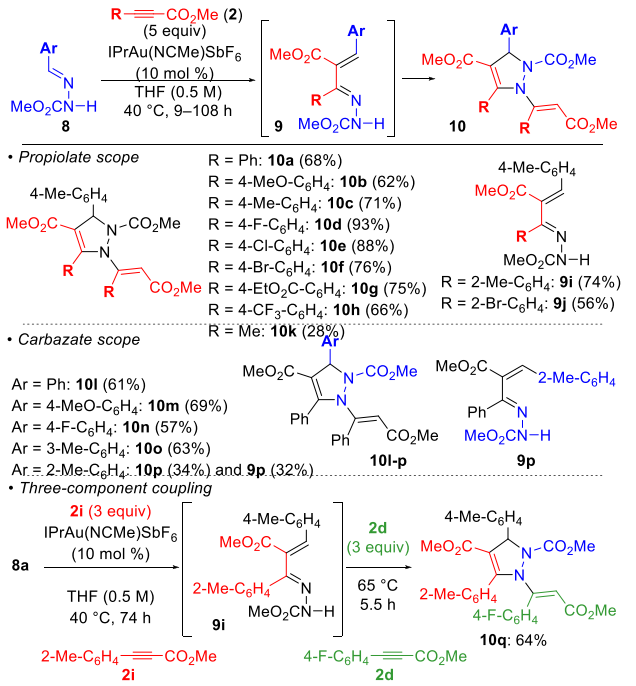


Scheme 2. Au-Catalyzed Pyrazoline Formation



product of the reaction was determined as being 1-azabutadiene **9a** (18%) by X-ray analysis,[15] and **9a** could be transformed into **10a** under the same Au-catalyzed conditions. These results implied that the overall reaction entailed aza-enyne metathesis and subsequent pyrazoline cyclization. Moreover, it was found that cationic gold was necessary for both steps of the reaction, and thus, this reaction system could be categorized as autotandem catalysis. To the best of our knowledge, the precedent work on an Au-catalyzed aza-enyne metathesis is limited to only one example.[10a] Furthermore, this is the first example of the autotandem Au-catalyzed pyrazoline formation involving aza-enyne metathesis.[16] Gratifyingly, we successfully optimized the one-pot conditions for the formation of pyrazoline **10a** (see the Supporting Information for details), which was obtained in 68% yield by heating **8a** in the presence of methyl phenylpropiolate (**2a**) (5 equiv) and IPrAu(NCMe)SbF_6[17] (10 mol %) in THF at 40 °C for 10 h (shown in Scheme 3).

Scheme 3. Reaction Scope of Pyrazoline Formation



The reaction scope for pyrazoline formation is shown in Scheme 3. Propiolates equipped with electron-rich or electron-poor aromatic rings at their termini were both suitable reaction substrates, providing densely substituted pyrazolines. Among them, halogenated aromatic rings gave the corresponding pyrazolines **10d–f** in high yields. Substitution with electron-withdrawing groups, $-CO_2Et$ and $-CF_3$, resulted in the generation of **10g** and **10h**, respectively. On the other hand, steric bulkiness around the triple bond prevented the second cyclization step, and 1-azabutadienes **9i** and **9j** were isolated instead. 3-Alkyl propiolate could be utilized in our system to deliver densely substituted pyrazoline **10k**. Furthermore, phenyl, 4-anisyl, and 4-fluorophenyl carbazates were applicable to the reaction, and the desired densely substituted pyrazolines **10l–n** were obtained in moderate to good yields. 3-Tolyl carbazate afforded the corresponding pyrazoline **10o** uneventfully; however, the reaction with the sterically congested 2-tolyl group resulted in a mixture of 1-azabutadiene **9p**[18] and pyrazoline **10p**. The observation that sterically demanding propiolate **2i** gave 1-azabutadiene **9i** without proceeding to the cyclization step suggested the possibility of stepwise incorporation of propiolate components into the pyrazoline product. In fact, we accomplished a one-pot, three-component assembly using **2i** to obtain **10q**, wherein a second propiolate, **2d**, was

https://doi.org/10.1021/acs.orglett.1c01171
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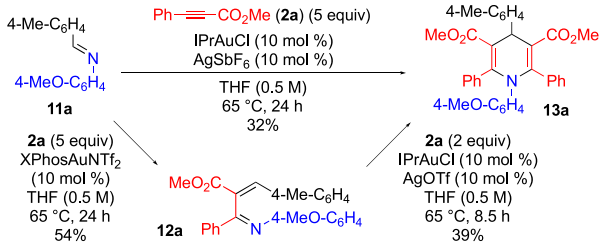
incorporated at an elevated temperature as the pendant substituent. This result implied that the gold-catalyzed N−C bond formation between 1-azabutadiene **9i** and the activated propiolate induced the 6π-electrocyclization to form the pyrazoline.

In parallel with our efforts on pyrazoline synthesis, we attempted to exploit the potential of *N*-arylimines as simple imine derivatives for autotandem Au-catalyzed reactions with propiolates. As expected, the reaction of aryl imine **11a** with propiolate **2a** proceeded with a 1:2 stoichiometry (one **11a** to two **2a** molecules) in the presence of IPrAuCl and $AgSbF_6$ (Scheme 4). Structural analyses revealed that the major

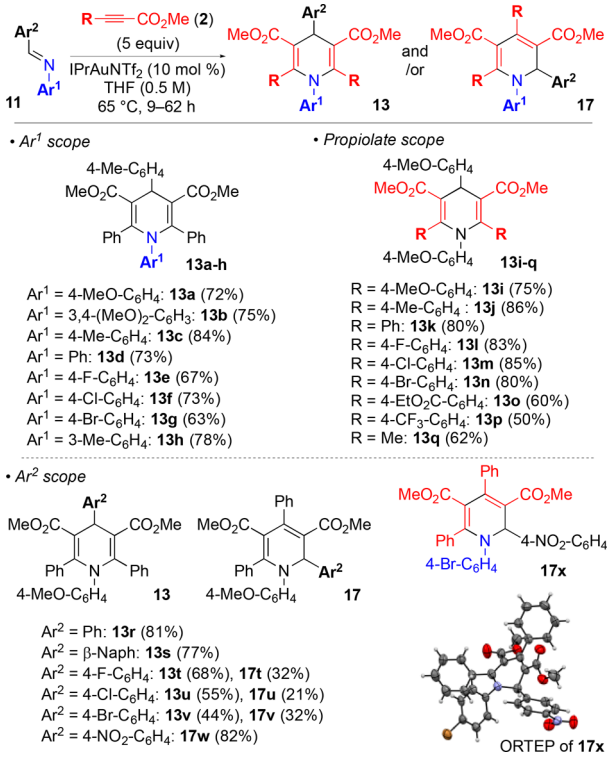
Scheme 4. Validation of Reaction Pathway for 1,4-Dihydropiridine formation



product was fully substituted 1,4-dihydropyridine **13a**. When using $XPhosAuNTf_2$,[19] the reaction terminated at the aza-enyne metathesis step to give 1-azabutadiene **12a**, which could be transformed into **13a** by further exposure to the gold catalyst. On the other hand, neither aza-enyne metathesis nor annulation could proceed at all in the absence of the gold catalyst. Thus, two distinct processes were catalyzed by a single cationic gold autotandem catalyst, as in the case of pyrazoline formation. After optimization of the autotandem catalysis conditions for 1,4-dihydropyridine formation (see the Supporting Information for details), imine **11a** and propiolate **2a** were converted into desired **13a** (72%) in the presence of $IPrAuNTf_2$[20] at 65 °C within 24 h in THF (shown in Scheme 5).

With the optimal conditions in hand, we investigated the scope and limitations of the transformation (Scheme 5). As for Ar^1, electron-rich or electron-deficient aryl groups were introduced into the dihydropyridine nucleus in satisfactory yields (**13a−g**). The substituent at the 3-position on the aryl group did not influence the reaction efficiency (**13b** and **13h**). The structures were unambiguously determined by X-ray crystallographic analyses of **13c** and **13g**. In particular, the structure of **13g** indicated that only the C=N bond of the imine was rearranged in the reaction. The propiolates possessing not only electron-rich aromatic groups but also halogenated or highly electron-deficient aromatic rings could participate in the reaction (**13a−p**). Methyl tetrolate (R = Me) gave the corresponding 2,5-dimehyl-1,4-dihydropyridine **13q** in satisfactory yield. Conversely, the electronic properties of the aryl group on the imine carbon had a marked effect on the reaction outcome (Ar^2 scope in Scheme 5). While **11** with the electron-donating group, phenyl, and sterically demanding β-Naph groups uneventfully gave the 1,4-dihydropyridines **13r−s** in good yield, derivatives of **11** bearing electron-deficient aromatic groups produced a mixture of 1,4-dihydropyridine **13t−v** and 1,2-dihydropyridines **17t−v**. Moreover, in the case of a nitro-substituted aromatic ring, 1,2-dihydropyridine **17w**

Scheme 5. Reaction Scope of 1,4-Dihydropyridine formation

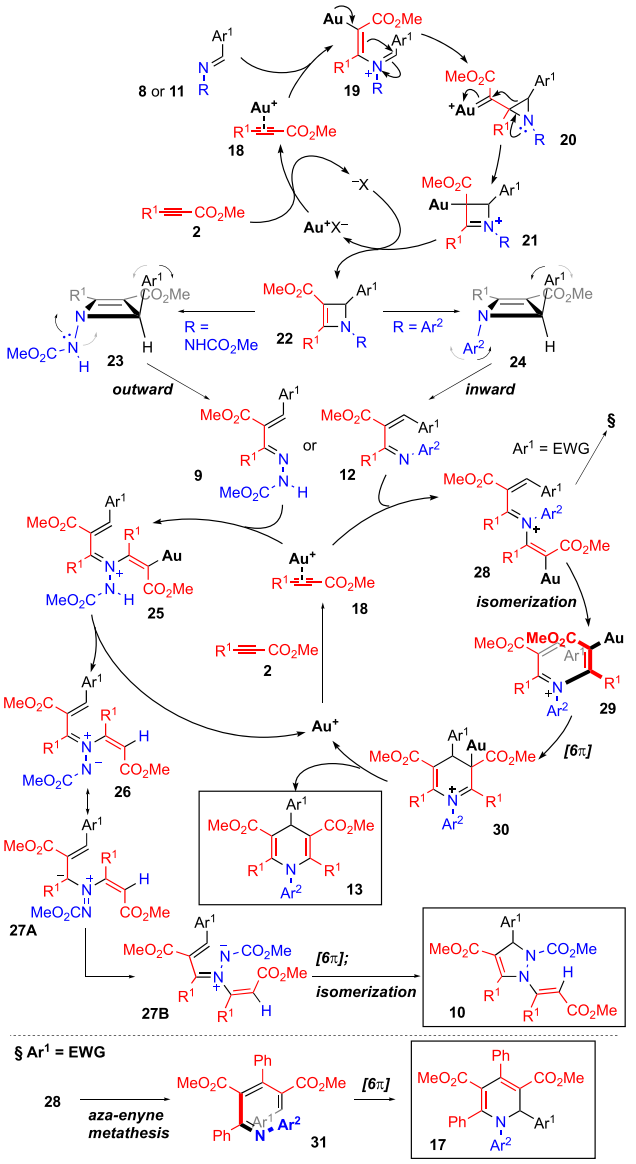


was generated exclusively. The structures of the 1,2-dihydropyridines were determined by comparison of their ^1H NMR spectra with that of **17x**, the structure of which was elucidated by X-ray crystallography. It is important to note that the positions of the aromatic substituents (Ar^2 and Ph) in 1,2-dihydropyridines **17** are switched in 1,4-dihydropyridine **13**, indicating that **17** is not derived from **13** through a simple isomerization of the double bond. Therefore, an independent pathway for the formation of 1,2-dihydropyridines **17** should be considered with a reasonable rationale for the observed reaction outcome leading to **13** or **17** (vide infra).

A plausible reaction mechanism is postulated in Scheme 6. Propiolate **2** can be activated by cationic gold to generate **18**, which undergoes carbazate **8** (or imine **11**) attack at the β-position to give iminium **19**.[21] Then internal electron transfer from vinyl Au to the iminium nitrogen of **19** generates aziridine **20**, which is rearranged to azetinium **21** with the assistance of the electrophilic cationic gold carbenium moiety.[10a,22] The cationic gold catalyst is regenerated from **21** to give the azetine **22**, the precursor for the 4π-ring opening reaction[23] that results in 1-azabutadienes **9** and **12**. The torquoselectivity in the ensuing 4π-ring opening step was directed by the R substituents on the nitrogen atom in the azetine **22**. When R = $-NHCO_2Me$ (**23**), the stereoelectronic effect dominates over the steric repulsion between R and R^1, and the lone pair on the exocyclic nitrogen atom stabilizes the σ^*_{N-C} to accelerate outward selective ring opening and generate 1-azabutadiene **9**. 1-Azabutadiene **9** then attacks a second molecule of **18** to yield **25**, the subsequent protodeauration of which gives ylide **26**, which can be smoothly isomerized into **27B** via **27A**. Finally, 6π-electrocyclization of the α,β-unsaturated hydrazone **27B** and subsequent isomerization of the pendant enamide moiety

https://doi.org/10.1021/acs.orglett.1c01171
Org. Lett. 2021, 23, 3981−3985

Scheme 6. Plausible Mechanism for the Reaction Cascade



provides pyrazoline **10**. On the other hand, when R = Ar^2 (**24**), the aforementioned stereoelectronic effect would be limited, and the Ar^2 on the azetine **24** induces inward selective ring cleavage, avoiding steric repulsion with the R^1 group to form 1-azabutadiene **12**. From the ORTEP diagram for **12a**, it is inferred that 1-azabutadiene is likely be twisted by the steric repulsion of the substituents and no longer in the planar conformation for the concerted [4 + 2] cycloaddition. Therefore, the stepwise addition−6π-electrocyclization mechanism would be suitable for the annulation step. The nucleophilic attack of **12** on **18**, followed by isomerization at the cationic C═N bond, furnishes 3-azahexatriene **29**. Finally, 6π-electrocyclization of **29** and regeneration of the cationic gold delivers 1,4-dihydropyridine **13**.[24]

When the Ar^1 is an electron-withdrawing group, the isomerization of **28** to 3-azahexatriene **29** would be restricted due to diminished polarization of the iminium moiety and the aza-enyne metathesis process of **28** via **20**−**24** would be dominant. Subsequent 6π-electrocyclization of the resulting 3-azahexatriene **31** affords 1,2-dihydropyridine **17**. The outcomes of experiments with deuterated substrates, which indicated that the reaction proceeded via metathesis between the C═N and the triple bond, were consistent with the mechanism described above (see the Supporting Information).

In summary, we have unveiled a novel Au(I) autotandem catalytic system that enables de novo syntheses of pyrazolines and dihydropyridines via aza-enyne metathesis followed by 6π-electrocyclization. This procedure realizes the ready access to densely substituted pharmacologically important heterocycles through a simple experimental operation. These findings, in addition to our previous reports,[7,8] would provide a useful strategy for constructing various versatile heterocyclic systems (pyrrolizidines, pyrroloisoquinolines, pyrazolines, and dihydropyridines) simply by changing the substituents on the imine substrates. Further investigation of the reactions and biological evaluation of the products are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01171.

Experimental procedures, characterization data for new compounds, additional experiments, and spectral data (PDF)

Accession Codes

CCDC 2072699−2072705 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Kenji Sugimoto − *Faculty of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan;* orcid.org/0000-0003-3735-9343; Email: ksugimo@pha.u-toyama.ac.jp

Yuji Matsuya − *Faculty of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan;* orcid.org/0000-0002-1073-9525; Email: matsuya@pha.u-toyama.ac.jp

Authors

Shuto Kosuge − *Faculty of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan*

Takae Sugita − *Faculty of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan*

Yuka Miura − *Faculty of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan*

Kiyoshi Tsuge − *Faculty of Science, University of Toyama, Toyama 930-8555, Japan;* orcid.org/0000-0003-1536-3261

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01171

Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acs.orglett.1c01171
Org. Lett. 2021, 23, 3981−3985

■ ACKNOWLEDGMENTS

This work was financially supported by JSPS KAKENHI Grant No. JP17K08207 and ASAHI KASEI PHARMA Award in Synthetic Organic Chemistry, Japan.

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(24) Although gold-catalyzed Hantzsch-type 1,4-dihydropyridine synthesis has been reported,[14b] the amine component is limited to $MeNH_2$ and aniline could not participate in the reaction. Therefore, that report could be distinguished from our aza-enyne metathesis/6π-electrocyclization sequence.

https://doi.org/10.1021/acs.orglett.1c01171
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