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Synthesis of substituted anilines via a goldcatalyzed three-component reaction[†]

Hirofumi Ueda, Ryota Yamamoto, Minami Yamaguchi and Hidetoshi Tokuyama 🕑 *

A three-component reaction for the synthesis of substituted anilines by a gold(i)-catalyzed domino reaction was developed. Cationic gold catalysts selectively and sequentially activated two different alkynes, which were involved in pyrrole synthesis and subsequent Diels–Alder reaction. The sequential formal (3 + 2) annulation/Diels–Alder reaction of three components provided a variety of substituted anilines in a modular fashion. Moreover, utility of the aniline products was demonstrated by derivatization to substituted benzoxazines, which are pharmaceutically important heterocycles.

Multicomponent reaction is a powerful tool for construction of complex molecules by integrating multiple molecules in a single flask.¹ Owing to its rapidity, convergency, versatility, and easy experimental operation, multicomponent reaction has attracted considerable attention in the area of synthetic organic chemistry.²⁻⁴ However, it is highly challenging to conduct mechanistically distinct sequential reactions with chemoselective activation of each substrate or intermediate and even more difficult when applied to a catalytic process. Recently, development of tandem catalysis, which consists of sequential catalytic cycles, is one of the most studied research topics in the area of catalysis.⁵ Generally, tandem catalysis is classified into three modes: first is hybrid catalysis (also known as orthogonal catalysis), which involves functionally distinct and noninterfering catalysts;⁶ second is auto-tandem catalysis, where a single catalyst promotes mechanistically distinct sequential reactions;⁷ and third is assisted tandem catalysis, where the *in situ* change of catalyst activity is induced by additives or the change of reaction conditions.⁸

Recently, we developed a versatile synthesis of substituted pyrroles through gold-mediated auto-tandem catalysis (Fig. 1a).⁹ The gold catalyst promotes the initial alkynylation of

E-mail: tokuyama@mail.pharm.tohoku.ac.jp

acetal *via* activation of the nucleophilicity of a terminal alkyne as a gold acetylide and subsequent intramolecular hydroamination on an internal alkyne *via* activation of its electrophilicity by π -coordination.¹⁰ In this research, we designed a threecomponent auto-tandem catalytic reaction for the synthesis of substituted anilines by the integration of pyrrole synthesis and subsequent Diels–Alder reaction with the additional alkyne. Herein, we described the novel aniline synthesis from three



Fig. 1 (a) Au(*i*)-Catalyzed substituted pyrrole synthesis *via* auto-tandem catalysis involving activation of nucleophilicity and electrophilicity of acetylenes (previous study). (b) Working hypothesis for the synthesis of substituted anilines through a Au-mediated multicomponent reaction.

Graduate School of Pharmaceutical Sciences, Tohoku University Aoba 6-3, Aramaki, Aoba-ku, Sendai, Miyagi 980-8578, Japan.

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components in the presence of a cationic gold catalyst and its application toward synthesis of benzoxazines.

The working hypothesis of the auto-tandem catalytic threecomponent reaction based on the selective activation of two different alkynes owing to the π -philicity of gold catalysts is shown in Fig. 1b. First, the abovementioned pyrrole formation would proceed by a reaction between aminoacetoaldehyde acetal and terminal alkyne *via* two catalytic cycles. Then, subsequent Diels–Alder reaction between the pyrrole and electrondeficient acetylene would be facilitated by the gold catalyst to provide 7-azabicyclo[2.2.1]heptane intermediate. Finally, cleavage of the C–N bond, followed by aromatization, would furnish the substituted anilines.¹¹ To examine the working hypothesis, a mixture of acetal amide 1^{12} and two different alkynes 2a and 3a was subjected to the conditions previously established for the pyrrole synthesis (Table 1, entry 1). As expected, aniline 4aa *via* the three-component reaction was obtained; however, the yield was only 25%. No aniline product due to Diels–Alder reaction with 2a was at all detected. With this promising result, we then conducted extensive optimizations. Changing solvent to xylene was not effective (entry 2). However, conducting the reaction at a higher reaction temperature and under more concentrated condition effectively reduced the reaction time and improved the yield of 4a (up to 47%, entries 3–5). Next, we surveyed a series of cationic gold catalysts and additives (entries 6–12).¹³

Table 1 Condition optimization

	i-PrO i-PrO 1	$HBz + \begin{vmatrix} H & CO_2Me \\ HBz + \end{vmatrix} + \begin{vmatrix} H & CO_2Me \\ Ph & CO_2Me \\ 2a & 3a \\ (5 equiv) & (5 equiv) \end{vmatrix}$	Catalysts (10 mol%) Solvent (x M) Temp., Time Ph 4aa	•	
Entry	Catalyst [10 mol%]	Solvent (\times M)	Temp. [°C]	Time [h]	Yield ^a [%]
1	RuPhosAuCl I, AgOTf	Toluene (0.1)	125	45	25
2	RuPhosAuCl I, AgOTf	Xylene (0.1)	125	45	27
3	RuPhosAuCl I, AgOTf	Xylene (0.1)	140	20	28
4	RuPhosAuCl I, AgOTf	Xylene (0.1)	160	22	42
5	RuPhosAuCl I, AgOTf	Xylene (0.25)	160	9	47
6	RuPhosAuCl I, AgBF ₄	Xylene (0.25)	160	50	9
7	JohnPhosAuCl II, AgOTf	Xylene (0.25)	160	9	47
8	IPrAuCl III, AgOTf	Xylene (0.25)	160	36	46
9	[(RuPhosAu) ₂ Cl]OTf IV	Xylene (0.25)	160	36	58
10	[RuPhosAu(BTZ-H)]OTf V	Xylene (0.25)	160	50	39
11	Ph ₃ PAu(BTZ-H)]OTf VI	Xylene (0.25)	160	50	21
12	[IPrAu(BTZ-H)]OTf VII	Xylene (0.25)	160	10	76
13	[IPrAu(BTZ-Me)]OTf VIII	Xylene (0.25)	160	17	75
14^b	[IPrAu(BTZ-H)]OTf VII	Xylene (0.25)	160	11	80
15^{c}	[IPrAu(BTZ-H)]OTf VII	Xylene (0.25)	160	20	67
$16^{b,d}$	[IPrAu(BTZ-H)]OTf VII	Xylene (0.25)	160	6.5	64
$17^{b,e}$	[IPrAu(BTZ-H)]OTf VII	Xylene (0.25)	160	10	61

^{*a*} Isolated yield. ^{*b*} The catalytic amount was 5 mol%. ^{*c*} The catalytic amount was 3 mol%. ^{*d*} Under microwave irradiation. ^{*e*} The corresponding dimethyl acetal was used instead of **1**.



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Addition of AgBF4 instead of AgOTf resulted in deceleration of the reaction and low yield (entry 6). Reaction using JohnPhosAuCl II and IPrAuCl III (entries 7 and 8) provided comparable results with those obtained with RuPhosAuCl I. Then, we examined a series of thermally stable cationic gold catalysts. A binuclear gold complex¹⁴ with RuPhos ligand increased the reaction time, but the yield of 4aa was slightly improved (entry 9). Screening of several gold-benzotriazole complexes¹⁵ revealed that the cationic gold catalyst having both N-heterocyclic carbene and benzotriazole ligands produced 4aa with the highest yield (76%) (entries 10-12). Although a new catalyst was synthesized with the expectation of a more stable cationic gold catalyst, the condition with [IPrAu(BTZ-Me)]OTf VIII increased the reaction time (entry 13). The catalyst loading was reduced from 10 to 5 mol% without the loss of the 4aa yield (entry 14). To shorten the reaction time, the reaction was conducted under microwave irradiation. We observed acceleration of reaction, however yield of aniline 4aa was slightly decreased (entry 16). While an amide having dimethyl acetal could be used instead of diisopropyl acetal 1, vield of aniline 4aa was slightly decreased (entry 17).¹⁶

Having established the optimal conditions, we then focused on the scope of acetylenes (Table 2). First, the scope of terminal acetylenes was investigated using various aryl and alkyl acetylenes. Phenyl acetylenes bearing methoxy group, methyl group, halogen atoms, and methoxy carbonyl group provided the corresponding anilines in moderate to high yields (entries 2–6). Reaction using phenylacetylene having protected amino group on the *para*-position gave **4ga** in low yield after a longer reaction time (entry 7). Nitro group was not compatible with the reaction, and the desired aniline **4ha** was not obtained (entry 8). In this case, formation of the expected



^a Isolated yield.

2-nitropyrrole intermediate was observed, suggesting that this failure could be attributed to the signifiantly low HOMO energy level of the 2-nitropyrrole intermediate to undergo Diels–Alder reaction. *Meta-* and *ortho-*methoxy-substituted phenylacetylene and 1-naphthyl acetylene gave the desired aniline **4ia–4ka** in high yields (entries 9–11). Eneyne and diyne also served as good substrates in the gold-catalyzed three-component reaction to provide desired anilines **4la** and **4ma** (entries 12 and 13). Finally, an aliphatic terminal alkyne (1-heptyne) was also feasible for the reaction (entry 14).

Next, the scope of electron-deficient acetylenes working as dienophiles for the Diels–Alder reaction was studied (Table 3). Internal acetylenes possessing two ethoxycarbonyl and iso-pro-poxycarbonyl groups instead of methoxycarbonyl group uneventfully afforded the corresponding anilines in high yields (entries 2 and 3). In contrast, the expected reaction did not proceed at all while using sterically hindered internal acetylene and terminal acetylene (entries 4 and 5).

To demonstrate the utility of the highly substituted aniline products, we transformed them to pharmaceutically important benzoxazine derivatives¹⁷ (Scheme 1). First, one of the two





^a Isolated yield.



Scheme 1 Derivatization of the synthesized substituted aniline to two types of benzoxazine derivatives.

Table 4 Control experiments in the Diels-Alder reaction



ester groups in 4 was chemoselectively saponified with KOH in MeOH.¹⁸ Then, the resultant anthranilic acid derivative 5 was treated with acetic anhydride to furnish 2,5,6-trisubstituted benzoxazine (Scheme 1a). Transformation to an isomeric benzoxazine derivative was initiated by Curtius rearrangement¹⁹ of anthranilic acid derivative 5 to give amino anthranilic acid ester 7. Finally, 2,5,8-trisubstituted benzoxazine **8** was obtained by the method used in Scheme 1a involving acylation, saponification, and cyclization, respectively.

To gain mechanistic insight regarding the role of the cationic gold catalyst in the sequential reaction especially for the Diels-Alder reaction step, we performed a series of control experiments (Table 4). Initially, a mixture of separately prepared pyrrole 9 and dimethyl acetylenedicarboxylate 3a was heated in the absence of catalyst. The expected Diels-Alder reaction and subsequent aromatization completed after 20 h to give the aniline 4aa in 61% yield (entry 1). The reaction time was substantially reduced with the addition of [IPrAu(BTZ-H)] OTf VII, and the reaction completed after 8 h (entry 2), indicating that the cationic gold catalyst promoted the Diels-Alder reaction step. To exclude the possibility of acceleration by a certain Brønsted acid species²⁰ generated from the gold catalyst, the Diels-Alder reaction was conducted in the presence of [IPrAu(BTZ-H)]OTf VII and 2,6-di-tert-pyridine (an acid scavenger). However, we observed no change in the reaction time and yield (entry 3). Finally, we confirmed that the Diels-Alder reaction was not affected by 1,2,3-benzotriazole, which could be generated by the decomposition of [IPrAu(BTZ-H)]OTf VII (entry 4).

Conclusions

In summary, we developed a novel synthesis of substituted aniline through auto-tandem catalytic three-component reaction using aminoacetoaldehyde acetal, two different acetylenes, and a cationic gold catalyst. The protocol is advantageous for divergent synthesis of a variety of substituted aniline derivatives in a modular fashion by simply changing the combination of three components. The successful sequential three-component reaction relied on the participation of the cationic gold catalyst in three distinct catalytic processes with selective activation of two different alkynes *via* gold acetylide and selective π -coordination: addition of terminal acetylene to the acetal component, intramolecular hydroamination, and Diels–Alder reaction.

Conflicts of interest

There are no conflicts to declare.

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