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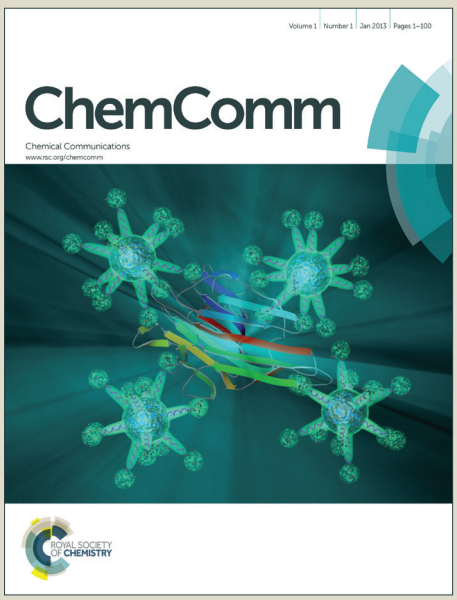

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Ag(I)-Catalyzed Tandem [6 + 3] Annulation/Isomerization of Isocyanoacetates with Fulvenes: An Expedient Approach to Fused Dihydropyridines

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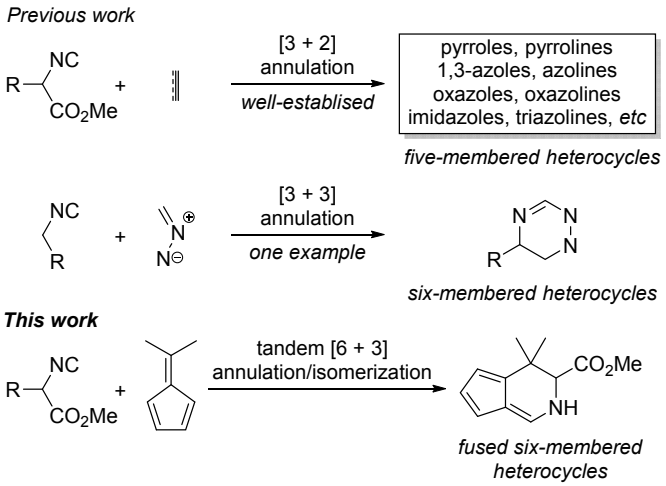
Zhao-Lin He,[a] and Chun-Jiang Wang[a,b]*

An unprecedented Ag(I)-catalyzed tandem [6 + 3] cycloaddition/isomerization of isocyanoacetates with fulvenes has been developed, affording the fused dihydropyridine derivatives in good yields with exclusive regioselectivities.

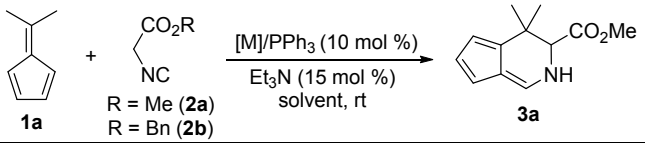
Intermolecular cycloadditions are the most efficient and powerful tools for the straightforward synthesis of diverse carbo- and heterocycles with molecular complexity from simple and readily-available starting materials.[1] Cyclization of isocyanides with carbon-carbon and carbon-heteroatom multiple bonds have proved to be a reliable platform for the concise construction of biologically active heterocycles.[2] The unique divalent property of isocyano group renders isocynides functions as both nucleophilies and electrophiles, and has made them as indispensable reagents in organic synthesis.[3] In particular, α-acidic isocyanoacetates, have been successfully utilized as crucial building blocks in [3 + 2]-cycloaddition reaction for the facile access to pyrrole,[4] pyrroline,[5] oxazoline,[6] oxazole,[7] imidazole,[8] and triazolines,[9] etc (Scheme 1).

Scheme 1. Isocyanoacetates as Hetero Three-Atom Synthons in [3 + 2], [3 + 3] (Previous Work) and [6 + 3] Cycloaddition (This Work).



In contrast, higher-order cycloaddition using isocyanides as the hetero three-atom synthons has received much less attention although such reaction models may provide the potential for the direct synthesis of a diverse array of non-five membered heterocycles. Most recently, a formal [3 + 3]-cycloaddition of isocyanoacetate with azomethine imines for the synthesis of 1,2,4-trizaoles was reported by Liu and co-workers.[10] However, to our knowledge, there has been no example of [6 + 3]-cycloaddition of isocyanoacetate so far. As part of our ongoing research interest in developing high order cycloaddition reactions,[11] herein, we reported the first example of Ag(I)-catalyzed tandem [6 + 3]-cycloaddition of isocyanoacetates with fulvenes followed by isomerization, affording the bioactive dihydropyridines[12] with exclusive regioselectivity.

Table 1. Optimization of tandem [6 + 3] annulation/isomerization of methyl 2-isocyanoacetate **2a** with fulvene **1a**[a]



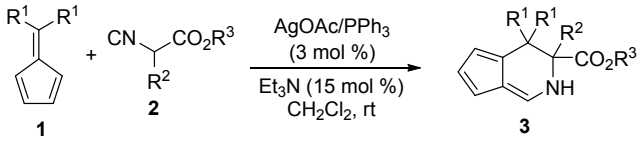
1a **3a**

Entry	[M]	Solvent	Time (h)	yield (%)[b]
1	AgOAc	CH_2Cl_2	3	87
2[c]	AgOAc	CH_2Cl_2	24	33
3[d]	AgOAc	CH_2Cl_2	24	30
4	$CuBF_4$	CH_2Cl_2	24	trace
5	AgOAc	$CHCl_3$	3	78
6	AgOAc	THF	3	78
7	AgOAc	PhMe	24	46
8	AgOAc	Et_2O	24	80
9[e]	AgOAc	CH_2Cl_2	12	90
10[e,f]	AgOAc	CH_2Cl_2	12	95

[a] All reactions were carried out with 0.6 mmol of **1a** and 0.4 mmol of **2a** in 2 mL of solvent. [b] Isolated yield. [c] Without Et_3N. [d] Without PPh_3. [e] 3 mol % catalyst loading. [f] Benzyl 2-isocyanoacetate **2b** was employed.

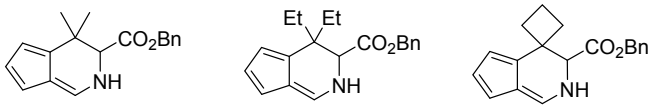
Our studies began with the examination of isocyanoacetate **2a** and fulvene **1a** with the AgOAc/PPh_3 as the catalyst and Et_3N as the base at room temperature in dichloromethane. To our delight, the reaction finished smoothly in 3 h, the tandem cycloaddition/isomerization product **3a** was obtained in 87% yield (Table 1, entry 1). Control experiments revealed that the absence of PPh_3 or base retarded the reaction remarkably (entries 2 and 3). No cycloaddition occurred when using Cu(I)/PPh_3 as the catalyst (entry 4). Other silver salts, such as $AgNO_3$, Ag_2CO_3 and $AgClO_4$, promoted this annulation albeit with a slightly lower yields. The evaluation of the solvent effect indicated that dichloromethane is the best solvent in terms of reaction rate and the yield (entry 1 and 5-8). The catalyst loading was successfully reduced to 3 mol % without loss of the reactivity and yield (entry 9). Variation of the ester group from methyl to benzyl has marginal influence on this reaction (entry 10).

Table 2. Substrate scope for Ag(I)-catalyzed tandem [6 + 3] annulation/ isomerization of 2-isocyanoacetate **2** with symmetrical fulvenes **1**[a]

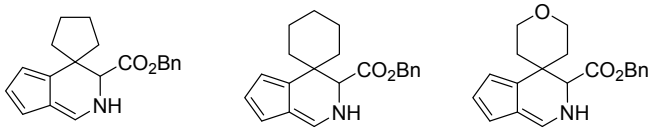


1 + **2** → **3**

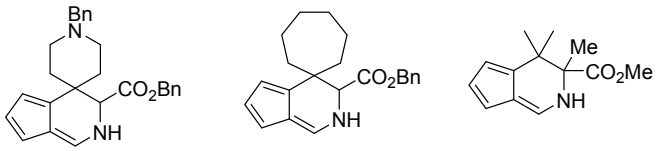
2a: R^2 = H, R^3 = Me
2b: R^2 = H, R^3 = Bn
2c: R^2 = Me, R^3 = Me
2d: R^2 = Pr, R^3 = Me
2e: R^2 = Bn, R^3 = Me



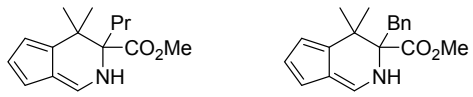
(**3b**) entry 1: 95% yield[b] (**3c**) entry 2: 78% yield[b] (**3d**) entry 3: 81% yield[b]



(**3e**) entry 4: 86% yield[b] (**3f**) entry 5: 78% yield[b] (**3g**) entry 6: 67% yield[b]



(**3h**) entry 7: 75% yield[b] (**3i**) entry 8: 77% yield[b] (**3j**) entry 9: 81% yield[b]

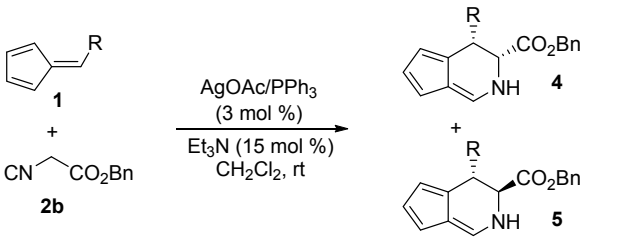


(**3k**) entry 10: 73% yield[b] (**3l**) entry 11: 72% yield[b]

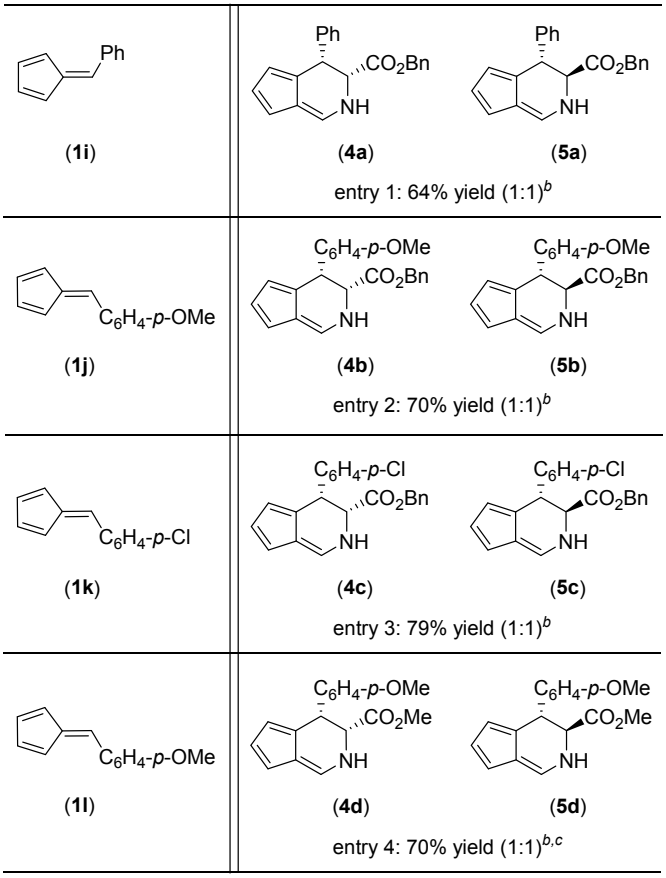
[a] All reactions were carried out with 0.6 mmol of **1** and 0.4 mmol of **2** in 2 mL of CH_2Cl_2. [b] Isolated yield.

With the optimal conditions established above, the substrate scope was investigated with various fulvenes and isocyanoacetates to test the generality of this annulation. As summarized in Table 2, the symmetrical fulvene **1b** derived from pentan-3-one proved to be viable substrate giving rise to the desired adduct **3c** in good yield (Table 2, entry 2). Symmetrical fulvenes derived from cyclic ketones were further evaluated. It was found that the tested fulvenes bearing different ring sizes have little influence on efficiency of the reaction (entries 3-8). Cyclic fulvenes derived from tetrahydro-4*H*-pyran-4-one and 1-benzylpiperidin-4-one was also compatible in this transformation delivering the corresponding adducts **3g** and **3h** in good yield (entries 6 and 7). In order to probe the feasibility for constructing fused pyridines bearing a quaternary center, the bulky α-branched isocyanoacetates have been examined. To our delight, under the optimal reaction conditions, good yield and high reactivity were observed for various α-substitution groups (entries 9-11), which highlighted the generality of this novel annulation.

Table 3. Substrate scope for tandem [6 + 3] annulation/isomerization of benzyl 2-isocyanoacetate **2b** with unsymmetrical fulvenes **1**[a]



1 + **2b** → **4** + **5**



(**1i**) → (**4a**) (**5a**) entry 1: 64% yield (1:1)[b]

(**1j**) → (**4b**) (**5b**) entry 2: 70% yield (1:1)[b]

(**1k**) → (**4c**) (**5c**) entry 3: 79% yield (1:1)[b]

(**1l**) → (**4d**) (**5d**) entry 4: 70% yield (1:1)[b,c]

[a] All reactions were carried out with 0.6 mmol of **1** and 0.4 mmol of **2** in 2 mL of CH_2Cl_2. [b] Isolated yield. [c] **2a** was used instead of **2b**.

Encouraged by the results with the symmetrical fulvenes, we next focused on the unsymmetrical fulvenes derived from aldehydes, and the representative results are tabulated in Table 3. In general, the unsymmetric fulvenes bearing one terminal substituent group

displayed much higher reactivity compared with the symmetrical fulvenes bearing two substituent groups, probably due to the reduced steric hindrance at the terminal position. All tested unsymmetrical fulvenes were tolerated in this novel [6 + 3] annulation. However, the additionally generated tertiary center renders this tandem annulation more intricate, and the cycloadducts were separated in good yields as *syn*- and *anti*-isomers with 1:1 ratio. The relative configuration of cycloadduct (±)-**4d** was determined by the single X-ray crystallographic analysis (Figure 2).

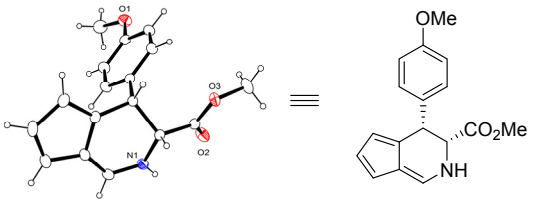
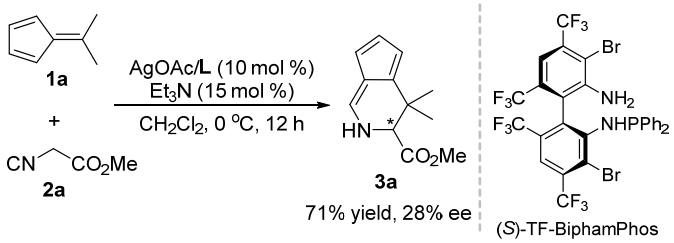


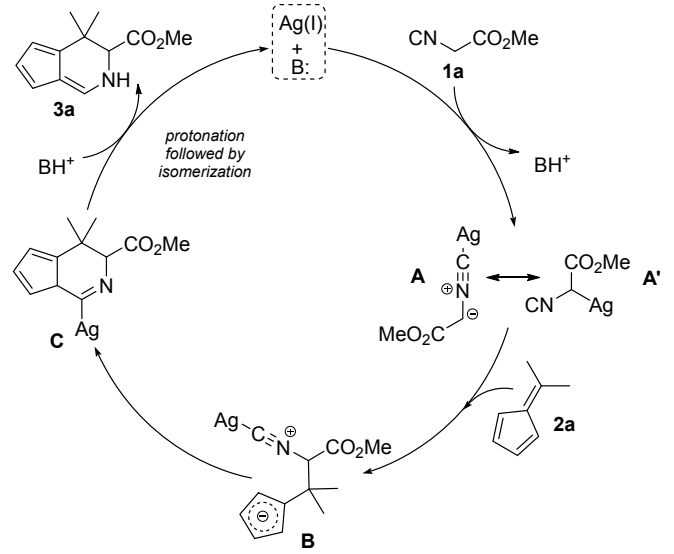
Figure 2. X-ray Crystal Structure of (±)-**4d**

The asymmetric version of this [6 + 3] cycloaddition was also preliminarily explored (Scheme 2). With AgOAc/TF-BiphamPhos complex[13] developed by my group as the catalyst, the tandem cycloaddition/isomerization of isocyanoacetate **2a** and fulvene **1a** proceed smoothly at 0 °C, affording the adduct **3a** in 71% yield and 28% ee without further optimizations.

Scheme 2. Preliminary result for catalytic asymmetric [6 + 3] cycloaddition reaction of methyl 2-isocyanoacetate **2a** with fulvenes **1a**



Scheme 3. Proposed Mechanism for [6 + 3]-Cycloaddition/Isomerization of Isocyanoacetates and Fulvenes



Based on the experimental results and literature analysis,[5,10] a postulated catalytic cycle was illustrated in Scheme 3. With the aid of the base, **A** or its tautomer **A'** was formed from **1a** via metalation and α-deprotonation. Initial nucleophilic attack of **A** to the fulvene **2a** delivered the zwitterionic intermediate **B**. Subsequent intramolecular cyclization followed by protonation/isomerization gave **3a** and regenerated the catalyst.

In summary, we have successfully developed the first Ag(I)-catalyzed [6 + 3] cycloaddition/isomerization of fulvenes and isocyanoacetates for the facile access to fused dihydropyridines with high functionality. The asymmetric fashion of this tandem annulation/isomerization can be also realized with AgOAc/TF-BiphamPhos. Further improvement of the catalytic asymmetric version and application in organic synthesis are underway.

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Notes and references

[a]*College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China. E-mail: cjwang@whu.edu.cn*
[b]*State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, China 300071, China*

† Electronic supplementary information (ESI) available: Experimental section. CCDC 1030081. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00000x

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