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A controlled selective synthesis of dihydropyrans through tandem reaction of alkynes with diazo compounds†

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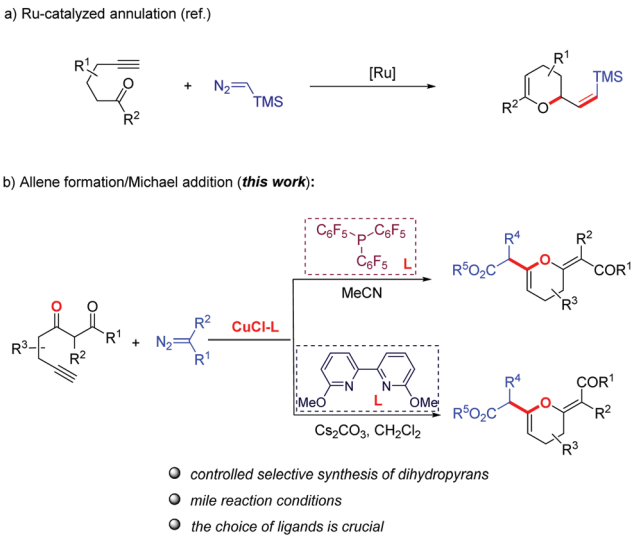
We report here an effective protocol to prepare highly functionalized dihydropyrans *via* sequential reaction of cross-coupling-intramolecular Michael addition of functionalized terminal alkynes and diazo compounds under mild reaction conditions. Importantly, by choosing different ligands, the configuration of exocyclic double bonds of dihydropyrans can be selectively controlled.

Five- and six-membered oxygen-containing heterocycles are common motifs found in a variety of bioactive natural products and pharmaceuticals.[1] Numerous efforts have been devoted to development of efficient protocols for the stereoselective synthesis of these compounds. However, despite great advances, highly substituted six-membered oxacycles, including pyrans and dihydropyrans, remain difficult to access. Thus, new methodologies are highly needed.

On the other hand, metal–carbene mediated cyclizations have received much attention due to their versatility in constructing synthetically useful molecular scaffolds.[2] Many valuable methodologies have been developed to prepare various ring systems including oxacycles *via* metal-catalyzed intermolecular reactions of diazo compounds with readily available substrates.[3] Such methods for the construction of 5-membered oxygenated heterocycles are many, including tetrahydrofurans[4] and dihydrofurans.[5] In contrast, approaches to synthesize 6-membered oxacycles are less. Recently, Saá and co-workers described an elegant protocol for synthesizing dihydropyrans from readily available alkynals and alkynones through ruthenium-catalyzed cyclizations (Scheme 1a).[6] In continuation of our interest in carbene chemistry,[7] we now report a novel controlled stereoselective synthesis of dihydropyrans from diazo compounds and alkynyl–carbonyl compounds (Scheme 1b).



Scheme 1 Previous report and our protocol.

Recently, we developed a copper-catalyzed protocol to synthesize five-membered heterocycles from diazoacetates and terminal alkynes under base free conditions.[7a] We envisaged that this protocol could be improved or modified to synthesize six-membered dihydropyrans by choosing specific functionalized alkynes. Thus, our plan starts from the copper-catalyzed cross-coupling reaction of terminal alkyne **1a** with diazoacetate **2a** (Scheme 2). This reaction would result in the formation of an allenoate intermediate in the presence of a base (from alkynes)[8] even under base-free conditions. Moreover, as a good Michael acceptor, this allenoate intermediate could undergo three types of cyclizations under different reaction conditions. First, in the absence of base, the direct intramolecular oxo-Michael addition of carbonyl oxygen atoms to allenoate would generate zwitterionic intermediate II, followed by H-migration to afford cycloaddition product **3a** (Scheme 2, path A). Alternatively, treatment of allenoate **I** with base would furnish nucleophilic enol anion **III** or carbon anion **IV**, respectively. We anticipated that these different addition modes would selectively yield dihydropyrans (**3a** or **4a**) through path

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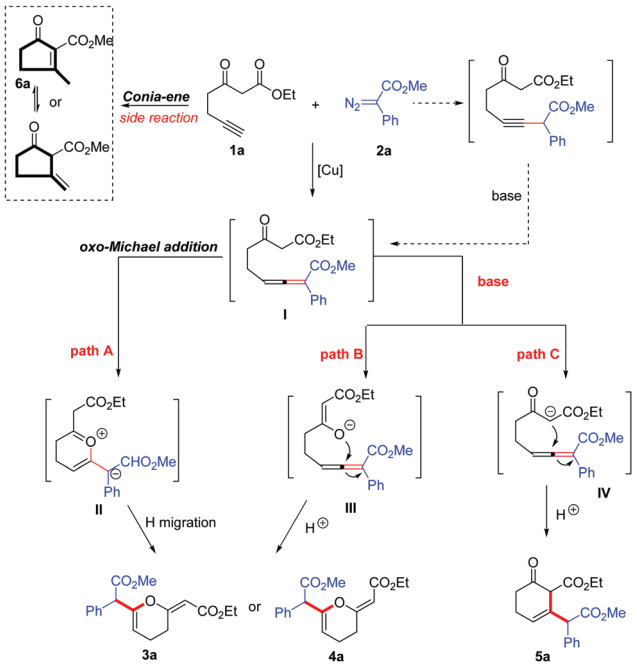
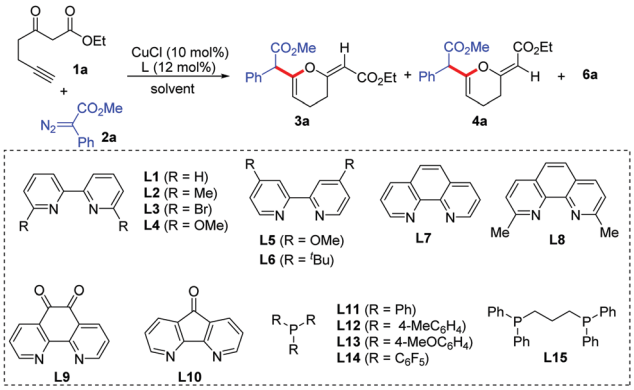


Scheme 2 Our strategy.

B (oxo-Michael addition), or carbocycle **5a** through path C (C–C bond formation). Nevertheless, it should be noted that this type of alkyne is prone to undergo Conia-ene reaction resulting in the formation of **6a** in the presence of a copper complex.[9]

Upon the above hypothesis, we started our investigation by using **1a** and **2a** as starting materials and CuCl as the catalyst to optimize the reaction conditions. Initially, we observed that the reaction did not give the cycloaddition products in acetonitrile at 50 °C in the absence of a ligand and base (Table 1, entry 1). The combination of CuCl with nitrogen-containing ligands **L1** to **L10** also did not furnish any product under the same conditions as in entry 1. However, when phosphine ligand **L11** was added, the yield of **3a** was improved to 55% associated with 36% yield of **4a** and 9% yield of **6a** (entry 3). The use of **L12** and **L13** gave similar results (entries 4 and 5). Gratifyingly, the combination of phosphine ligand **L14** with CuCl resulted in 70% isolated yield of **3a** with a small amount of **4a** and **6a** (entry 6). When diphosphine ligand **L15** was employed, the reaction selectivity was poor (entry 7). Next, we examined the role of base in the reaction. The use of CuCl followed by addition of Cs_2CO_3 gave **3a** and **4a** in 33% and 27% isolated yield associated with a small amount of Conia-ene product **6a** in dichloromethane at room temperature (entry 8). However, the addition of **L1** or **L2** to the reaction gave very low conversion (entry 9). To our delight, using **L3** as a ligand, the reaction furnished **4a** in 52% yield, without the detection of **3a** (entry 10). The isolated yield of **4a** was further improved to 65% when 2,2′-bipyridine ligand **L4** was used (entry 11). Ligand **L10** gave **4a** in 60% yield associated with a small amount of **3a** and **6a** (entry 13). Other ligands did not promote the reaction (entries 12 and 14). Next, screening other bases did not give better results (entries 15 to 17). The formation of an allenoate intermediate was

Table 1 Selected optimization[a]



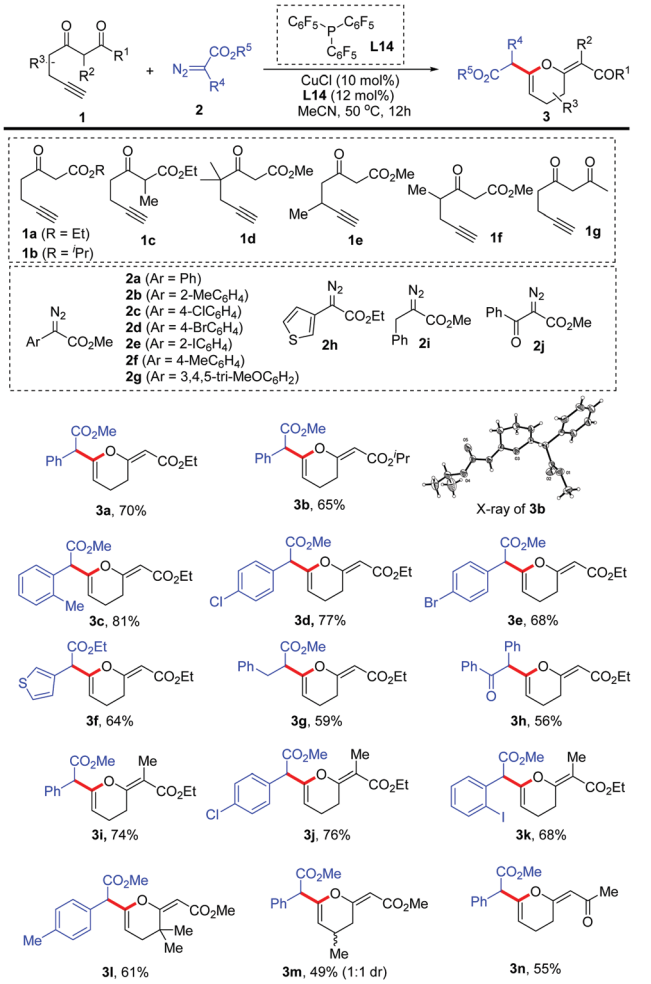
Entry	Ligand	Base	Solvent	T (°C)	**3a**/**4a**/**6a**[b] (%)
1	—	—	MeCN	50	—
2	**L1–L10**	—	MeCN	50	—
3	**L11**	—	MeCN	50	55/36/9
4	**L12**	—	MeCN	50	49/40/11
5	**L13**	—	MeCN	50	51/32/17
6	**L14**	—	MeCN	50	(70)/10/8
7	**L15**	—	MeCN	50	35/30/35
8	—	Cs_2CO_3	CH_2Cl_2	25	(33)/(27)/7
9	**L1–L2**	Cs_2CO_3	CH_2Cl_2	25	<5
10	**L3**	Cs_2CO_3	CH_2Cl_2	25	0/(52)/5
11	**L4**	Cs_2CO_3	CH_2Cl_2	25	0/(65)/7
12	**L5–L9**	Cs_2CO_3	CH_2Cl_2	25	<5
13	**L10**	Cs_2CO_3	CH_2Cl_2	25	9/(60)/7
14	**L11–L15**	Cs_2CO_3	CH_2Cl_2	25	<5
15	**L4**	KO^{t}Bu	CH_2Cl_2	25	0/53/8
16	**L4**	LiO^{t}Bu	CH_2Cl_2	25	0/19/12
17	**L4**	K_2CO_3	CH_2Cl_2	25	7/22/<5

[a] Reaction conditions: **1g** (0.2 mmol), **2a** (0.24 mmol), CuCl (10 mmol%), ligand (12 mmol%), at 50 °C for 12 h (entries 1 to 7). Then base (0.24 mmol) was added and the reaction mixture was continuously stirred for another 2 h (entries 8 to 17). [b] NMR yields. Isolated yields in parentheses.

observed in the absence of base (this intermediate is unstable, see the ESI† for details). The above optimization revealed that **3a** and **4a** with opposite double bond configuration could be selectively obtained as the major products by changing the reaction conditions. The experiment results disclosed that the addition of a base favored the formation of the *E*-isomer of the dihydropyran. It should be noted that compound **5a** (described in Scheme 2, path C) was not detected in the whole screening process. Moreover, the use of CuI, CuBr and other copper salts resulted in very low yields of the dihydropyrans.

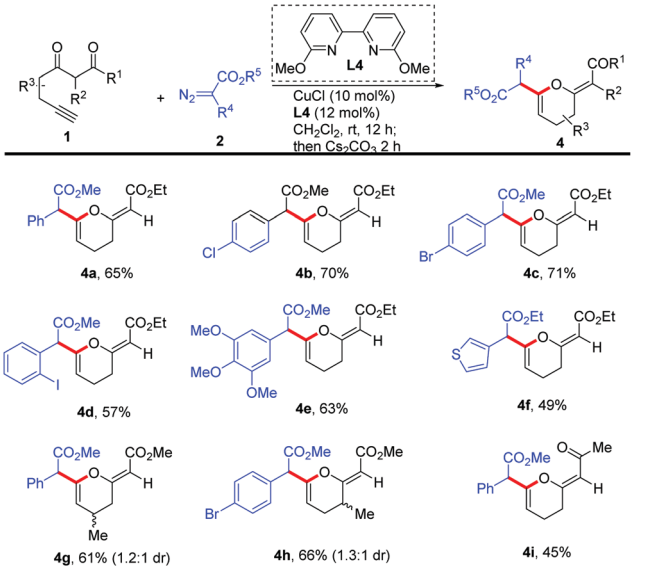
With the optimal reaction conditions in hand, we then used the combination of CuCl and **L14** to investigate the substrate scope (Table 2). Both alkynes and diazo compounds were examined. Gratifyingly, a wide range of aryl diazoacetates with different substitution patterns could be utilized in this reaction, providing the corresponding dihydropyrans in moderate to excellent yields. Either electron-donating or electron-withdrawing groups were tolerated on the aryl ring of the diazoacetates (**3a** to **3e**). The reaction of **1a** with thiophene derived diazoacetate **2h** furnished **3f** in 64% yield. Alkyl diazoacetate **2i** was tolerated in the reaction and the corresponding product **3g** was isolated in 59% yield. The ketone diazo compound **2j** also reacted well and **3h** was isolated in 56% yield. Moreover, the reaction of **1b** with phenyl diazoacetate **2a**

Table 2 Substrate scope for dihydropyrans **3**[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), CuCl (0.02 mmol), **L14** (0.024 mmol), in MeCN (3 mL) at 50 °C for 12 h. [b] Isolated yields.

Table 3 Scope for dihydropyrans **4**[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), CuCl (0.02 mmol), **L4** (0.024 mmol), in CH_2Cl_2 (3 mL) at RT for 12 h; then Cs_2CO_3 (0.24 mmol) was added and stirred for another 2 h. [b] Isolated yields.

provided **3b** in 65% yield. The structure of **3b** was confirmed by X-ray crystallographic analysis.[10] Then, the alkyne substrates bearing methyl groups at different positions (**1c** to **1f**) were employed in the reaction. The corresponding products were obtained in moderate to good yields (**3i** to **3m**). Moreover, alkyne with di-ketone moieties (**1g**) was also tolerated and **3n** was obtained in 55% yield.

Next, by using CuCl and **L4** in dichloromethane followed by addition of Cs_2CO_3 under standard reaction conditions, the tandem reactions of alkynes **1** and diazo compounds **2** were conducted to prepare dihydropyrans **4** (Table 3). As observed, the reaction tolerated a series of aryl diazoacetates bearing either electron-donating or electron-withdrawing substituents on the aryl ring, and the corresponding dihydropyrans were obtained in moderate yields (**4a** to **4e**). Different alkynes were also subjected to reaction and the corresponding products were isolated in moderate yields too (**4g** to **4i**). It should be noted that for alkynes **1e** and **1f**, the products were obtained as a mixture of two isomers in 1.2 : 1 and 1.3 : 1 ratios, respectively.

In conclusion, we have developed an efficient protocol to prepare polysubstituted dihydropyrans in a stereoselective mode. This protocol tolerated a wide range of functionalized terminal alkynes as well as diazo substrates. Importantly, by choosing suitable ligands and catalytic systems, dihydropyrans with opposite exocyclic double bonds can be synthesized in a controlled manner.

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