A Highly Diastereoselective Cyclocarbonylation of Allene-Aldehyde Mediated by Mo(CO)6: Synthesis of Bicyclic Lactones[†]

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Among a variety of synthetic methods for the construction of cyclic compounds, reactions involving the use of transition metals are some of the most attractive methodologies since reactions can directly construct complicate molecules from readily available starting materials.[1] As a consequence, many advances in the cylcization mediated by transition metals have been made through a variety of ways in synthetic strategy.[2] Of particular interest is a cyclization strategy between carbonyl and unsaturated bonds to find practical way of chemical routes for the preparation of lactones mainly because the chemical process could dominate over the classical methods in simple trial.[3] In this regard, an allene has been proven to be an useful substrate for a variety of transition metal catalytic reactions, particularly for the cyclizations in the construction of carbo- and heterocycles.[4] For example, the transition metal promoted cyclization of allene-aldehydes has emerged as a highly convergent method for the stereoselective synthesis of cyclic alkenols.[5]

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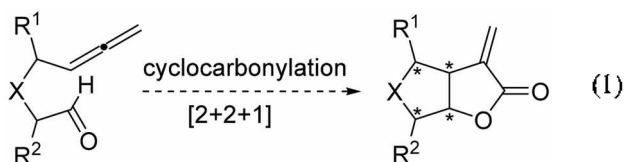
Recently, we have disclosed our investigations of stepwise or direct cyclization methods for the synthesis of bicyclic 3-methylenebutyrolactones from allene-carbonyl functionalities involving the use of transition metals,[6] as a part of the allylic transfer strategy utilizing an allene as substrates or intermediates.[7] The characteristic features of this protocol in terms of chemical efficiency through a three component coupling process and structural features of products have encouraged us to carry out more investigations to introduce other groups, which would expand the scope and utility of this reaction. As a consequence, we became quite interested in carrying out investigation with substituted allene-aldehydes to demonstrate the remote stereocontrol by substituent R^1 or R^2 during the process as shown in eq (1). This research led to the discovery of the remarkable solvent effect for the conversion which expedites the reaction process with good diastereoselectivity.

With this issue in mind, several allene-aldehydes were

Table 1. Preliminary investigations with **1a**

Entry	M	Solvent	T/°C	Time/h	Yield[a]
1	Ru3(CO)12, CO[b]	Dioxane	120	16	34
2	C7H8Mo(CO)3[c]	toluene	110	12	37
3	C7H8Mo(CO)3[c]	CH2Cl2	100	12	54
4	Mo(CO)3(DMF)3	toluene	110	12	trace
5	Mo(CO)3(DMF)3	CH2Cl2	100	12	trace
6	Mo(CO)6[c]	toluene	110	12	41
7	Mo(CO)6[c]	CH2Cl2	80	6	88
8	Mo(CO)6[c]	CH3CN	100	12	37

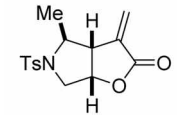[a]refer to isolated product. [b]CO (20 atm) [c]additive, DMSO (10 equiv)
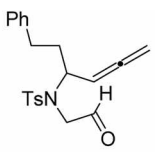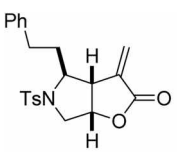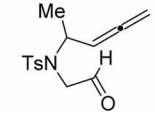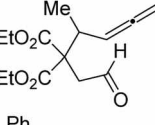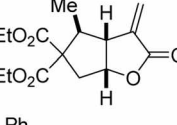
prepared by modified method.[6] As a starting point, the allene-aldehyde **1a** was selected as a model substrate because both diasteromers of products **2a** wer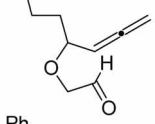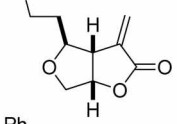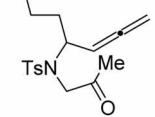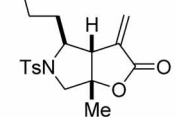e synthesized from **1a** by the three steps sequence from our laboratory.[6c] Initial attempts to cyclocarbonylation of **1a** under the previous conditions employed for unsubstituted allene-aldehydes indicated that the conversion to the corresponding lactone **2a** could not be satisfied in terms of chemical conversion, even though **2a** was isolated as a single diastereomer (Table 1).

After surveying numerous conditions for orienting experiments as summarized in Table 1, we were delighted to find a dramatic solvent effect along with several key findings as follows: i) Ru3(CO)12 tuned out to be unpromising; ii) the use of Mo(CO)6 was superior to other molybdenum carbonyls such as C7H8Mo(CO)3, and Mo(CO)3(DMF)3;[8] iii) the introduction of DMSO as an additive proved to be most effective in comparison with other sulfoxides such as tetramethylene sulfoxide and methyl phenyl sulfoxide; iv) dramatic solvent effect was observed by introducing CH2Cl2 compared to other solvents such as toluene, THF, and CH3CN in terms of reactivity and chemical yields; v) reaction performed at 80 °C in CH2Cl2 resulted in the best chemical yield.

Under optimal conditions (entry 7 in Table 1), the reaction was conducted by an addition of **1a** (1 equiv) and DMSO (10 equiv) in CH2Cl2 at 20 °C to a solution of Mo(CO)6 (1.5 equiv) in CH2Cl2 in a seal tube. After stirring at 20 °C for 1

Table 2. Cyclocarbonylation of **1** with Mo(CO)$_6$

Entry	Allene-carbonyl (1)	Product (2)	Yield (%)
1	**1a**	**2a**	88
2	**1b**	**2b**	83
3	**1c**	**2c**	75
4	**1d**	**2d**	63
5	**1e**	**2e**	77

3a (X = NTs, R^2 = CH$_2$Ph)	67%	**4a**	83:17	**5a**
3b (X = O, R^2 = CH$_2$Ph)	44%	**4b**	71:29	**5b**

Scheme 1. Cyclocarbonylation of **3a** and **3b**.

Scheme 2. Plausible stereochemical pathway.

h, the reaction mixture was immediately immersed into a pre-heated oil bath at 100 °C. After 6 h at 100 °C, the reaction mixture was cooled to rt and then filtered through a sintered glass filter containing celite with additional CH$_2$Cl$_2$. After removal volatile materials under reduced pressure, final purification was effected by column chromatography to yield **2a** in 88% yield.

With the notion that this approach might lead to a general and efficient method for the synthesis of **2**, we set out to determine the scope to produce structurally various products. Indeed, the method is successful with **1b-e** to yield the bicyclic lactones **2b-e** as a single adduct, respectively, in moderate to high yields as shown in Table 2.

In the light of the above results for the carbocyclization with the excellent remote stereocontrol by R^1, we next turned our attention to extend the strategy with **3** to figure out the influence of diastereoselctivity by R^2. Unfortunately, the reaction of **3a** under the same conditions as described in Table 1 gave the two diastereomers **4a** and **5a** in 67% yield as a 83:17 mixture. Reaction of **3b** was shown to produce **4b** and **5b** in 44% yield with even worse diastereoselectivity in a 71:29 ratio as illustrated in Scheme 1. Diastereomerical relationships were unambiguosly proved by the nOe experiments. All products were characterized by ^{1}H & ^{13}C NMR, IR, and MS.

The stereochemical outcome for the transformations can be explained by the analysis of stereochemical models as depicted in Scheme 2. The remote chiral center attached to R^1 or R^2 was envisioned to impact stereoselectivity during the conversion of **A** to **B** as depicted in Scheme 2. The preference for the stereoselectivity controlled by R^1 or R^2 could be predicted on the basis of a stereochemical model **A**
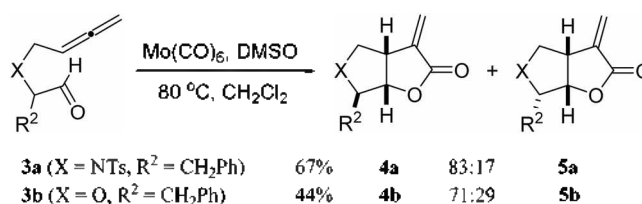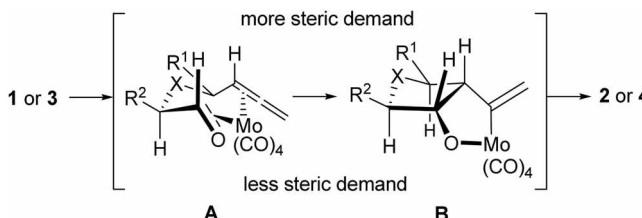
and **B**. The exceptional stereoselectivity for **2** can also be explained by more steric demand in **A**, whereas less steric demand with R^2 during the conversion resulted in the moderate diastereoseletivity for **4**.

In summary, this communication describes diastereoselective synthetic routes to **2** and **4** to realize a remote stereocontrol in a general and efficient way which promises to be synthetically useful. Studies are in progress to incorporate with chiral environment into an enantioselective synthesis of biologically interesting natural product.

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