Reaction Mechanisms

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Tunable Carbonyl Ylide Reactions: Selective Synthesis of Dihydrofurans and Dihydrobenzoxepines**

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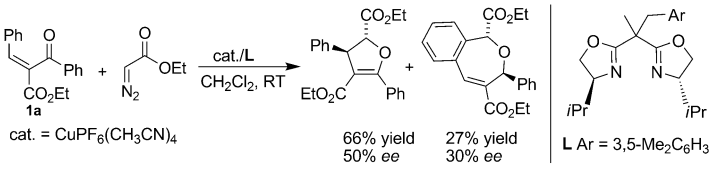
The stereoselective preparation of highly substituted oxygen heterocycles has attracted considerable attention.[1] Over the past decades, it has been well established that the transition-metal-catalyzed decomposition of diazo compounds can generate transient carbonyl ylides, which can either be trapped by suitable dipolarophiles or cyclize intramolecularly for the synthesis of oxygenated heterocycles.[1c,2–7] Asymmetric versions of some of these reactions have also been developed.[1c,7] However, for these reactions, the five-membered furan derivatives are usually obtained as the major products and very few reactions gave the seven-membered oxepine derivatives. For example, Anaç et al. recently reported that α-benzylidene-β-dicarbonyl compounds reacted with dimethyl diazomalonate to afford dihydrofurans or mixtures of dihydrofurans and dihydrobenzoxepines (about 1:1).[5h] During our investigations into the asymmetric reaction of α-benzylidene-β-dicarbonyl compound **1a** and ethyl diazoacetate, the seven-membered heterocyclic product was observed together with the desired dihydrofuran (Scheme 1).[5l] Noticeably, both products were obtained with moderate *ee* values, thus suggesting that the ligand has a strong influence on the chemoselectivity and stereochemistry of the reaction. Considering the importance of both products in organic synthesis and pharmaceutical science, we wondered whether the product distribution could be controlled by using different ligands. Herein we report the first successful realization of this aim and density functional theory (DFT) studies that give an understanding of how these tunable processes occur.

On the basis of our initial optimization of the copper catalysts (see Scheme S1 in the Supporting Information) we decided to study the influence of the ligands (Figure 1) on the reaction when using $CuSbF_6$ as the catalyst in CH_2Cl_2 at room temperature with molecular sieves (4 Å) as an additive, which can ensure a clean reaction system. As shown in Table 1, the structure of the ligand had a significant influence on both the reactivity and the chemoselectivity of the reaction.

When using 2,2′-bipyridine as the ligand, the dihydrofuran **3** was mainly obtained but with low diastereoselectivity (Table 1, entry 1). However, when the 1,2-diimine **L1**, which contains two bulky 2,6-diisopropylphenyl groups, was used as the ligand the reaction gave dihydrobenzoxepine **4a** as the major product but also dihydrofurans **3a** and **3a′** as by-products (Table 1, entry 2). We were gratified to find that the bulky and structurally rigid Brookhart-type ligand **L4**[8a,b] gave **4a** predominately in 71% yield (Table 1, entry 5). Interestingly, we observed that the substituents on the 1,2-diimine



Scheme 1. An attempt towards the asymmetric ylide cycloaddition reaction.

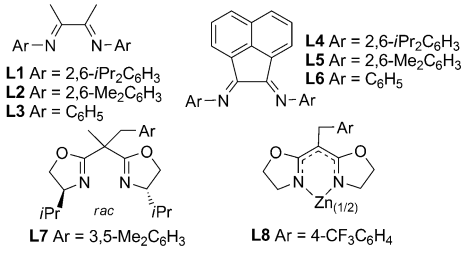


Figure 1. Ligands screened for the carbonyl ylide chemistry.

ligands played a very important role; the ratio of **3/4** increased sharply as the bulk of the aryl group of the ligand decreased (Table 1, entries 2–4 and entries 5–7). Other types of diimine ligands that are structurally more flexible, and the diphosphine ligands gave low yields of **4a** (Table S1 in the Supporting Information). These results indicated that both the backbone and the bulk of the ligand strongly affected the reaction. Further studies revealed that the combination of the

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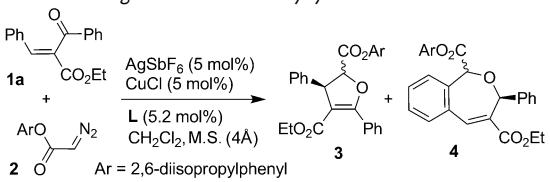
Table 1: Effect of ligand on the carbonyl ylide reaction.[a]



Entry	Ligand	Conv. [%][b]	**3**/**4**[b]	**3a**/**3a′** [b,c]	**4a**/**4a′** [b,c]
1	2,2′-bpy	100	96:4	60:40	>99:1
2	**L1**	72	50:50	60:40	94:6
3	**L2**	100	71[d]:6	80:20	>99:1
4	**L3**	100	89:11	54:46	>99:1
5	**L4**	100	16:71[d]	>99:1	>95:5
6	**L5**	88	89:11	60:40	>99:1
7	**L6**	27	85:15	65:35	>99:1
8	**L7**	100	96[d]:0	>99:1	–
9	**L8**	100	86[d]:<5	>99:1	>99:1
10[e]	**L4**	100	27:73	80:20	88:12
11[f]	**L4**	100	15:76[c]	>99:1	85:15

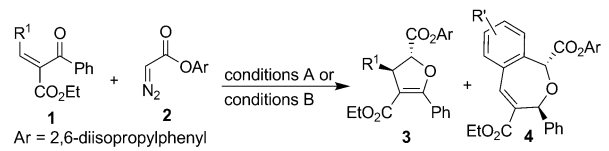
[a] Reaction conditions: CuCl (0.025 mmol), $AgSbF_5$ (0.025 mmol), M.S. (4 Å; 200 mg), ligand (0.026 mmol), CH_2Cl_2, RT, **1a** (0.5 mmol), **2** (2.0 mmol). [b] Determined by ^{1}H NMR spectroscopy. [c] Both **3a**/**3a′** and **4a**/**4a′** are for *trans*/*cis* isomers. [d] Yield of the isolated product. [e] 5 mol% of $[Cu(CH_3CN)_4]PF_6$ was used. [f] 8 mol% of $[Cu(CH_3CN)_4]PF_6$ and 8.4 mol% of **L4** were used. bpy = 2,2′-bipyridine, M.S. = molecular sieves.

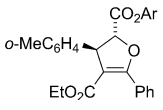
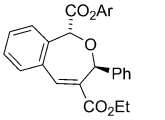
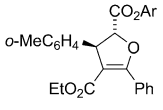
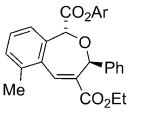
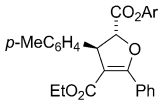
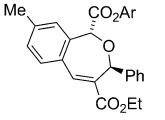
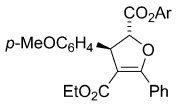
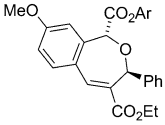
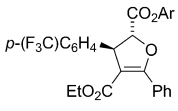
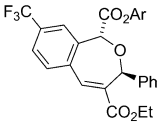
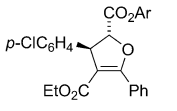
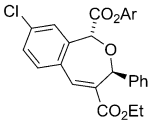
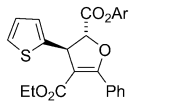
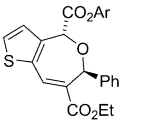
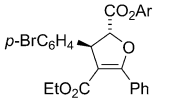
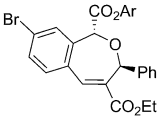
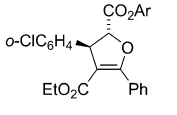
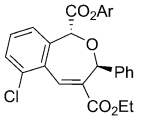
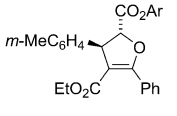
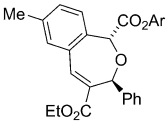
commercially available and more stable $[Cu(CH_3CN)_4]PF_6$ with ligand **L4** was a slightly more suitable system, thus giving more reproducible results for the selective generation of **4a** (Table 1, entries 10 and 11); a 76% yield of the isolated **4a** was obtained under the optimized reaction conditions (reaction conditions B: $[Cu(CH_3CN)_4]PF_6$ (8.0 mol%), **L4** (8.4 mol%), CH_2Cl_2 (4 mL), M.S. (4 Å; 200 mg), 31 °C).

Pleasingly, when bisoxazoline ligands (**L7** and **L8**)[8c,d] were used the major product was **3a**; this product was obtained with excellent diastereoselectivity and the formation of **4** was almost completely suppressed (Table 1, entries 8 and 9). For example, dihydrofuran **3a** can be obtained in 96% yield as the sole product in the presence of ligand **L7** combined with $CuSbF_6$ as the catalyst (reaction conditions A: CuCl/$AgSbF_6$ (5.0 mol%), **L7** (5.2 mol%), CH_2Cl_2 (4 mL), M.S. (4 Å; 200 mg), 25 °C).

With the optimized reaction conditions for the selective syntheses of dihydrofurans and dihydrobenzoxepines in hand, we evaluated the generality of these reactions. As shown in Table 2, a variety of substrates were examined. The reaction displayed excellent generality with respect to the synthesis of the 2,3-dihydrofuran derivatives because all the substrates reacted smoothly under reaction conditions A to produce the desired products **3** in moderate to excellent yields (50–99%) with excellent diastereoselectivity (>99:1), regardless of the nature and the position of the substituent of R^1 (Table 2, entries 1–10). For the construction of dihydrobenzoxepine derivatives **4** under reaction conditions B, the reaction showed good tolerance towards electron-rich, electron-neutral, and electron-poor R^1 groups, thus giving products **4** in moderate to good yields (66–85%) with the ratio of the *trans*/*cis* diastereomers ranging from 85:15 to 95:5. Noticeably,

Table 2: Generality of the two tunable reactions.

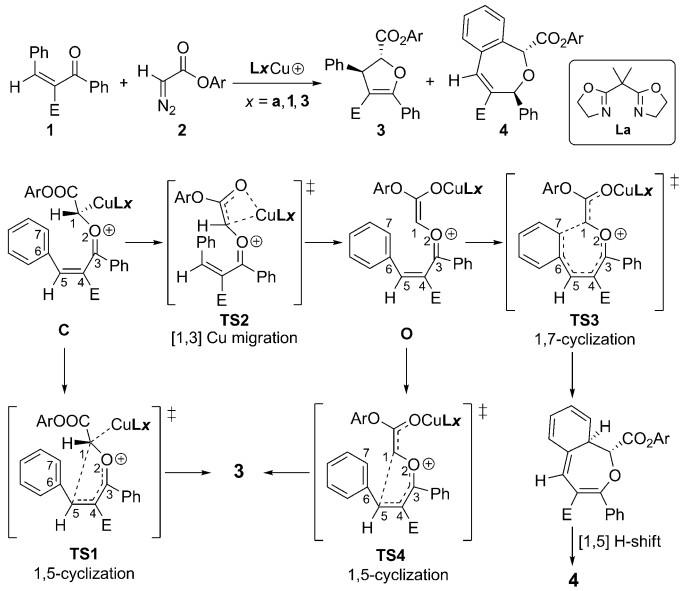


Entry	Reaction conditions A[a] **3**	Yield [%][d,e]	Reaction conditions B[b,c] **4**	Yield [%] (d.r.)[d,f]
1	 **3a**	96	 **4a**	76 (85:15)
2	 **3b**	94	 **4b**	85 (90:10)
3	 **3c**	99	 **4c**	76 (90:10)
4	 **3d**	72	 **4d**	78 (90:10)
5	 **3e**	97	 **4e**	71 (88:12)
6	 **3f**	92	 **4f**	75 (89:11)
7	 **3g**	50	 **4g**[g]	34 (95:5)
8	 **3h**	94	 **4h**	66 (91:9)
9	 **3i**	95	 **4i**	73 (86:14)
10	 **3j**	92	 **4j**	66 (95:5)

[a] Reaction conditions A (0.5 mmol scale): CuCl/$AgSbF_6$ (5.0 mol%), **L7** (5.2 mol%), CH_2Cl_2 (4 mL), M.S. (4 Å; 200 mg), 25 °C. [b] Reaction conditions B (0.5 mmol scale): $[Cu(CH_3CN)_4]PF_6$ (8.0 mol%), **L4** (8.4 mol%), CH_2Cl_2 (4 mL), M.S. (4 Å; 200 mg), 31 °C. [c] Under reaction conditions B the trace amount of **3** synthesized could not be isolated accurately from the reaction system, and therefore the yield and d.r. of **3** were determined by ^{1}H NMR spectroscopy (see Table S2 in the Supporting Information). [d] Yield of the isolated product. [e] The d.r. was >99:1 for **3**. [f] The d.r. of **4** was determined by ^{1}H NMR spectroscopy and is for the *trans*/*cis* isomers. [g] At 40 °C.

under both reaction conditions, substrate **1g** only afforded relatively low yields of **3g** and **4g**; this result is probably due to the sulfur atom disrupting the formation of the carbonyl ylide (Table 2, entry 7).

We applied DFT calculations with the B3LYP functional to study the reaction mechanism and rationalize how the ligands influence the selection of the final products **3** and **4**.[9] Our mechanistic studies focused on the reaction pathways and started from the commonly accepted carbonyl ylide **C**, in which the carbon anion is coordinated to the copper center of the copper(I)/ligand complex (Scheme 2).[10–13] DFT calculations revealed that this carbonyl ylide leads to dihydrofuran **3** via the 1,5-cyclization transition state **TS1**.[14] In addition to this widely accepted ylide **C**, this reaction can proceed through another ylide **O**, in which the carbonyl oxygen atom of the ester group is coordinated to the copper center (Scheme 2). The ylide **O** is generated from ylide **C** by a [1,3] copper migration via the transition state **TS2**. In contrast to ylide **C**, which can only give product **3**,[14] ylide **O** can give either product **3** via the 1,5-cyclization transition state **TS4**, or product **4** through a process that involves a 1,7-cyclization (via transition state **TS3**) and a [1,5] H-shift.[15] Therefore, the ratio of products **3** and **4** depends on the relative energies of the transition states **TS1–4,** which are involved in these transformations. DFT calculations indicate that the ligands are important in controlling the chemoselectivity of this reaction.



Scheme 2. DFT studies on the carbonyl ylide cyclizations involving different ligands. E = CO_2Me, Ar = 2,6-diisopropylphenyl.

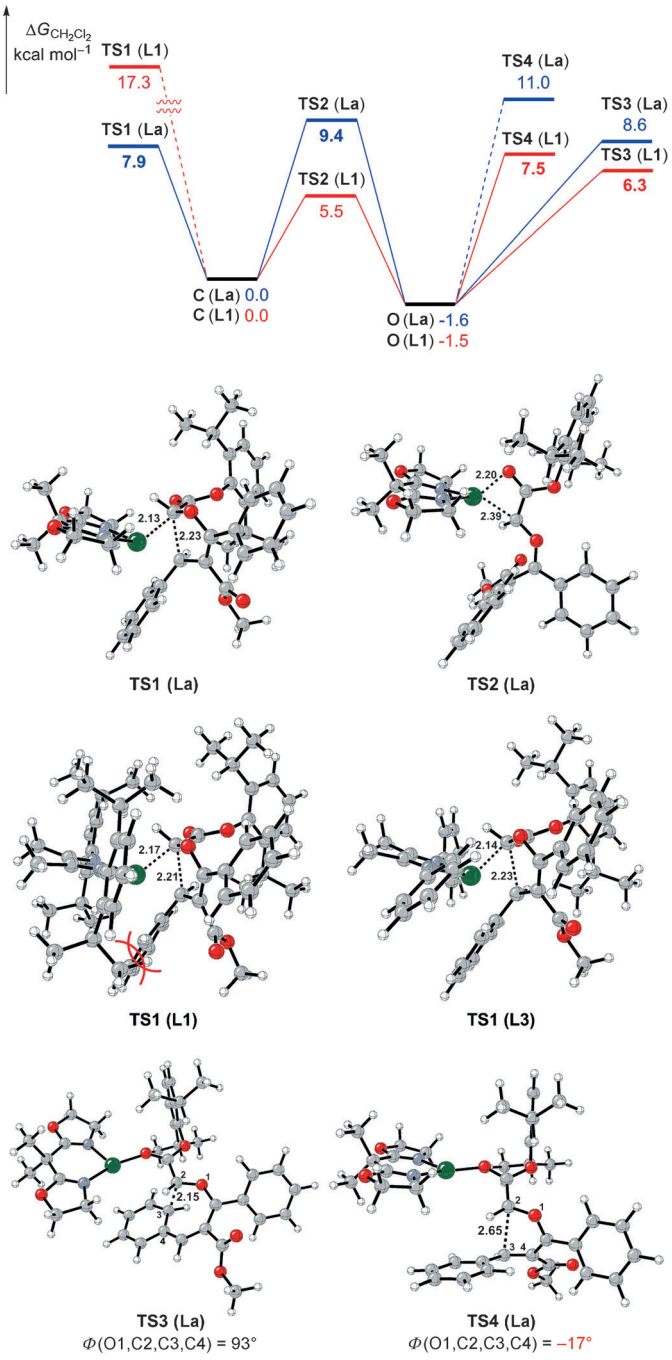
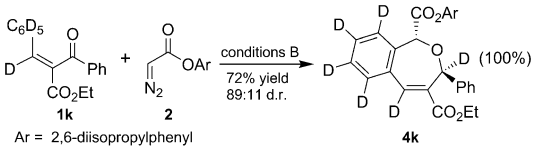


Figure 2. DFT-calculated free-energy surfaces for the processes shown in Scheme 2 using ligands **La** (blue line) and **L1** (red line), and the structures of several representative transition states (C gray; H white; O red; N blue; Cu green; distances are given in Å).

When using bisoxazoline **La** (see Scheme 2 for structure) as the ligand, the 1,5-cyclization of ylide **C** to generate the five-membered ring product **3** is facile, thus requiring an activation free energy of 7.9 kcal mol^{-1} in a dichloromethane solution (Figure 2, blue line).[16] The activation free energy of the isomerization of ylide **C** into **O** is 1.5 kcal mol^{-1} higher than that of the competing 1,5-cyclization (9.4 versus 7.9 kcal mol^{-1}, Figure 2), thus suggesting that only a minor amount of ylide **O** will be generated when **La** is used as ligand. Ylide **O** will predominantly give product **4** via **TS3** and a [1,5] H-shift, because the transition state **TS4**, which gives product **3**, is higher in energy than **TS3** by 2.4 kcal mol^{-1}. Therefore, our DFT calculations show that, when the bisoxazoline ligand is employed, the major product is dihydrofuran **3**, which is generated from ylide **C** via the 1,5-cyclization transition state **TS1**, and a minor amount of **4** might be generated from ylide

O via the 1,7-cyclization transition state **TS3**. This conclusion is in agreement with the experimental results when using reaction conditions A.[17]

When ligand **L1** (Figure 1) is used, the five-membered ring product **3** will not be generated from ylide **C** because the 1,5-cyclization transition state **TS1** is 11.8 kcal mol^{-1} higher in energy than the competing isomerization transition state **TS2** (Figure 2, red line).[18] Consequently, ylide **C** will isomerize to ylide **O**, which gives **3** as a minor product and **4** as a major product because **TS3** (1,7-cyclization) is lower in energy than **TS4** (1,5-cyclization) by 1.2 kcal mol^{-1}. Therefore, when using a sterically hindered diimine ligand the major product is dihydrobenzoxepine **4**, which is generated from ylide **O** via the 1,7-cyclization transition state **TS3** and a subsequent [1,5] H-shift, and a minor amount of **3** is generated also from ylide **O** via **TS4**. This is consistent with the experimental results when using reaction conditions B.[19] The [1,5] H-shift process[15] for the generation of product **4** was proved by the reaction of the deuterium-labeled substrate **1k** under reaction conditions B (Scheme 3).



Scheme 3. The reaction of the deuterium-labeled substrate **1k**.

The key for controlling the final product distribution (**3**/**4**) is the competition between the 1,5-cyclization of ylide **C** (via **TS1**) and the isomerization of ylide **C** to **O** (via **TS2**). When **La** is used as the ligand, the required energy to reach **TS1** is 7.9 kcal mol^{-1} (Figure 2, blue line). However, when sterically hindered ligand **L1** is used, the energy barrier for the 1,5-cyclization of ylide **C** dramatically increases to 17.3 kcal mol^{-1} (red line, Figure 2). Through analyzing the structure of the transition state **TS1** (**L1**), we found that there are significant steric repulsions between the phenyl group of the carbonyl ylide and the isopropyl group of ligand **L1** (Figure 2). To further confirm the steric effect of ligand **L1**, we also located the 1,5-cyclization transition state **TS1** (**L3**), in which the isopropyl groups of the ligand are replaced by hydrogen atoms (Figure 2). As expected, the energy barrier for the 1,5-cyclization in this case is greatly decreased to 7.9 kcal mol^{-1}. Therefore, DFT calculations reveal that when a bulky ligand is used **TS1** is disfavored. In contrast, the presence of a bulky ligand favors the isomerization of ylide **C** into **O** via **TS2**. For example, when the ligand in the reaction is changed from **La** to **L1**, the isomerization energy (via **TS2**) decreases from 9.4 to 5.5 kcal mol^{-1} (Figure 2). Here we can conclude that when using a sterically hindered diimine ligand the generation of the five-membered ring product **3** from ylide **C** will be suppressed because of the much higher energy barrier for the 1,5-cyclization (via **TS1**) with respect to the isomerization of ylide **C** to **O** (via **TS2**).

In the comparison of **TS3** and **TS4**, we found that the 1,7-cyclization transition state **TS3** is always energetically favored. This is because of the increased ring strain in **TS4** compared to that in **TS3**, as evidenced by a longer C2–C3 distance (2.65 versus 2.15 Å) and a smaller O1-C2-C3-C4 dihedral angle (17° versus 93°) in **TS4** (**La**; Figure 2). Therefore, once ylide **O** is formed, the seven-membered ring product **4** will be generated as the major product.

In conclusion, we have developed a novel strategy to control the product distribution of the reaction between α-benzylidene-β-dicarbonyl compounds and diazoacetate **2** by choosing the appropriate ligand, thus providing an efficient protocol for the selective synthesis of either dihydrofurans or dihydrobenzoxepines from the same starting materials in moderate to good yields and with good to excellent diastereocontrol. From the DFT calculations we discovered that, when a bulky ligand is used, the reaction occurs through the **C**→**TS2**→**O**→**TS3** pathway to give the seven-membered ring product **4** because the 1,5-cyclization of ylide **C**, which gives **3**, is energetically disfavored. However, when a less bulky ligand is used the reaction prefers to take place through the **C**→**TS1** pathway to afford the five-membered product **3**. These mechanistic insights will be helpful in understanding other transition-metal-catalyzed carbonyl ylide reactions and should provide useful information for the rational design of new ligands to control the selectivity in related reactions. Further investigation into a catalytic asymmetric version is ongoing in our laboratory.

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[14] We also tried to locate the 1,7-cyclization transition state from ylide **C**. However, all efforts to locate such a hypothetical transition state led to the location of the 1,7-cyclization transition state **TS3**, which is connected to ylide **O** but not ylide **C**. This prompted us to locate transition state **TS2** to connect ylides **C** and **O**.

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[17] When ligand **La** was employed in the model reaction shown in Table 1 (for details, see the Supporting Information) the ratio of **3a** and **4a** is 90:10, which is very close to the computationally predicted ratio of 93:7.

[18] The DFT-calculated structure of transition state **TS2** (**L1**) is given in the Supporting Information.

[19] When ligand **L1** is used, the experimental ratio of **3a** and **4a** is 39:61 (Table 1), close to the computational result of 12:88.

