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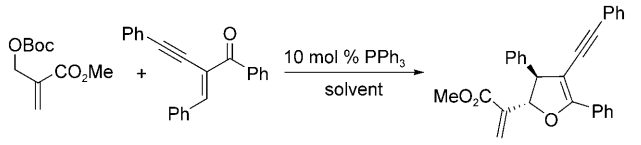
An Unexpected Phosphine-Catalyzed Regio- and Diastereoselective [4+1] Annulation Reaction of Modified Allylic Compounds with Activated Enones

Zuliang Chen[a] and Junliang Zhang*[a, b]

Nucleophilic phosphines are known to be useful mild catalysts for the synthesis of cyclic and heterocyclic compounds.[1] Generally, tertiary-phosphine-mediated annulations are triggered by nucleophilic addition of phosphines to activated compounds. The resultant zwitterionic intermediates can react with various electrophiles such as aldehydes, imines, and activated polarized C=C bonds to furnish cyclic compounds.[2] Herein, we report a phosphine-catalyzed highly diastereoselective synthesis of tetrasubstituted 2,3-dihydrofurans,[3] which are subunits of a range of biologically active compounds (e.g., aflatoxin B_1 and clerodin),[4] via [4+1] annulations of Morita–Baylis–Hillman carbonates with activated enones. In these annulations, Morita–Baylis–Hillman carbonates act as the one-carbon unit, which is distinguished from the modified allylic compounds reported by Lu et al. as the three-carbon units, such as in [3+2],[5h,5j] [3+3],[5n] [3+4],[5m] and [3+6][5e] annulation reactions.

In recent years, Morita–Baylis–Hillman adducts have been illustrated as suitable starting materials for the synthesis of a variety of multifunctional compounds.[5] During our study of the new chemistry of electron-deficient enynes,[6] we became interested in the annulation between Morita–Baylis–Hillman carbonate **1a** and conjugated yne-enone **2a**. We were pleased to find that the reaction proceeded smoothly in toluene at room temperature under catalysis with 10 mol% PPh_3, leading to a [4+1] adduct, 2,3-dihydrofuran **3a**, in 72% yield of isolated product with 20:1 diastereoselectivity (Table 1, entry 1). The structure of **3a** was established by X-ray crystallography analysis of the analogous product 3f ($R^2 = p$-BrC_6H_4; Figure 1).[7] To improve the yield of **3a**, various solvents and tertiary phosphines were tested and the results are summarized in Table 1. A higher product yield was obtained when the reaction was performed in CH_2Cl_2, while the selectivity was slightly decreased (Table 1, entry 2). Good yields with high selectivity were also obtained in DCE, Et_2O, and 1,4-dioxane, albeit the reactions require a longer time to go to completion (Table 1, en-

Table 1. Screening the reaction conditions of annulation reaction of compound **1a** and **2a**.[a]



1a **2a** **3a**

Entry	Solvent	t [h]	Yield [%][b]	d.r.[c]
1	toluene	26	72	20:1
2	CH_2Cl_2	12	81	18:1
3	DCE	29	81	20:1
4	Et_2O	48	82	20:1
5	1,4-dioxane	48	82	20:1
6	hexane	48	75	20:1
7	THF	24	75	20:1
8	EtOAc	48	74	20:1
9	DMF	13	72	20:1
10	DMSO	12	70	20:1
11[d]	CH_3CN	12	0	–
12[e]	CH_3CN	24	0	–
13[f]	CH_3CN	24	0	–
14[g]	CH_3CN	4	42	5:1
15	CH_3CN	11	82	20:1

[a] Reaction conditions: Under Ar, a mixture of **1a** (65.0 mg, 0.3 mmol), **2a** (62.0 mg, 0.2 mmol), and PPh_3 (5.3 mg, 0.02 mmol) in solvent (2 mL) was stirred at room temperature. [b] Yield of isolated product. [c] The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d] 10 mol% PCy_3 was used. [e] 10 mol% trifuran-2-ylphosphine was used. [f] 10 mol% tri-*o*-tolylphosphine was used. [g] The reaction was carried out at reflux.

[a] Z. Chen, Prof. Dr. J. Zhang
Shanghai Key Laboratory of Green Chemistry and Chemical Processes
Department of Chemistry
East China Normal University
3663 N. Zhongshan Road, Shanghai 200062 (P.R. China)
Fax: (+86) 21-6223-3213
E-mail: jlzhang@chem.ecnu.edu.cn

[b] Prof. Dr. J. Zhang
State Key Laboratory of Organometallic Chemistry,
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032, (P.R. China)

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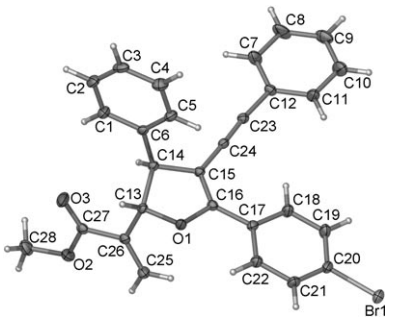
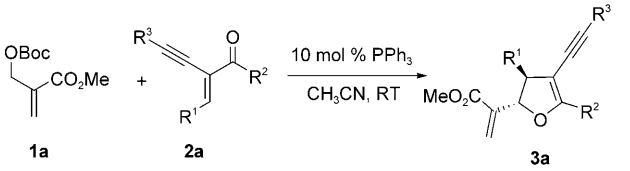


Figure 1. ORTEP representation of compound **3f**. Thermal ellipsoids for non-hydrogen atoms are shown at the 30% probability level.

tries 3–5). No reaction occurs for other tested phosphines such as PCy_3, trifuran-2-ylphosphine, and tri-*o*-tolylphosphine (Table 1, entries 11–13). The product yield and the diastereoselectivity decreased dramatically when the reaction was carried out at reflux in CH_3CN with 10 mol% PPh_3 (Table 1, entry 14). Finally, it was found that CH_3CN was the best solvent, providing **3a** in 82% yield of isolated product with a 20:1 d.r. in 11 h at room temperature (Table 1, entry 15).

With the optimal reaction conditions in hand, we next examined the scope of this phosphine-catalyzed [4+1] annulation reaction, and the results are summarized in Table 2. These results showed that all three substituents (R^{1-3}) could be not only aromatic but also aliphatic groups to afford the corresponding tetrasubstituted 2,3-dihydrofurans. The annulations of **1a** with conjugated yne-enones **2b–d** bearing a 4-

Table 2. Synthesis of highly functionalized 2,3-dihydrofurans.[a]



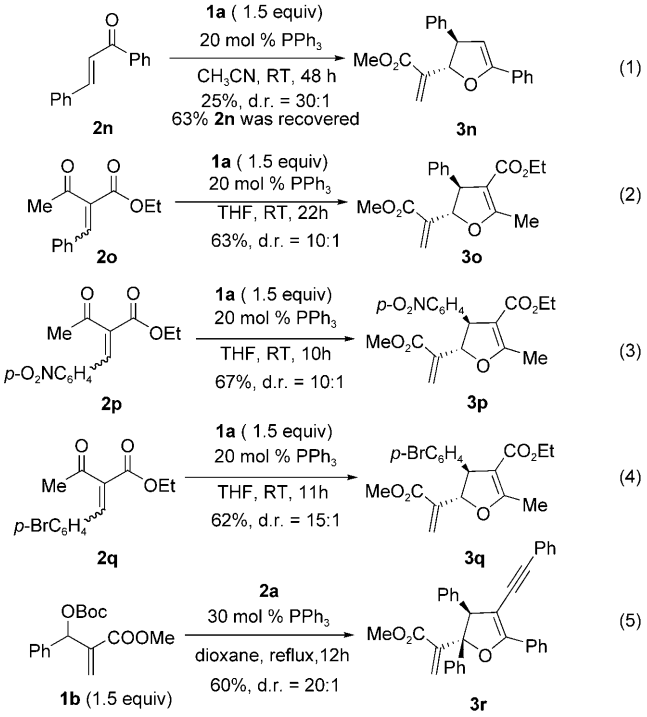
1a **2a** **3a**

Entry	Enyne **2** $R^1/R^2/R^3$	t [h]	**3** Yield [%][b]	d.r.[c]
1	Ph/Ph/Ph (**2a**)	11	**3a** (82)	20:1
2	Ph/Ph/4-$NO_2C_6H_4$ (**2b**)	10	**3b** (63)	14:1
3	Ph/Ph/4-$MeOC_6H_4$ (**2c**)	18	**3c** (70)	30:1
4[d]	Ph/Ph/1-cyclohexenyl(**2d**)	13	**3d** (60)	20:1
5	Ph/4-ClC_6H_4/Ph (**2e**)	8	**3e** (81)	16:1
6	Ph/4-BrC_6H_4/Ph (**2f**)	8	**3f** (76)	13:1
7	2-BrC_6H_4/Ph/Ph (**2g**)	10	**3g** (80)	10:1
8[d]	Ph/4-$MeOC_6H_4$/Ph (**2h**)	12	**3h** (59)	11:1
9	4-ClC_6H_4/Ph/Ph (**2i**)	8	**3i** (74)	14:1
10[d]	4-$MeOC_6H_4$/Ph/Ph (**2j**)	16	**3j** (59)	10:1
11[d]	Ph/Me/Ph (**2k**)	12	**3k** (72)	20:1
12[d]	Ph/Me/1-naphthyl (**2L**)	22	**3l** (67)	16:1
13[d]	*n*Butyl/Me/Ph (**2m**)	20	**3m** (47)	20:1

[a] Reaction conditions: Under Ar, a mixture of **1a** (97.0 mg, 0.45 mmol), **2** (0.3 mmol), and PPh_3 (7.9 mg, 0.03 mmol) in solvent (3 mL) was stirred at room temperature. [b] Yield of isolated product. [c] The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d] 20 mol% PPh_3 was used.

nitrophenyl, 4-methoxyphenyl, or 1-cyclohexenyl substituent at the alkyne (R^3) worked well to give the expected products in 60–70% yields (Table 2, entries 2–4). Furthermore, substitutents such as chloro, bromo, and methoxyl groups at R^1 or the R^2 phenyl ring are also tolerant (Table 2, entries 5–10). Finally, the substituents R^1 and R^2 could also be an aliphatic group. For example, annulations of **2k–m** with **1a** could give 2,3-dihydrofurans **3k–m**, albeit with a higher catalyst loading (20 mol% PPh_3) (Table 2, entries 11–13). It is noteworthy that all these annulations are highly diastereoselective (d.r. = 10:1–30:1).

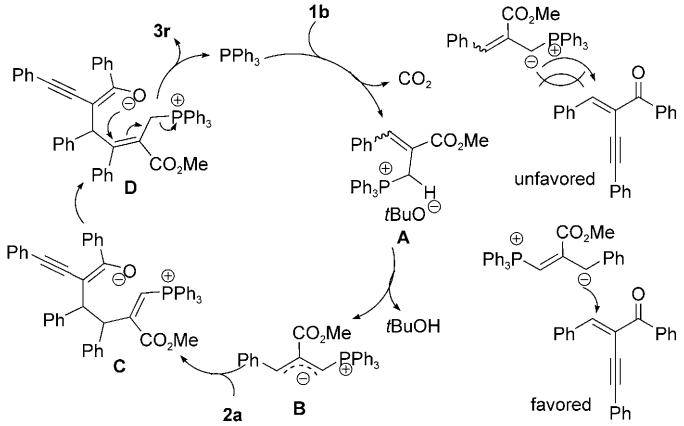
Since the alkyne moiety of yne-enones **2** was not involved in the [4+1] annulations, we envisaged that other types of activated enones may undergo similar transformation. Indeed, this hypothesis was proved by further investigation [Eqs. (1)–(5)]. For example, the reaction of **1a** with chalcone



2n could give the desired product **3n** in 25% yield along with 63% yield of recovered **2n**, indicating that the alkyne moiety in the yne-enones acts as an activating group to make them more reactive by lowering the LUMO energy level.[6h] Pleasingly, activated enones **2o–q** are appropriate substrates to give the corresponding cycloadducts **3o–q** in 60–67% yields. In these cases, THF was found to be a better solvent [Eqs. (2)–(4)]. Moreover, the methyl 2-((*tert*-butoxycarbonyl-oxy)(phenyl)methyl)acrylate **1b** could also react with **2a** in refluxing dioxane to give product **3r** in 60% yield as a single diastereomer [Eq. (5)].

The detailed mechanism of this unexpected annulation reaction has not been clarified, and the reason why it did not undergo [3+2] annulations[5] is unclear. According to these

experimental results and some literature precedents[2a,5h,j] for phosphine-catalyzed reactions, we propose a plausible mechanism for this unexpected phosphine-catalyzed regio- and diastereoselective [4+1] annulation reaction as follows (Scheme 1). The reaction might be triggered by the formation of the phosphonium salt **A** via the addition–elimination mechanism.[2a] Subsequent deprotonation by the in situ generated *tert*-butoxide anion would generate ylide **B**. Nucleophilic addition of the resultant intermediate **B** to conjugated yne-enone **2a** would yield intermediate **C** via favored γ-carbon addition. Intermediate **C** would isomerize into intermediate **D** under the conditions via 1,3-H shift. Subsequent intramolecular S_N2' nucleophilic substitution would give the final product (**3r**) and regenerate Ph_3P. The reaction pathway via addition of α-carbon of the ylide **B** to **2a** is unfavored owing to the steric hindrance of the bulky phosphine group and the substituent R^1 of **2a**.



Scheme 1. A plausible mechanism.

In summary, we have discovered an unexpected phosphine-catalyzed regio- and diastereoselective [4+1] annulation reaction of readily available Morita–Baylis–Hillman carbonates and activated enones, which provided a simple, efficient, and practical method for the synthesis of highly functionalized 2,3-dihydrofurans. Further studies will focus on the development of related organocatalytic transformations of activated enones, as well as synthetic applications of the functionalized 2,3-dihydrofurans.

Experimental Section

Typical procedure for the synthesis of **3a** (Table 2, entry 1): Under Ar, a mixture of **1a** (97.0 mg, 0.45 mmol), **2a** (93.0 mg, 0.3 mmol), and PPh_3 (8.0 mg, 0.03 mmol) in CH_3CN (3 mL) was stirred at room temperature until the reaction was complete (monitored by TLC). Then the reaction mixture was diluted with water (3 mL) and extracted with CH_2Cl_2. The organic layers were combined, washed with brine (10 mL), and dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified by flash column chromatography on silica gel (hexanes/AcOEt = 20:1) to afford 100 mg (82%) of **3a** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, J = 7.2 Hz, 2H), 7.40–7.11 (m, 13H), 6.28 (s, 1H), 5.81 (s, 1H), 5.30 (d, J = 4.5 Hz, 1H), 4.07 (d, J = 4.5 Hz, 1H), 3.66 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.68, 157.34, 142.07, 139.07, 131.00, 129.85, 129.58, 128.60, 128.32, 128.18, 127.70, 127.63, 127.16, 126.59, 124.75, 123.78, 96.39, 95.75, 85.59, 85.06, 59.50, 51.82 ppm; MS (EI) m/z (%): 406 [M^+] (54.17), 105 (100); HRMS calcd for $C_{28}H_{22}O_3$: 406.1569, found: 406.1564. For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

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Keywords: annulation reactions · diastereoselectivity · dihydrofurans · enynes · phosphines

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[7] CCDC 736940 (**3 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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