

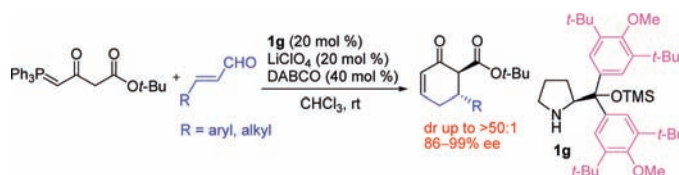
Asymmetric Tandem Michael
Addition—Wittig Reaction to
Cyclohexenone AnnulationYan-kai Liu,[†] Chao Ma,[†] Kun Jiang,[†] Tian-Yu Liu,[†] and Ying-Chun Chen^{*,†,‡}

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Received May 13, 2009

ABSTRACT



A highly stereoselective tandem Michael addition-Wittig reaction of (3-carboxy-2-oxopropylidene)triphenylphosphorane and α,β -unsaturated aldehydes has been developed by employing the combined catalysis of a newly designed bulky chiral secondary amine **1g**, LiClO₄, and DABCO. The multifunctional 6-carboxycyclohex-2-en-1-ones were generally obtained in excellent diastereo- and enantioselectivities (dr up to >50:1, 86–99% ee).

Phosphorus ylides are versatile reagents for the construction of carbon–carbon bonds in synthetic organic chemistry, especially in the reaction with carbonyl compounds, well-known as the Wittig reaction.¹ However, the application of

phosphorus ylide-containing reagents in asymmetric synthesis is limited.² Phosphorus ylides adjacent to an electron-withdrawing carbonyl group are stable materials and can be easily handled without much caution. They have been extensively applied to introduce further functional groups into organic substrates. In 1983, Pietrusiewicz et al. designed an elegant tandem Michael addition–Wittig reaction of (3-carboxy-2-oxopropylidene)triphenylphosphorane and α,β -unsaturated aldehydes to afford highly functionalized 6-carboxycyclohex-2-en-1-ones,³ which may find wide synthetic utility for molecular complexity, in a formal [3 + 3] annulation manner.⁴ A strong base, NaH, was used for the enolate generation, which would facilitate the addition to conjugated double bond of α,β -unsaturated aldehydes. Nevertheless, only low to fair yields were attained. In our

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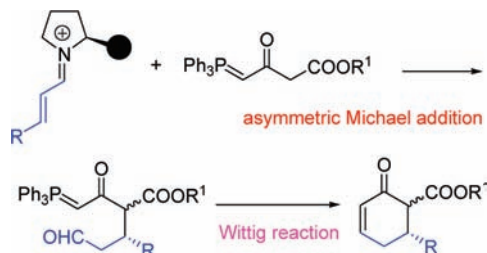
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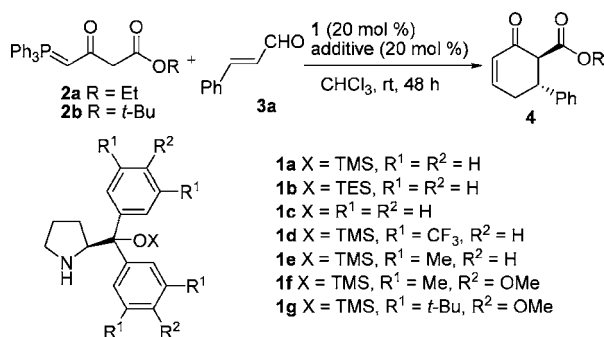
continuing efforts to develop the catalytic asymmetric reactions of phosphorus ylides,⁵ we envisaged that the stereoselective version of the above reaction might be realized via the iminium activation of the electrophilic α,β -unsaturated aldehydes with a chiral secondary amine.⁶ A following intramolecular Wittig reaction would deliver the desired chiral cyclohex-2-en-1-one derivatives (Scheme 1).^{7,8}

Scheme 1. Chiral Iminium Catalysis as the Key Step in the Asymmetric Formal [3 + 3] Cyclohexenone Annulation



Based on such considerations, the possible tandem reaction of stabilized phosphorus ylide **2a**³ and cinnamaldehyde **3a** was initially investigated by the catalysis of a secondary amine α,α -diphenylprolinol *O*-TMS ether **1a** (see Table 1)

Table 1. Screening Studies of the Tandem Reaction of Stabilized Ylides **2** and Cinnamaldehyde **3a**^a



entry	1	additive	2	yield ^b (%)	dr ^c	ee ^d (%)
1 ^e	1a	BzOH	2a	-	-	-
2 ^e	1a	NaOAc	2a	4a , <10	-	-
3 ^e	1a	DBACO	2a	4a , 21	6:1	65
4 ^e	1a	DABCO + LiClO ₄	2a	4a , 53	9:1	75
5	1a	DABCO + LiClO ₄	2a	4a , 62	7:1	74
6 ^f	1a	DABCO + LiClO ₄	2a	4a , 71	6:1	72
7 ^f	1b	DABCO + LiClO ₄	2a	4a , 46	7:1	80
8 ^f	1c	DABCO + LiClO ₄	2a	-	-	-
9 ^f	1d	DABCO + LiClO ₄	2a	-	-	-
10 ^f	1e	DABCO + LiClO ₄	2a	4a , 75	8:1	80
11 ^f	1f	DABCO + LiClO ₄	2a	4a , 79	8:1	79
12 ^f	1g	DABCO + LiClO ₄	2a	4a , 82	8:1	97
13 ^f	1g	DABCO + LiClO ₄	2d	4b , 85	41:1	98

^a Unless noted otherwise, reactions were performed with ylide **2** (0.1 mmol), cinnamaldehyde **3a** (0.2 mmol), 20 mol % of **1**, and 20 mol % of additive in CHCl₃ (0.8 mL) for 48 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d Determined by chiral HPLC analysis. ^e For 24 h. ^f With 40 mol % of DABCO.

and BzOH in CHCl₃ at room temperature.⁹ It was disappointing that almost no reaction occurred after 24 h (Table 1, entry 1).¹⁰ Fortunately, the expected product **4a** was detected in the presence of a basic additive NaOAc, albeit in very low yield (<10%) (entry 2).¹¹ Moreover, a better yield was obtained when DABCO (20 mol %) was used, while the diastereo- and enantioselectivity was modest (entry 3). To our gratification, the yield and enantioselectivity could be significantly improved when LiClO₄ (20 mol %) and DABCO were employed together (entry 4). Probably, LiClO₄ would coordinate with β -keto ester groups of **2a**, which would be helpful for its enolization process and thus enhance the nucleophilic addition to cinnamaldehyde **3a**. Other lithium salts (LiOAc or LiBr) gave much inferior results in the model reaction. A slightly higher yield was obtained when the reaction time was extended to 48 h (entry 5), and even a better yield was isolated when 40 mol % of DABCO was applied (entry 6). Subsequently, more secondary amine catalysts **1b–g** were screened in order to improve the enantioselectivity. *O*-TES ether **1b** gave a higher ee value but with much lower yield (entry 7). No reaction occurred catalyzed by free prolinol **1c** or *O*-TMS ether **1d** with strong electron-withdrawing aryl groups (entries 8 and 9, respectively). On the contrary, *O*-TMS **1e** and **1f** with electron-donating aryl groups afforded good yield and stereocontrol (entries 10 and 11).¹² Finally, we were pleased to find that the newly designed bulky secondary amine **1g** exhibited excellent enantioselectivity without effects on the catalytic efficacy (entry 12).¹³ In addition, more remarkable enantio- and diastereoselectivities (98% ee, dr 41:1) were achieved for the ylide **2b** bearing a bulky *tert*-butyl ester motif (entry 13).

With the optimal reaction conditions in hand, we then examined the tandem reaction of a spectrum of α,β -unsaturated aldehydes with phosphorus ylide **2b** by the combined catalysis of the secondary amine **1g** (20 mol %), LiClO₄ (20 mol %), and DABCO (40 mol %). The reactions were generally conducted in CHCl₃ at room temperature for 48 h. The results were summarized in Table 2. α,β -Unsaturated aldehydes bearing a diversity of electron-withdrawing or -donating aryl groups could be well tolerated, and excellent diastereo- and enantioselectivities were obtained in good to high isolated yields (Table 2, entries 2–10). It should be noted that α,β -unsaturated aldehyde with an *o*-bromophenyl group exhibited lower reactivity, and 30 mol % of **1g** was employed for 72 h (entry 8). On the other hand, outstanding ee values were obtained for α,β -unsaturated

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Table 2. Asymmetric Tandem Reaction of Stabilized Ylide **2b** and α,β -Unsaturated Aldehydes **3**^a

entry	R	yield ^b (%)	dr ^c	ee ^d (%)
1	Ph	4b , 85	41:1	98
2	<i>p</i> -NO ₂ -C ₆ H ₄	4c , 67	17:1	99
3	<i>p</i> -CF ₃ -C ₆ H ₄	4d , 85	36:1	98
4	<i>m</i> -CN-C ₆ H ₄	4e , 81	21:1	98
5	<i>p</i> -Br-C ₆ H ₄	4f , 74	>50:1	99 ^e
6	<i>p</i> -Cl-C ₆ H ₄	4g , 78	>50:1	99
7	<i>m</i> -Cl-C ₆ H ₄	4h , 81	>50:1	98
8 ^f	<i>o</i> -Br-C ₆ H ₄	4i , 56	10:1	99
9	<i>p</i> -MeO-C ₆ H ₄	4j , 82	>50:1	98
10	<i>m</i> -Me-C ₆ H ₄	4k , 76	>50:1	98
11	2-furyl	4l , 80	3:1	96
12	2-thienyl	4m , 82	8:1	98
13	1-naphthyl	4n , 82	10:1	96
14 ^f	Me	4o , 65	25:1	86
15 ^f	<i>n</i> -Pr	4p , 62	4:1	93
16 ^g	Ph	4b , 60	>50:1	99

^a Unless noted otherwise, reactions were performed with ylide **2b** (0.1 mmol), α,β -unsaturated aldehyde **3** (0.2 mmol), 20 mol % of **1g**, 20 mol % of LiClO₄, and 40 mol % of DABCO in CHCl₃ (0.8 mL) at rt for 48 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d Determined by chiral HPLC analysis. ^e The absolute configuration of enantiopure **4f** was determined by X-ray analysis; see Figure 1. The other products were assigned by analogy. ^f With 30 mol % of **1g** for 72 h. ^g At 0.6 mmol scale, for 72 h.

aldehydes possessing heteroaryl groups, albeit moderate diastereoselectivities were observed (entries 11 and 12). Good results were also attained for 1-naphthyl-substituted enal (entry 13). Importantly, α,β -unsaturated aldehydes with alkyl substitutions could be successfully utilized, while higher catalytic loadings and longer reaction time were required (entries 14 and 15). Nevertheless, enals with β -branched alkyl groups failed to give the desired products probably due to steric reasons. A catalytic reaction has been conducted at a larger scale, and good results were obtained after 72 h (entry 16).

As an illustration of the utility of this method, the cyclic product **4** could be readily converted to some interesting compounds with more complexity (Scheme 2). The methylation of **4a** could be easily conducted under phase-transfer catalysis to give intermediate **I**, which was further trans-

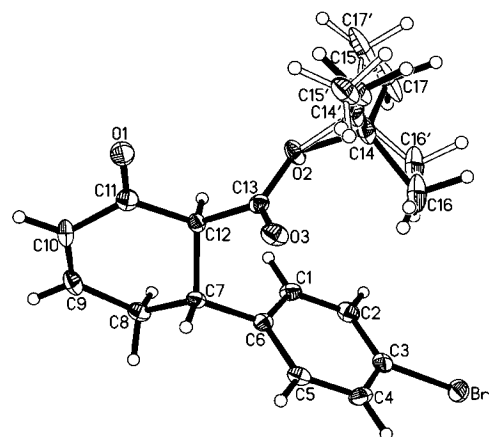
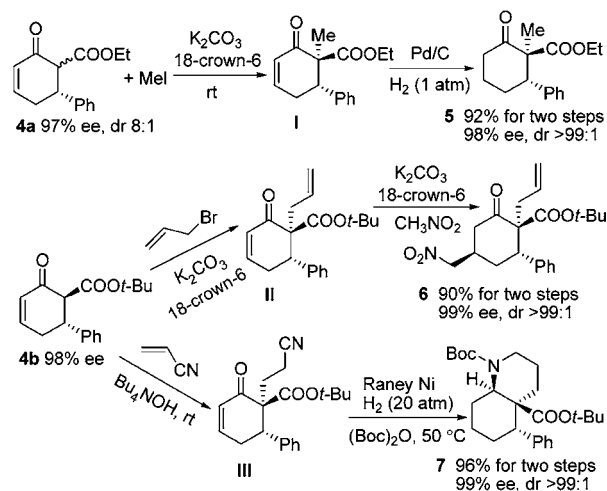


Figure 1. X-ray structure of enantiopure **4f**.

Scheme 2. Synthetic Transformations of Cyclohexanone Products



formed to diastereo- and enantiomerically pure **5** with adjacent quaternary and tertiary stereogenic centers. On the other hand, the asymmetric Michael addition of nitromethane to the allylation intermediate **II** from cyclohexanone **4b** also exhibited excellent diastereoselectivity; thus, another tertiary chiral center was introduced in the highly substituted cyclohexanone **6**. Moreover, the asymmetric Michael addition of **4b** to acrylonitrile gave intermediate **III**, which underwent a tandem reductive ring closure process to afford decahydroquinoline derivative **7** in excellent yield and stereoselectivity.

In conclusion, we have developed the highly stereoselective formal [3 + 3] cycloaddition reaction of (3-carboxy-2-oxo-propylidene)triphenylphosphorane and α,β -unsaturated aldehydes by the combined catalysis of a newly designed bulky chiral secondary amine, LiClO₄ and DABCO. This

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(12) For solvent screenings with catalyst **1f**: DCM, 64% yield, 65% ee; THF, 50% yield, 73% ee; dioxane, 54% yield, 77% ee; MeCN, 61% yield, 74% ee (all dr ratios were less than 10:1).

tandem process, including an asymmetric Michael addition and a following Wittig reaction in one pot, generally provided synthetically important cyclohexenone derivatives in excellent diastereo- and enantioselectivities for a broad spectrum of α,β -unsaturated aldehyde substrates (dr up to >50:1, 86–99% ee). Currently, the further development of asymmetric reactions of phosphorus ylide-containing reagents is underway in our laboratory.

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of

China (20772084) and Sichuan Province Government (07ZQ026-027).

Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products; CIF of enantiopure **4f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) For the synthesis of the bulky catalyst **1g**, see the Supporting Information.