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N,*N*,*N*′,*N*′-Tetramethyl-1,3-propanediamine as the catalyst of choice for the Baylis–Hillman reaction of cycloalkenone: rate acceleration by stabilizing the zwitterionic intermediate via the ion–dipole interaction

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Abstract—*N*,*N*,*N*′,*N*′-Tetramethyl-1,3-propanediamine (TMPDA) can be used as an efficient catalyst for the Baylis–Hillman reaction of cycloalkenones. The increased reaction rate was thought be derived from the stabilizing effect of the zwitterionic intermediate via the ion–dipole interaction.

The Baylis–Hillman reaction provides a simple and atom economic synthesis of β-hydroxy-α-methylene esters, nitriles, ketones, etc.[1,2] The Baylis–Hillman adducts have many versatile functionality thus make these adducts as valuable synthetic intermediates.[1,2] In these contexts many research groups are studying the reaction extensively.

However, the Baylis–Hillman reaction has some limitations. One of the major drawbacks in the Baylis–Hillman reaction is the extremely slow reaction rate.[3–5] Thus, the improvement of the reaction rate has been studied most deeply by many research groups.[3–5] Numerous physical and chemical methods have been developed to fasten the reaction rate.[1,3–5] Of these methods, the chemical methods have the advantage of not requiring specialized equipment, and so are more attractive.

Among the activated alkenes cycloalkenones are famous for their slow reaction rate.[4–14] Under the normal reaction conditions using DABCO (1,4-diazabicyclo[2.2.2]octane) no reaction was observed. Recently, various methods for the synthesis of the Baylis–Hillman adducts of cycloalkenones have been developed with certain limitations.[4–14] The combination of 2,6-diphenyl-4*H*-chalcogenopyran-4-ones (or -4-thiones) and $TiCl_4$ in methylene chloride[6a] and related methods were developed for the reactive *p*-nitrobenzaldehyde and 2-cyclohexen-1-one or 2-cyclopenten-1-one.[6] The combination of $LiClO_4$ and DABCO in ether could be used for the Baylis–Hillman reaction of benzaldehyde and 2-cyclohexen-1-one.[7] The use of Et_2AlI in CH_2Cl_2 for the reaction of enone isolevoglucosenone and C-β-D-galactopyranosylformaldehyde furnished the corresponding Baylis–Hillman adduct.[8] 4-(Dimethylamino)pyridine (DMAP)-catalyzed hydroxymethylation of 2-cyclohexenones with formaldehyde was carried out effectively in aqueous medium.[9] Tributylphosphine combined with BINOL (1,1′-bi-2-naphthol) was used effectively for cycloalkenone system.[10] Lewis base effects in the Baylis–Hillman reaction of 2-cyclohexen-1-one and arylaldehydes or arylaldehyde *N*-tosylimines were examined including DMAP, tributylphosphine and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[11] Recently, it was known that $TiCl_4$ without the use of Lewis base could be applied to highly reactive aldehydes.[12] Lithium phenylselenide (PhSeLi) induced Baylis–Hillman reaction was applied successively to α,β-unsaturated lactone system.[13] In summary, for the Baylis–Hillman reaction of cycloalkenone derivatives, the combination of Lewis acid and Lewis base system[6,7,10] seemed the only choice except for

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the reactive formaldehyde.[9] Moreover, most of the reported methods were limited to reactive aldehydes with low to moderate yields of products.

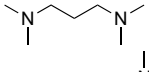
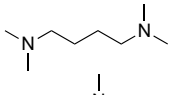
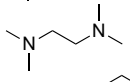
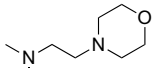
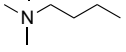
Most recently, Verkade and co-workers have reported a novel catalyst system for the effective Baylis–Hillman reaction of cycloalkenones, proazaphosphatrane sulfide combined with $TiCl_4$.[4] But, the method can also be categorized as the acid–base combination system. Imidazole-catalyzed Baylis–Hillman reaction, especially in basic water solution,[5b] was found to be effective for cycloalkenones.[5] We also have reported the DMAP-catalyzed Baylis–Hillman reaction of cycloalkenones in aqueous THF.[14] Although the yields were moderate (53–64%), DMAP-catalyzed Baylis–Hillman reaction of cyclohexenones seemed the most simple and convenient method until now. However, there is still scope for further improvements. In order to shed more lights on our efforts to increase the reaction rate of Baylis–Hillman reaction of cycloalkenones, we intended to search more efficient catalyst. Fortunately, we found a good catalyst, TMPDA, and wish to report herein the results.

Nonbonding electron pairs on the nitrogen or phosphorous atom could stabilize intramolecularly the neighboring cationic character developed on the N or P atom.[15] However, such a simple concept has not been applied much to the Baylis–Hillman reaction.[4,6c,11b] In the Aggarwal's paper involving the use of DBU, the intermediate β-ammonium enolate is stabilized through conjugation, which increases its equilibrium concentration, and this results in significantly enhanced rate.[11b] Verkade[4] and Kataoka[6c] have mentioned about the stabilization effects of the zwitterionic species by intrabridgehead interaction or transannular interaction in their excellent papers. The use of chiral phosphine, BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), has been used in order to prepare Baylis–Hillman adducts as enantiomerically enriched form.[16] In these contexts, we intended to study on the catalytic effects of such tertiary diamines, which can stabilize the intermediate zwitterionic species during the Baylis–Hillman reaction by intramolecular ion–dipole interaction as shown in Scheme 1.

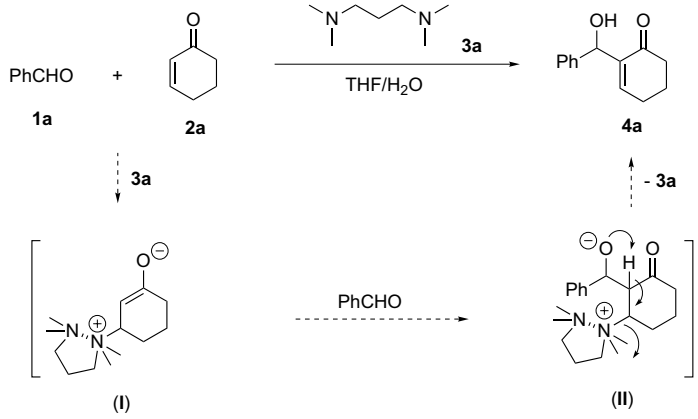
As a model study, we have chosen the reaction of benzaldehyde (**1a**) and 2-cyclohexen-1-one (**2a**) with various commercially available diamines **3a–d** (see Table 1). The reaction showed almost no reaction when we used DABCO or triphenylphosphine as the catalyst. However, to our surprise, 87% isolated yield of the desired adduct **4a** was isolated in 72 h at room temperature with *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA) catalyst.[17] As shown in Table 1, *N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine (**3b**), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (**3c**), 4-[2-(dimethylamino)ethyl]morphorine (**3d**), and *N*,*N*-dimethylbutylamine (**3e**) showed lower yields of product. As generally expected, the diamines **3a** and **3b**, which can stabilize the zwitterionic intermediate via the intramolecular five- and six-membered ring, showed better results than other amine catalysts.

The increased reaction rate when we use TMPDA as the catalyst might be attributed partly to (1) stabilizing effect of the zwitterionic intermediates (**I** and **II**) by intramolecular ion–dipole interaction as shown in Scheme 1, (2) statistically, two equivalents of Lewis basic site as in DABCO, (3) relatively small steric hindrance around the nitrogen atom as in DABCO or Me_3N.[3h,18] Due to the above plausible reasons increased

Table 1. Synthesis of **4a** from **1a** and **2a** with amine catalyst **3**[a]

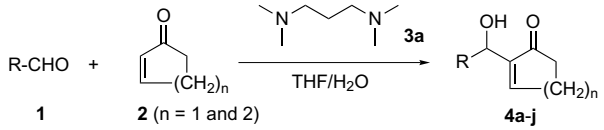
Entry	Amine catalyst		Yield of **4a** (%)
1		**3a**	87
2		**3b**	80
3		**3c**	61
4		**3d**	46
5		**3e**	66 (67)[b]

[a] Conditions: **1a/2a/3a–e** = 1:2:1, aq THF, rt, 72 h.
[b] Conditions: **1a/2a/3e** = 1:2:2, aq THF, rt, 72 h.



Scheme 1. General reaction pathway.

Table 2. Synthesis of Baylis–Hillman adducts **4** with TMPDA (**3a**)[a]



1 **2** (n = 1 and 2) **4a-j**

Entry	Aldehyde **1**	Cycloalkenone **2**	Time (h)	Product **4** (% yield)[b]
1	PhCHO (**1a**)	2-Cyclohexen-1-one (**2a**)	72	**4a** (87)[4]
2	4-MeOPhCHO (**1b**)	**2a**	72	**4b** (69)[8b]
3	2-MeOPhCHO (**1c**)	**2a**	72	**4c** (83)[4]
4	HCHO (**1d**)[c]	**2a**	72	**4d** (94)[3i]
5	Hexanal (**1e**)	**2a**	72	**4e** (83)[14]
6	**1a**	2-Cyclopenten-1-one (**2b**)	72	**4f** (65)[3i]
7	**1b**	**2b**	48	**4g** (85)[3e]
8	**1c**	**2b**	60	**4h** (78)[19]
9	**1d**[c]	**2b**	72	**4i** (56)[5a]
10	**1e**	**2b**	48	**4j** (74)[14]

[a] Conditions: **1/2/3a** = 1:2:1, aq THF, rt.
[b] Reference.
[c] Excess amount of formaldehyde (ca. 5.0 equiv as aq solution) was used.

amounts of zwitterion could be generated and resulted in increased reaction rate. Thus, we applied the reaction conditions toward some aldehydes including the unreactive *ortho*- and *para*-anisaldehydes, and the results are listed in Table 2. As shown, moderate to good yields of the Baylis–Hillman adducts **4a**–**j** were obtained even with *p*-anisaldehyde and *o*-anisaldehyde. 2-Cyclopenten-1-one showed similar reactivity.[19,20]

However, the application of TMPDA in the reaction of acyclic alkene such as acrylonitrile (74%) and methyl vinyl ketone (55%) under the same reaction conditions did not show good results. Similar to lower yields of products were obtained as compared with the reported methods.[3] Especially, the reaction with methyl acrylate produced only trace amounts of product, unfortunately. The reason for the unfavorable results of acyclic alkenes than the cycloalkenones is hard to explain at this point. However, we are tentatively supposing the reason might be arised due to the conformational mobility in the zwitterions of acyclic alkenes.

Next we examined the reaction of benzaldehyde and 2-cyclohexen-1-one with TMPDA in the presence of acid co-catalyst such as $LiClO_4$[7] or 1,1,1-trifluoroethanol.[1d] The acid catalyst did not improve the results significantly in view of reaction rate or yield of product. We examined some diphosphine catalysts including 1,3-bis(diphenylphosphino)propane, 1,2-bis(diphenylphosphino)ethane, and 1,4-bis(diphenylphosphino)butane, which did not show significant catalytic activity, unfortunately. The unfavorable results of diphosphines might be derived from the steric hindrance of phenyl substituents and the facile air oxidizable nature of phosphine.

In summary, we found a useful catalyst, TMPDA, for the Baylis–Hillman reaction of cycloalkenones.[20] We are expecting the simple catalyst system would be used widely for the preparation of various types Baylis–Hillman adducts of cycloalkenones.

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19. General procedure: A mixture of cycloalkenone (2 mmol), aldehyde (1 mmol), and TMPDA (1 mmol) in aq THF (1:1, 0.8 mL) was stirred for 72 h at room temperature. After appropriate aqueous workup and column chromatographic purification (hexanes/ether/CH_2Cl_2, 4:1:1) we obtained analytically pure products. All the compounds except **4h** have been reported (Table 2). The spectroscopic data of **4h** is as follows. IR (neat) 3433, 1697, 1242 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44–2.47 (m, 2H), 2.55–2.61 (m, 2H), 3.83 (s, 3H), 3.87 (d, $J = 5.4$, 1H), 5.84 (d, $J = 5.4$ Hz, 1H), 6.88 (dd, $J = 8.1$ and 0.9 Hz, 1H), 6.97 (td, $J = 7.8$ and 0.6 Hz, 1H), 7.23–7.30 (m, 2H), 7.38 (dd, $J = 7.8$ and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 29.97, 49.61, 55.15, 67.19, 109.99, 120.43, 126.24, 128.22, 130.65, 134.16, 155.71, 165.49, 211.18; Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.48; H, 6.51.
20. For the convenient comparison, we summarized the known methods for the synthesis of **4a**: 55% (**1a/2a**/DMAP = 1:1:0.2, aq THF, rt, 72 h),[14] 90% (**1a/2a**/proazaphosphatrane sulfide/$TiCl_4$, 1:3:0.05:1, CH_2Cl_2, rt, 10 min),[4] 82% (**1a/2a**/3-HDQ = 1:2:1, H_2O, rt, 4 h),[3i] 60% (**1a/2a**/DBU = 1:1:1, rt, 0.5 h),[11b] 69% (**1a/2a**/imidazole = 2:1:0.1, aq THF, rt, 65 days),[5a] 61% (**1a/2a**/imidazole = 2:1:0.1, aq THF, 50 °C, 20 days),[5a] 45% (**1a/2a**/imidazole = 1:2:1, 1 M $NaHCO_3$/THF, rt, 90 h),[5b] 25% (**1a/2a**/$Me_2S/TiCl_4$ = 1:3:0.1:1, CH_2Cl_2, rt, 1 h),[6b] 57% (**1a/2a**/BINOL/Bu_3P = 1:1.5:0.1:0.2, THF, rt, 48 h),[10] 56% (**1a/2a**/$LiClO_4$/DABCO = 1:1:0.7:0.15, ether, 0 °C, 20 h).[7]