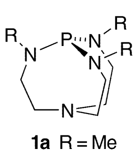
**Baylis–Hillman Reaction**

# A Highly Active and Selective Catalyst System for the Baylis–Hillman Reaction**

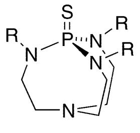
*Jingsong You, Juhua Xu, and John G. Verkade**

The Baylis–Hillman (BH) reaction, i.e., coupling of an activated alkene or alkyne with an aldehyde or ketone, has recently become a very attractive goal.[1] These reactions usually require Lewis bases as catalysts, such as tertiary phosphanes or tertiary amines, among which 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most popular. However, this approach suffers from slow reaction rates (reaction times of weeks and even months[1,2]) which limit the scope of substrates. Numerous chemical and physical methods have been developed to accelerate BH reactions.[1,3] One of the Lewis acids typically used to activate the carbonyl group[4] is $TiCl_4$, used with or without additives (e.g., quaternary ammonium salts, an organic chalcogenide, phosphanes, a diol or a bisoxazoline).[1,4,5] Although the rates of BH reactions are improved significantly with the assistance of $TiCl_4$, the yields are generally only moderate, and limitations are encountered on the structures of the Michael acceptors and the aldehydes which undergo addition, frequently producing complex mixtures.[5–7]

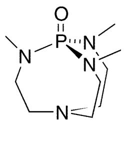
The commercially available bicyclic proazaphosphatranes **1a**–**1c**, first synthesized in our laboratories, have attracted considerable interest in recent years as versatile, exceedingly strong nonionic bases and as catalysts for a variety of useful transformations.[8] Recently, we reported that in the presence of proazaphosphatrane **1c**, activated allylic compounds such as acrylonitrile react efficiently with aromatic aldehydes to afford BH adducts as the only product.[9] However, when activated alkenes (cyclohex-1-en-1-one, vinyl ketones, acrylates, and allyl cyanide) were used as substrates in the presence of **1a**–**1c**, the BH reactions failed whether with or without a Lewis acid ($TiCl_4$ or $AlCl_3$) present. Herein we report the surprising discovery that the proazaphosphatrane sulfide **2a**, easily prepared from commercially available **1a**, facilitates unparalleled speed and selectivity in BH reactions catalyzed by $TiCl_4$.



**1a** R = Me
**1b** R = *t*Bu
**1c** R = *i*Pr



**2a** R = Me
**2b** R = *t*Bu
**2c** R = *i*Pr



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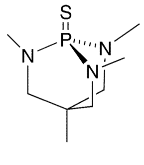

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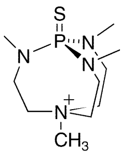

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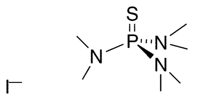
Initially, we examined the model reaction of *p*-nitrobenzaldehyde (1 mmol) with comparatively unreactive cyclohex-2-en-1-one (3 mmol) in $CH_2Cl_2$ (2 mL) under argon at room temperature.[10] When 20 mol% catalyst **2a** was employed without any additives, this reaction gave only a 5% product yield (based on the aldehyde) after four days. However, we found that the rate improved remarkably when one equivalent of some Lewis acids was added. After screening a variety of such acids (e.g., $MgSO_4$, $BF_3{\cdot}OEt_2$, $BCl_3$, $SnCl_4$, $AlCl_3$, $Ti(O\textit{i}Pr)_4$, and $TiCl_4$), we found that $TiCl_4$ gave the best results. The model reaction carried out in the presence of 20 mol% **2a** and 1.0 equiv of $TiCl_4$ gave a 95% yield of the product in only 5 min at room temperature.[11] Even with as little as 5 mol% **2a**, a 94% yield was observed in 10 min at room temperature. Proazaphosphatrane sulfides **2b** and **2c** showed slightly reduced activities over the same time period (perhaps due to steric hindrance of the R group), giving yields of 85 and 78%, respectively. To our knowledge, **2a**/$TiCl_4$ is the most effective catalyst system thus far reported for BH reactions.

To shed light on the possible origin of the remarkable activity of **2a** in $TiCl_4$-promoted BH reactions, proazaphosphatrane oxide **3** was first chosen for comparison. The BH reaction catalyzed by 0.05 equiv of **3** proceeded in 48% yield in only 10 minutes, similar to the yield realized with 1 equiv of $TiCl_4$ by itself (44%) over 2 h. This finding suggests a key role for the sulfur atom in **2a** in its catalytic activity. Interestingly, reactions catalyzed by 0.05 equivalents of the analogous bases **4**, lacking the bridgehead nitrogen of **2a**, and **5** led to dramatic decreases in yield (69 and 55%, respectively) after a reaction time of 10 minutes, and the acyclic analogue **6** (0.05 equiv) showed only moderate activity (59% yield) compared with that of **2a** over the same time period. The stronger cocatalytic activity of **2a** compared with that of **4**–**6** appears to be associated with the potential for $N_{ax}\rightarrow P$ intrabridgehead interactions, which enhances reaction rates and the nucleophilicity of the sulfur atom. Although the molecular structure of **2a** reveals an $N_{ax}\rightarrow P$ distance only 3% shorter than the sum of van der Waals radii of the P and N atoms (3.34 Å),[12] it is conceivable that additional shortening of this distance occurs during the reaction.

The first mechanism suggested for BH reactions mediated by a chalcogenide/metal halide catalyst system involved attack of the sulfur atom from $R_2S$ on the activated alkene.[6a] However, it is currently believed that these reactions proceed by attack of a halide ion released from a Lewis acid by $R_2S$.[7b] Supporting evidence for this was the unsuccessful use of $BF_3{\cdot}OEt_2$ as the Lewis acid, from which release of a halide ion is far less likely.[6] Very recently a BH reaction of methyl vinyl ketone with aldehydes mediated by tetrahydrothiophene/$BF_3{\cdot}OEt_2$ was developed which gave moderate product yields, indicating the unambiguous requirement of the sulfide for attack on the activated alkene.[13] In accord with these observations, the use of 1.0 equiv of $BF_3{\cdot}OEt_2$ in the reaction of cyclohex-2-en-1-one with *p*-nitrobenzaldehyde in the presence of **2a** (0.2 equiv) at room temperature gave a



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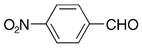
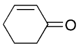
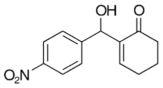
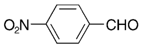
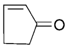
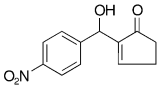
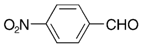
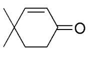
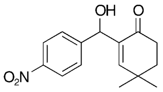
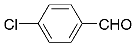
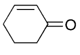
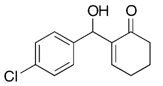
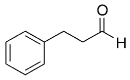
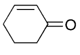
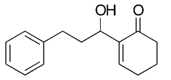
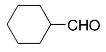
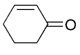
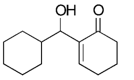
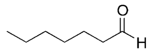
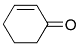
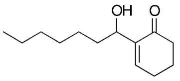
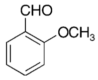
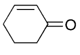
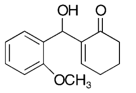
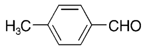
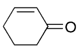
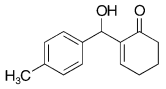
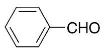
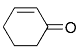
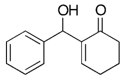
50 % yield of the BH adduct in four hours, while no desired adduct was isolated in the absence of **2a**.[14] It is reasonable to suggest that coordination of $BF_3$ to the carbonyl oxygen of the alkene activating group is followed by attack of the sulfur atom of **2a** on the carbon β to the carbon of the activating groups of the alkene, with a concomitant $N_{ax}\rightarrow P$ intrabridgehead interaction that electronically enriches the carbon α to the activating group[15] for nucleophilic attack on the aldehyde carbon. The low yield (53 %) of BH product achieved in 10 min in the reaction of *p*-nitrobenzaldehyde with 3-methylcyclohex-2-ene-1-one in the presence of $TiCl_4$ (1 equiv) and 0.05 equiv of **2a** is also in agreement with attack of **2a** (although impeded by the methyl group) at the 3-position of the 3-substituted enone.[16]

BH reactions mediated by **2a**/$TiCl_4$ tolerate a relatively wide scope of Michael acceptors and aldehydes at room temperature. As is evident in Table 1, cyclic enones (which are less reactive than acyclic analogues) were efficiently coupled with a wide variety of aldehydes to give BH adducts. Additionally, reactions of electron-deficient aromatic aldehydes afforded excellent yields in very short times (Table 1, entries 1–4). We were also delighted to find that electron-neutral aromatic aldehydes such as *p*-methylbenzaldehyde and benzaldehyde gave BH adducts with cyclohex-2-en-1-one in 91 % and 90 % yields, respectively, in only 10 min (entries 9 and 10). Surprisingly, the reaction of the notoriously recalcitrant hindered and deactivated *o*-anisaldehyde with cyclo-hex-2-en-1-one proceeded in 88 % yield (entry 8). In sharp contrast, BH reactions of inactive aromatic aldehydes such as this are sluggish with other reported catalyst systems, and the related reactions with cyclic enones are generally limited to the use of aromatic aldehydes with strong electron-withdrawing groups.[6] Whereas BH reactions with simple aliphatic aldehydes using $TiCl_4$/Lewis base copromoters often give low product yields,[6] our catalytic system provided very good yields (entries 5–7).

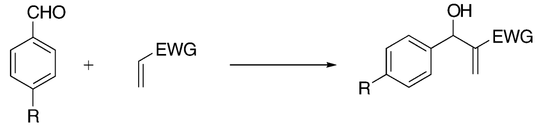
Noncyclic Michael-type acceptors were also examined under our aforementioned conditions (Table 2). Methyl vinyl

***Table 1:*** Baylis–Hillman reactions of aldehydes with cyclic enones catalyzed by **2a**/$TiCl_4$.[a]

| Entry | Aldehyde | Enone | Product | *t* [min] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 |  |  |  | 10 | 94 |
| 2 |  |  |  | 10 | 92 |
| 3 |  |  |  | 10 | 91 |
| 4 |  |  |  | 10 | 94 |
| 5 |  |  |  | 10 | 88 |
| 6 |  |  |  | 30 | 81 |
| 7 |  |  |  | 30 | 89 |
| 8 |  |  |  | 10 | 88 |
| 9 |  |  |  | 10 | 91 |
| 10 |  |  |  | 10 | 90 |

[a] The reactions were carried out with 1.0 mmol of aldehyde and 3.0 mmol of enone in the presence of **2a** (0.05 mmol) and $TiCl_4$ (1.0 mmol) in $CH_2Cl_2$ under Ar at room temperature. [b] Yield of isolated product based on aldehydes.

***Table 2:*** Baylis–Hillman reactions of aromatic aldehydes with acyclic Michael-type acceptors catalyzed by **2a**/$TiCl_4$.[a] EWG = electron-withdrawing group.



| Entry | Aldehyde | EWG | *t* [min] | Yield [%][b] |
|---|---|---|---|---|
| 1 | $4\text{-}O_2NC_6H_4CHO$ | $COCH_3$ | 5 | 92 |
| 2 | $C_6H_5CHO$ | $COCH_3$ | 5 | 85 |
| 3 | $4\text{-}O_2NC_6H_4CHO$ | $COOC_2H_5$ | 10 | 92 |
| 4 | $4\text{-}O_2NC_6H_4CHO$ | $COOCH_3$ | 10 | 92 |
| 5 | $4\text{-}ClC_6H_4CHO$ | $COOCH_3$ | 10 | 92 |
| 6 | $C_6H_5CHO$ | $COOCH_3$ | 10 | 88 |
| 7 | $4\text{-}CH_3OC_6H_4CHO$ | $COOCH_3$ | 10 | 87 |
| 8 | $C_6H_5CHO$ | CN | 20 | 95 |
| 9 | $4\text{-}O_2NC_6H_4CHO$ | CN | 10 | 88 |

[a] The reactions were carried out with 1.0 mmol of aldehyde and 3.0 mmol of alkene in the presence of **2a** (0.05 mmol) and $TiCl_4$ (1.0 mmol) in $CH_2Cl_2$ under Ar at room temperature. [b] Yield of isolated product based on aldehyde.

ketone gave exclusively BH products in high yields (entries 1 and 2), and side products were not observed by $^1$H NMR spectroscopy. This result remarkably contrasts previous findings that reactions of α,β-unsaturated acyclic ketones with aldehydes mediated by metal and non-metal halides resulted in complex reaction mixtures.[7] Acrylates are normally very unreactive in Lewis acid catalyzed BH reactions, and very low to zero yields of coupling products are obtained.[6b,7c,7d] Interestingly, our new methodology works very well for both electron-poor and electron-rich aromatic aldehydes, giving excellent yields of Baylis–Hillman products in only 10 min (entries 3–7). When acrylonitrile was employed, reactions with aromatic aldehydes also gave high product yields (entries 8 and 9).

In summary, we have developed a highly active and selective catalyst system (**2a**/$TiCl_4$) for the BH reaction, which to our knowledge is the most generally effective one so far described. Our protocol is applicable to activated alkenes such as enones (including less reactive β-substituted derivatives), acrylonitrile, and acrylates. We believe that $N_{ax}\rightarrow P$ intrabridgehead interaction in **2a** may play an important role in stabilizing a **2a**/activated alkene/$TiCl_4$ intermediate in the reaction pathway. Further development of this methodology, including its application to asymmetric reactions using chiral proazaphosphatrane sulfides, is in progress.

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**Keywords:** Baylis–Hillman reaction · heterocycles · Lewis bases · titanium

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[10] An excess of α,β-unsaturated ketone required for complete consumption of aldehyde and optimized yields.

[11] Typical procedure for the BH reaction: To a solution of aldehyde (1.0 mmol), activated alkene (3.0 mmol), and **2a** (0.05 mmol) in anhydrous dichloromethane (2.0 mL) was added $TiCl_4$ (1.0 mmol) under an Ar atmosphere at room temperature. The mixture was stirred for 10 min and then it was quenched with saturated aqueous $NaHCO_3$ (5.0 mL). The inorganic precipitate was filtered through Celite. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate/hexane 1:3).

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[14] Under the same conditions the reaction of methyl vinyl ketone with *p*-nitrobenzaldehyde gave the BH adduct in 75 % yield.

[15] Attempts to detect this intermediate by NMR spectroscopy have thus far failed.

[16] Electron-rich aromatic aldehydes such as anisaldehyde do not provide BH adducts when a more sterically hindered 3-substituted cyclohex-2-en-1-one is used.