

# Infrared spectroscopic investigations on the metallation of terminal alkynes by $\text{Zn}(\text{OTf})_2$

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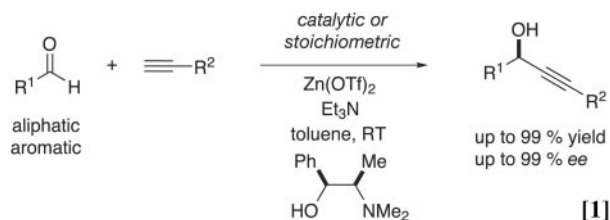
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**An IR study of terminal acetylenes and  $\text{Zn}(\text{OTf})_2$  in the presence of amine bases provides evidence that is consistent with the generation of Zn-acetylides.**

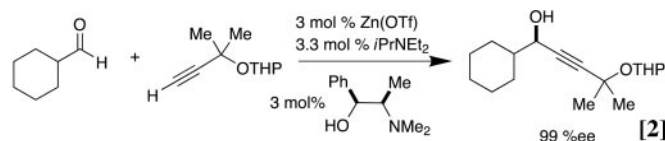
The addition reactions of nucleophilic acetylides to ketones, aldehydes, and  $\text{C}=\text{N}$  electrophiles are important processes in organic synthesis (1, 2). Such reaction processes can be intrinsically efficient in the production of useful building blocks of great synthetic versatility, because a new stereogenic center and a new  $\text{C}-\text{C}$  bond are established in a single operation. The acetylides typically used in such reactions are commonly prepared by deprotonation of terminal alkynes with strong bases ( $\text{BuLi}$ ,  $\text{RMgX}$ , and  $\text{R}_2\text{NLi}$ ) (3, 4), or dialkyl zinc reagents, such as  $\text{Et}_2\text{Zn}$  or  $\text{Me}_2\text{Zn}$  (5–11). When it is of interest to effect additions to electrophiles such as aldehydes or ketones, the alkyne metallation must necessarily be carried out as a separate preparative step because of the incompatibility of reagents used in the metallation reaction with electrophilic substrates. We have reported a series of reactions in which terminal acetylenes undergo additions to aldehydes and nitrones in the presence of  $\text{Zn}(\text{II})$  and amine bases (12–21). The propargylic alcohols or *N*-hydroxyl amines can serve as versatile useful building blocks (22, 23). In the presence of a chiral amino alcohol such as (–)-*N*-methyl ephedrine, optically active propargylic alcohols can be formed. As part of our working model, we hypothesize that under these conditions a Zn-acetylide is generated that subsequently participates in nucleophilic addition reactions (8). To provide insight on the mechanistic aspects, and in particular whether a Zn-acetylide is an intermediate in these processes, we decided to undertake a series of IR spectroscopic investigations involving ReactIR that we report herein. The outcome of these studies provides spectroscopic evidence that is consistent with the formation of a Zn-acetylide when a terminal acetylene is mixed with  $\text{Zn}(\text{OTf})_2$  and amine base.

The complexation of terminal alkynes with metals, such as  $\text{Cu}(\text{I})$  or  $\text{Ag}(\text{I})$ , yields  $\pi$  complexes that labilize the terminal  $\text{C}-\text{H}$  bond such that weak amine bases can effect deprotonation and concomitant formation of the corresponding metal acetylide (24). Unfortunately, acetylides generated under these conditions, in general, fail to participate in nucleophilic  $\text{C}=\text{O}$  additions. By contrast, it has been known for some time that with heating,  $\text{Cu}$ -acetylides will participate in imminium additions (25, 26).

We surmised that the ability to carry out nucleophilic additions to  $\text{C}=\text{O}$  with metal acetylides generated under the mild conditions that parallel those used in the formation of  $\text{Cu}(\text{I})$  or  $\text{Ag}(\text{I})$  acynylides would offer new opportunities for catalytic  $\text{C}-\text{C}$  bond formation. We have observed that  $\text{Zn}(\text{OTf})_2$ , in combination with a tertiary amine base and a terminal alkyne, leads to the generation of a nucleophilic species that participates in aldehyde and nitron addition reactions. The addition reactions to aldehydes were first reported employing stoichiometric quantities of  $\text{Zn}(\text{II})$  and amine base (Eq. 1),



a protocol that offers great opportunity for reaction optimization, because the system can respond favorably to variation in the relative stoichiometry of the various components. Indeed, this procedure has been used in our own laboratories in the context of complex natural products synthesis (27–31) as well as by others (32). Subsequently, we have developed a catalytic variant of the addition reaction (Eq. 2).



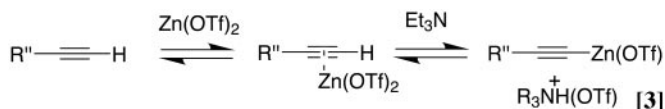
Key to this advance was the realization that catalytic turnover can be effected when the reaction is conducted at elevated temperatures, i.e.  $60^\circ\text{C}$  (Eq. 2) (12). The  $\text{Zn}(\text{II})$  process is unique in that it can also be conducted neat, thus minimizing the generation of the usual waste in the form of solvent. In unpublished work, we have noted that for certain classes of substrates, this solvent-free protocol permits the use of catalyst loadings that are substantially lower than those we documented in our initial reports (Eq. 2). Subsequent to our work, other groups have established the use of transiently generated metal acetylides in catalytic enantioselective imine and carbonyl additions, including metal catalysts such as  $\text{Cu}$ ,  $\text{Ag}$ , and  $\text{Au}$  (13, 33–37).

It has been known for some time that metal salts such as  $\text{Cu}(\text{I})$ ,  $\text{Ag}(\text{I})$ , and  $\text{Au}(\text{I})$  metallate terminal acetylenes in the presence of mild bases. This forms the basis of a number of useful  $\text{C}-\text{C}$  coupling reactions including Eglinton and Sonogoshira coupling reactions (2). The metallation reaction of terminal acetylenes by  $\text{Cu}(\text{I})$  and other salts has been suggested to proceed by deprotonation of the corresponding metal-alkyne  $\pi$  complex (Eq. 3) (24). We have used a similar mechanistic model in the analysis of the  $\text{Zn}$ -mediated reactions: in its simplest rendition, following formation of a  $\pi$  complex, deprotonation of the terminal acetylene ensues with concomitant generation of a Zn-acetylide.

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The ready availability of a convenient bench-top IR instrumentation, such as ReactIR, that permits real-time, continuous *in situ* observation of chemical reactions by using attenuated total reflection methods has provided a powerful tool for the investigation of reaction processes (38, 39). In prior work in our group, we have used this technique in studies aimed at understanding a new class of Mukaiyama aldol additions that proceed by enolate activation and thus complement the more common approach by using Lewis acid activation of aldehydes (40). In such investigations, the use of IR spectroscopic studies substantiated a process wherein the silyl enolate undergoes *in situ* activation by  $\text{CuF}\cdot(p\text{-tolBINAP})$  and conversion to the corresponding metalloenolate. In a similar fashion, we embarked on a study aimed at applying this same technique to the reaction of terminal acetylenes with  $\text{Zn(OTf)}_2$  and amines.

In the initial investigations, a control experiment was carried out in which phenylacetylene was deprotonated under standard conditions; namely, by treatment with an organometallic base. Thus, at  $t = 0$  a solution of phenylacetylene in  $\text{CH}_2\text{Cl}_2$  displays a prominent C—H stretch resonance at  $3,296\text{ cm}^{-1}$  in the IR spectrum. As expected, treatment of this solution with 1 eq  $\text{EtMgBr}$  resulted in the quantitative disappearance of this band within 150 min at ambient temperature, signifying that the terminal alkyne had undergone deprotonation (Fig. 1). Although additional changes in the spectrum can be observed in the fingerprint region, interpretation of these shifts are rather difficult; thus, the spectral window spanning  $3,250\text{--}3,360\text{ cm}^{-1}$  proved most effective for analysis.

We next monitored by IR spectroscopy the stepwise reaction of phenylacetylene,  $\text{Zn(OTf)}_2$ , and triethylamine, sequentially in acetonitrile at  $23^\circ\text{C}$ . Although the Zn-mediated acetylide addition reactions can be successfully conducted in a number of different solvents and even solvent-free, acetonitrile was chosen as the media for the spectroscopic investigations, because the reactions conducted in this solvent are routinely homogeneous, thus facilitating the spectroscopic studies. As shown in Fig. 2, the C—H stretch signal of a solution of

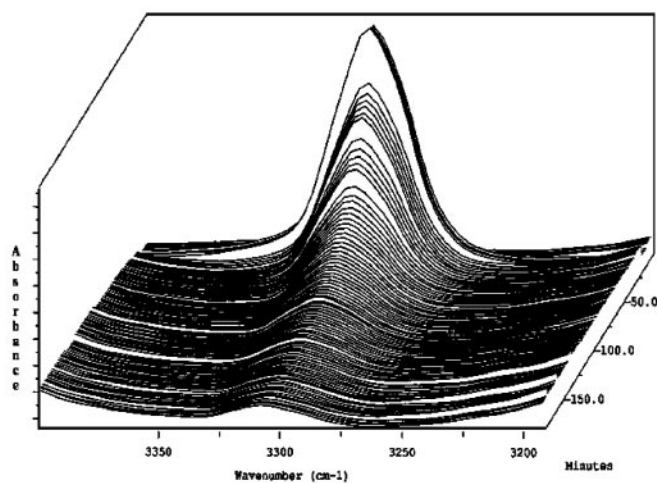


Fig. 1. ReactIR spectra showing the disappearance of the acetylenic C—H stretch resonance at  $3,296\text{ cm}^{-1}$  due to deprotonation of phenylacetylene by  $\text{EtMgBr}$  ( $t = 0$  at rear back right corner).

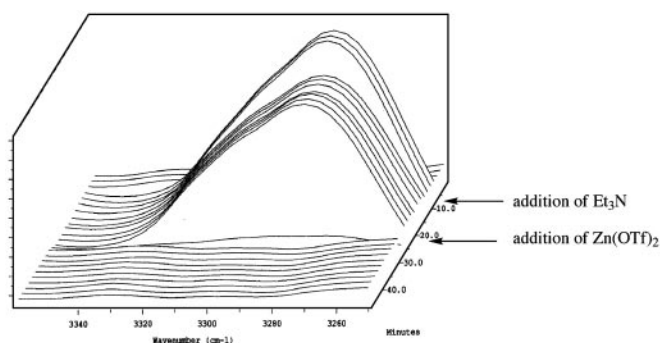


Fig. 2. ReactIR spectra of the C—H stretch resonance signal of phenylacetylene in  $\text{CH}_3\text{CN}$ . The IR band at  $3,277\text{ cm}^{-1}$  completely disappears within 4 min after the addition of  $\text{Zn(OTf)}_2$  to a mixture of phenylacetylene and  $\text{NEt}_3$ .

phenylacetylene in acetonitrile is observed at  $3,277\text{ cm}^{-1}$ . Treatment of this solution with excess  $\text{Et}_3\text{N}$  leads to a small diminution in the absorbance intensity due to dilution effects. In a separate control experiment, we could show that a solution of various aldehydes along with phenylacetylene and  $\text{Et}_3\text{N}$  did not lead to product formation; thus, background deprotonation by  $\text{Et}_3\text{N}$  can be reasonably excluded. Importantly, however, subsequent addition of 1 eq  $\text{Zn(OTf)}_2$  led to rapid disappearance of the signal at  $3,277\text{ cm}^{-1}$  within 4 min. Similar observations were made when the IR experiment was carried out in the presence of added amino alcohol ligand and otherwise identical conditions to those described above. Thus, analysis by ReactIR of a reaction mixture consisting of phenylacetylene,  $\text{Zn(OTf)}_2$ ,  $\text{NEt}_3$ , and (–)-*N*-methyl ephedrine in acetonitrile reveals a rapid disappearance of the terminal C—H stretch, in an analogous manner to that observed in Fig. 2.

Further evidence for the metallation reaction of terminal acetylenes on exposure to  $\text{Zn(OTf)}_2$  and base was obtained by examining whether the metallation reaction was reversible. Indeed, this could be demonstrated by the addition of Brønsted acid to the reaction mixture produced as described above from mixing phenylacetylene,  $\text{Zn(OTf)}_2$ , and  $\text{Et}_3\text{N}$ . Thus, when trifluoromethane sulfonic acid was added in a piecemeal fashion in proportion to the amount of base used, the signal corresponding to the terminal C—H stretch for phenylacetylene was observed to resurface (Fig. 3). Subsequent to reappearance of the C—H stretch, addition of base to the solution in amounts exceeding the stoichiometry of acid used led again to disappearance of the C—H signal. The fact that we have never observed any side products derived exclusively from the acetylene fragment in these reactions, even when conducted on large scale, in conjunction with the IR studies delineated above, is consistent with a simple metallation process for Zn(II), in analogy with that accepted for Cu(I) and Ag(I).

In summary, we carried out ReactIR spectroscopic investigations of the nucleophilic acetylide species generated from terminal alkynes in the presence of  $\text{Zn(OTf)}_2$  and  $\text{NEt}_3$ . The spectroscopic observations strongly support the working hypothesis in these reactions wherein the combination of an amine base and  $\text{Zn(OTf)}_2$  leads to the generation of a Zn-acetylide. The discovery and study of new reactive intermediates is of critical importance for the continuing evolution of asymmetric catalysis. The results reported herein permit the rationalization of the results that have been observed and encourage additional developments and experimentation in the use of zinc alkynylides as reactive intermediates in asymmetric catalysis.

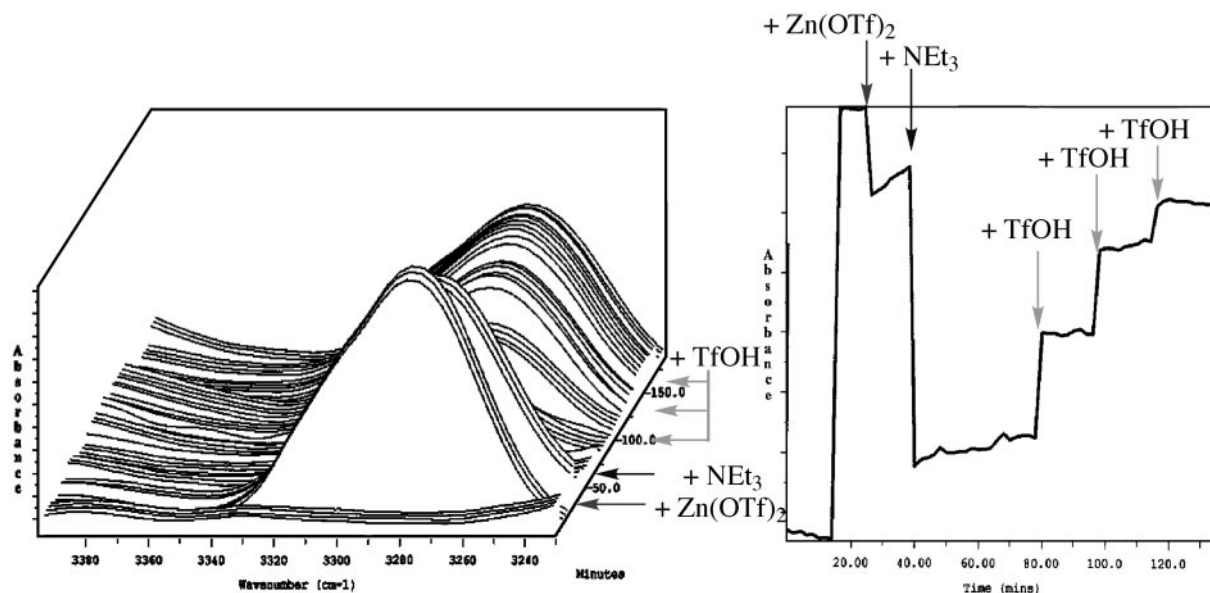


Fig. 3. ReactIR data obtained during deprotonation and reprotonation of phenylacetylene in acetonitrile in the presence of  $\text{Zn}(\text{OTf})_2$  and triethylamine. (Left) Accumulated spectra, time-resolved. (Right) Profile taken at the absorbance maximum at  $3,277\text{ cm}^{-1}$ .

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