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Catalytic Enone Cycloallylation via Concomitant Activation of Latent Nucleophilic and Electrophilic Partners: Merging Organic and Transition Metal Catalysis

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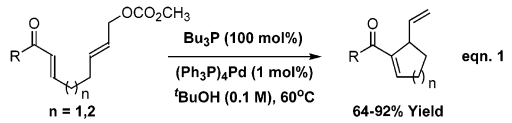
Modular design of catalytic transformations based on the use of enones as latent enolates is currently under development in our lab.[1] Through variation of the method of enone nucleophilic activation (hydrometalation, carbometalation or nucleophilic organocatalysis), coupled with the use of diverse electrophilic partners, a family of catalytic cycloreductions,[2] cycloadditions[3] and cycloisomerizations[4] has emerged. While use of "classical" electrophilic partners such as appendant aldehydes, ketones and enones has been demonstrated,[1−4] an opportunity for further development resides in catalytic couplings to "nonclassical" electrophiles, such as allylic carbonates. The use of allylic carbonates as latent electrophiles mandates activation via metallo-π-allyl formation. In this regard, palladium complexes have proven especially effective.[5] The compatibility of palladium-based catalysts and tertiary phosphines suggests the feasibility of catalytic enone allylation processes, whereby activation of latent nucleophilic (enone) and electrophilic (allyl carbonate) partners is achieved through phosphine addition and π-allyl formation, respectively. Such "two-component catalyst systems" are uncommon.[6] Moreover, the use of *nucleophilic catalysis* as a means of enolate generation in metal-catalyzed cross-coupling is without precedent.[5,7] The feasibility of this proposal is borne out by the results reported herein. Upon exposure of mono-enone mono-allylic carbonates to tributylphosphine and substoichiometric quantities of $Pd(Ph_3P)_4$, efficient conversion to the corresponding cycloallylated products is achieved. This transformation combines the nucleophilic features of the Morita−Baylis−Hillman reaction with the electrophilic features of the Trost−Tsuji reaction (eq 1).



eqn. 1

Recently, the present author and Roush disclosed a trialkylphosphine-catalyzed cycloisomerization of electron-deficient 1,5- and 1,6-dienes.[4,8,9] This discovery stimulated interest in the design of related transformations potentially developed through variation of the electrophilic partner. In accordance with this goal, and the aforementioned rationale for concomitant activation of latent nucleophilic and electrophilic partners, the following mechanism for catalytic enone cycloallylation was envisioned. In this scenario, catalysis is contingent upon the separate yet concomitant action of organic and metallic promoters (Scheme 1).

To assess the feasibility of the proposed transformation, catalytic intramolecular cycloallylation of mono-enone mono-allylic acetate **1a** was attempted using tributylphosphine and $Pd(Ph_3P)_4$ as nucleophilic and electrophilic activators, respectively. Initial experiments performed in aprotic media using 10 mol % $Pd(Ph_3P)_4$ and 50 mol % PBu_3 resulted in a poor yield of cycloallylation product **1b** (Table 1, entry 1). It was postulated that capture of the metallo-π-allyl intermediate would be facilitated were the lifetime of the transiently generated enolate to be extended through solvation in the form of hydrogen-bond interactions. Accordingly, the use of *tert*-butyl alcohol as solvent increased the yield of **1b** to 21% at reduced loading of $Pd(Ph_3P)_4$ (Table 1, entry 2). To further promote trapping of the metallo-π-allyl, the loading of PBu_3 was doubled, which raised the yield of cycloallylation product to 67% (Table 1, entry 3). The preceding experiments were performed using the allylic acetate of **1a**, which upon ionization generates acetate ion and, ultimately, acetic acid. It was recognized that the corresponding methyl carbonate would generate methoxide ion upon ionization, potentially facilitating β-elimination of PBu_3 in the final step of the catalytic cycle (Scheme 1). Indeed, the allylic carbonate of **1a** provides cycloallylation product **1b** in 92% yield (Table 1, entry 4). This yield was found to persist at 1% loading of $Pd(Ph_3P)_4$ (Table 1, entry 5).

Given the preceding result, a concise and modular synthetic route to cycloallylation substrates **1a**−**8a** was sought. Remarkably,

Scheme 1. Proposal: Catalytic Cycloallylation via Concommitant Activation of Latent Nucleophilic and Electrophilic Partners

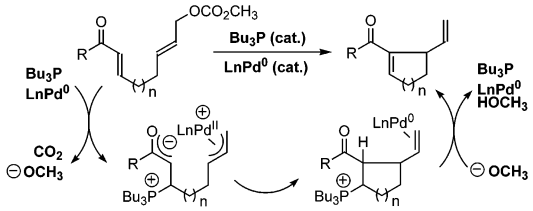
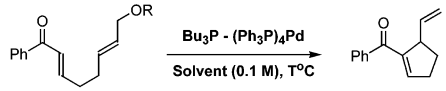


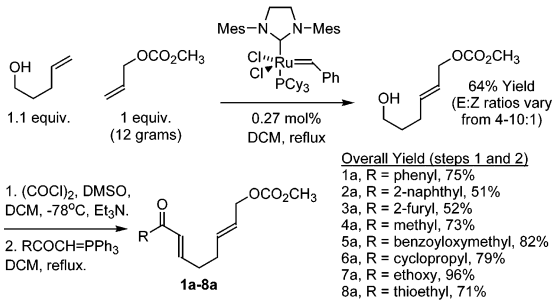
Table 1. Optimization of the Catalytic Cycloallylation of **1a**



entry	R	solvent	$(Ph_3P)_4Pd$ (mol %)	PBu_3 (mol %)	*T* (°C)	yield[a] (%)
1	$COCH_3$	THF	10	50	60	6
2	$COCH_3$	*t*-BuOH	4	50	30	21
3	$COCH_3$	*t*-BuOH	4	100	60	67
4	CO_2CH_3	*t*-BuOH	5	100	60	92
5	CO_2CH_3	*t*-BuOH	1	100	60	92

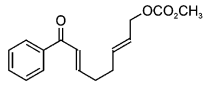
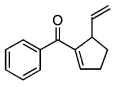
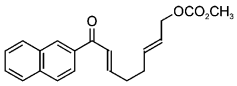
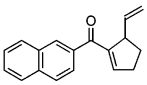
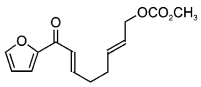
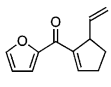
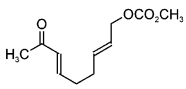
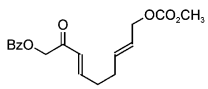
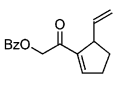
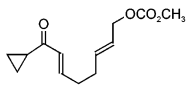
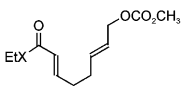
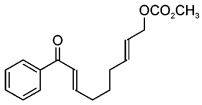
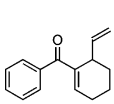
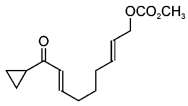
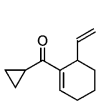
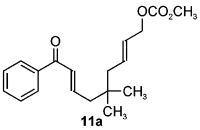
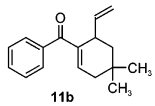
[a] Isolated yields after purification by silica gel chromatography.

Scheme 2. Synthesis of Mono-enone Mono-allylic Carbonates **1a**−**8a**



10.1021/ja0301469 CCC: $25.00

Table 2. Catalytic Cycloallylation of Mono-enone Mono-allylic Carbonates[a]

Entry	Substrate	Product	Yield (%)[b]
1			
	1a	**1b**	**92**
2			
	2a	**2b**	**82**
3			
	3a	**3b**	**83**
4			
	4a	**4b**	**71**
5			
	5a	**5b**	**81**
6			
	6a	**6b**	**76**[c]
7			
	7a, X = O **8a, X = S**	**7b, X = O** **8b, X = S**	**>5** **73**
8			
	9a	**9b**	**64**
9			
	10a	**10b**	**66**
10			
	11a	**11b**	**65**

[a] *Procedure*: Tributylphosphine (100 mol %) and $Pd(PPh_3)_4$ (1 mol %) were added to a 0.1 M solution of substrate in *tert*-butyl alcohol, and the reaction was allowed to stir at 60 °C until complete consumption of starting material, at which point the reaction mixture was evaporated onto silica and purified via silica gel chromatography. [b] Isolated yields were calculated after purification by silica gel chromatography. [c] 5 mol % of $Pd(PPh_3)_4$ was used for this single example. At 1 mol % catalyst loading the yield of **6b** was 65%.

exposure of methyl allyl carbonate and 4-penten-1-ol to the second-generation Grubb's catalyst provides the cross-metathesis product in moderate yield. Tandem Moffatt−Swern oxidation−Wittig olefination then affords substrates **1a**−**8a** (Scheme 2).

With a set of structurally diverse cycloallylation substrates in hand, the scope of the catalytic cycloallylation was examined. As demonstrated by the catalytic cycloallylation of substrates **1a**−**6a**, aromatic, heteroaromatic and aliphatic enones represent viable reacting partners (Table 2, entries 1−6). The cycloallylation of cyclopropyl substituted enone **6a** is noteworthy, as cyclopropanes possessing adjacent π-unsaturation are known to react readily with low-valent transition-metal complexes.[10] Whereas enoate **7a** provides only trace quantities of cycloallylation product **7b**, the corresponding thioenoate **8a** is readily cyclized (Table 2, entry 7). This result is consistent with the enhanced performance of thioenoates in Morita−Baylis−Hillman-type cyclizations[11,4b] and is remarkable in view of the well-established susceptibility of thioesters to oxidative addition by low-valent palladium.[12] Finally, as demonstrated by the catalytic cycloallylation of substrates **9a**−**11a**, six-membered ring formation proceeds smoothly, albeit in diminished yield (Table 2, entries 8−10).

In summary, we demonstrate the feasibility of nucleophilic catalysis as a means of enolate generation in metal-catalyzed cross coupling, as evidenced by the development of a catalytic enone cycloallylation methodology. This transformation is achieved through the use of a two-component catalyst system that unites the nucleophilic features of the Morita−Baylis−Hillman reaction with the electrophilic features of the Trost−Tsuji reaction. Future studies will be devoted to the development of related catalytic transformations, including enantioselective variants of the methodology described herein.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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