Letter

Rhodium-Catalyzed Tandem Isomerization-Allylation: From Diallyl Carbonates to #-Quaternary Aldehydes

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Rhodium-Catalyzed Tandem Isomerization-Allylation: From Diallyl Carbonates to α-Quaternary Aldehydes

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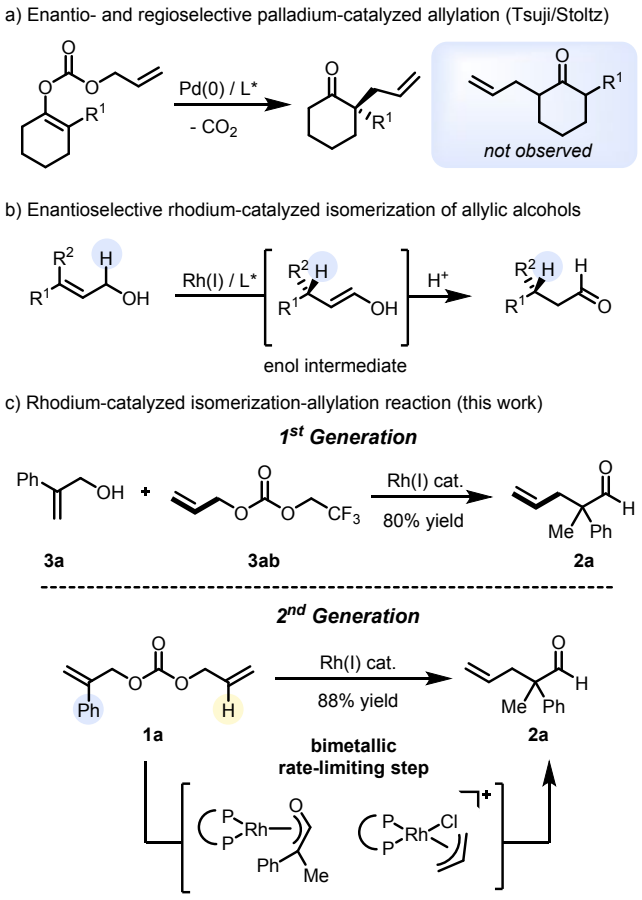
ABSTRACT: We report a Rh-catalyzed tandem isomerization-allylation sequence for the generation of α-quaternary aldehydes starting from unsymmetrical diallyl carbonates. This reaction features a highly selective oxidative addition of the rhodium catalyst, leading to the discrimination of electrophilic and nucleophilic elements of various diallyl carbonates. A rhodium-enolate and an allyl electrophile are produced catalytically *in situ* in a controlled fashion, enabling this reaction to occur with high chemo- and regioselectivity. Mechanistic investigation via reaction progress kinetic analysis (RPKA) uncovered second order kinetics in rhodium, suggesting that an unexpected dual metal pathway may be operative for the key C–C bond forming step.

The palladium-catalyzed rearrangement of allyl enol carbonates is an efficient and a versatile method to access stereochemically enriched α-allylated carbonyl containing compounds (Scheme 1a).[1] In contrast to classical enolate alkylation chemistry, these reactions avoid the requirement of stoichiometric strong base, allowing for better functional group tolerance and high chemo- and regioselectivity.[2]

Since the seminal report by Tsuji in 1983,[3] the reaction has been further elaborated by the Stoltz and Trost groups and utilized by others in numerous syntheses.[4] Although there exists an abundance of reports describing the allylation of cyclic ketones, amides and esters, methods to directly α-allylate aldehydes via this method are limited.[5] Moreover, despite the excellent chemo- and regioselectivity achieved through this masked enol strategy, the ability to use simpler starting materials, that do not require the use of strong base, will potentially enhance the utility of this methodology.

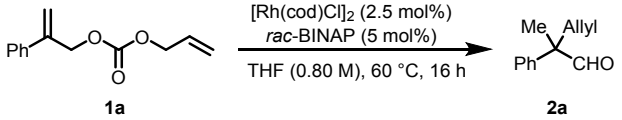
Among the catalytic approaches for the production of enols or enolates in situ, the rhodium-catalyzed isomerization of allylic alcohols and amines represents an appealing process as it occurs under very mild and neutral conditions (Scheme 1b).[6] Reports by Bosnich and Motherwell demonstrated that the in situ generated enols were sufficiently stable in solution to be further reacted with suitable electrophiles.[7] Despite the potential synthetic utility of this transformation, there are limited reports on catalytic tandem reactions exploiting the nucleophilic properties of the enol intermediates generated from the allylic alcohol.[8]

Considering rhodium is known to catalyze both the isomerization of allylic alcohols and the allylation of enolates derived from aldehydes,[9] we postulated that allylic alcohols could be used as enolate surrogates in allylation reactions. Herein we demonstrate allylic alcohols (**3a**) as aldehyde enolate surrogates in rhodium-catalyzed isomerization-allylation reaction (Scheme 1c). Additional atom-economical rearrangement of unsymmetrical diallyl carbonates (**1a)** to α-quaternary allylated aldehydes (**2a**) is presented (Scheme 1c).[10]



Scheme 1. Metal-Catalyzed Allylation and Isomerization Reactions

Table 1. Deviations from Standard Conditions[a]



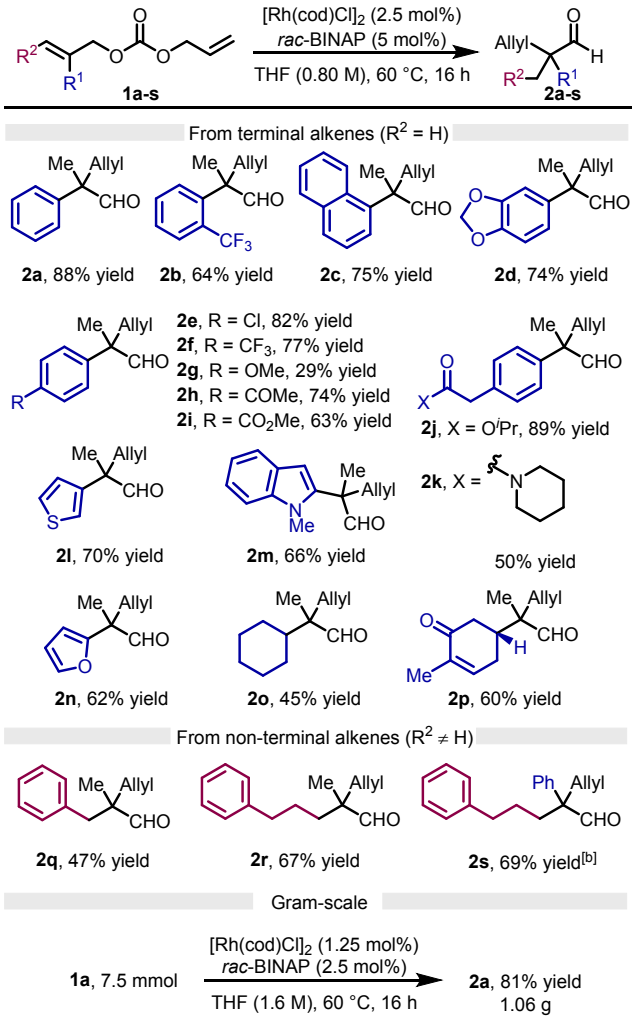
Entry	Deviations	%Conversion[b]	%Yield[b]
1	None	>95	88
2	no *rac*-BINAP	<5	0
3	$[Rh(cod)_2]BF_4$ instead of $[Rh(cod)Cl]_2$	<5	0
4	$Pd_2(dba)_3$ instead of $[Rh(cod)Cl]_2$	84	0
5	$[Ir(cod)Cl]_2$ instead of $[Rh(cod)Cl]_2$	65	5
6	PPh_3 (10 mol%) instead of *rac*-BINAP	46	0
7	dppe instead of *rac*-BINAP	>95	0
8	40 ºC instead of 60 ºC	44	13
9	DCE instead of THF	>95	85
10	PhMe instead of THF	>95	74
11	acetone instead of THF	74	30
12	THF (0.20 M)	51	36

[a] Standard conditions: $[Rh(cod)Cl]_2$ (2.5 mol%, 4.9 mg), *rac*-BINAP (5 mol%, 6.2 mg) and allyl carbonate **1a** (0.20 mmol, 44 mg) in THF (0.25 mL), under argon atmosphere, heated at 60 °C for 16 hours. [b] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

At the outset of our investigation, we noted that the rhodium(I)-(±)-BINAP combination was a particularly efficient catalyst for the desired transformation (Table 1, entry 1), in accordance with several reports utilizing this catalyst for the isomerization of allylic alcohols.[11] Reactions conducted in the absence of bidentate phosphine ligand (entry 2) or with $[Rh(cod)_2]BF_4$ (entry 3) did not afford any product. The isomerization of allylic alcohols seems to be unique to rhodium, as using palladium or iridium catalysts led to no appreciable yields of the desired product (entry 4 and 5). Employing other common phosphine ligands such as triphenylphosphine (entry 6) and dppe (entry 7) failed to promote this transformation. The yield of **2a** decreases with lower temperatures (entry 8). Various solvents can be used for this reaction. The product can be obtained in similar yield in dichloroethane (entry 9) and in slightly lower yield in toluene (entry 10). Acetone gives lower yields of the desired product (entry 11). Conducting the reaction at a lower concentration leads to lower conversion into the product (entry 12).[12]

Next we investigated the scope of this transformation (Table 2). Substrates with ortho-substituents on the aromatic ring reacted to yield products **2b** and **2c**. In general, it was found that electron-neutral or electron-poor substrates (**2a**–**2f**) worked well but the anisole derived product (2g) was obtained in low yield..

Table 2. Scope Table[a]

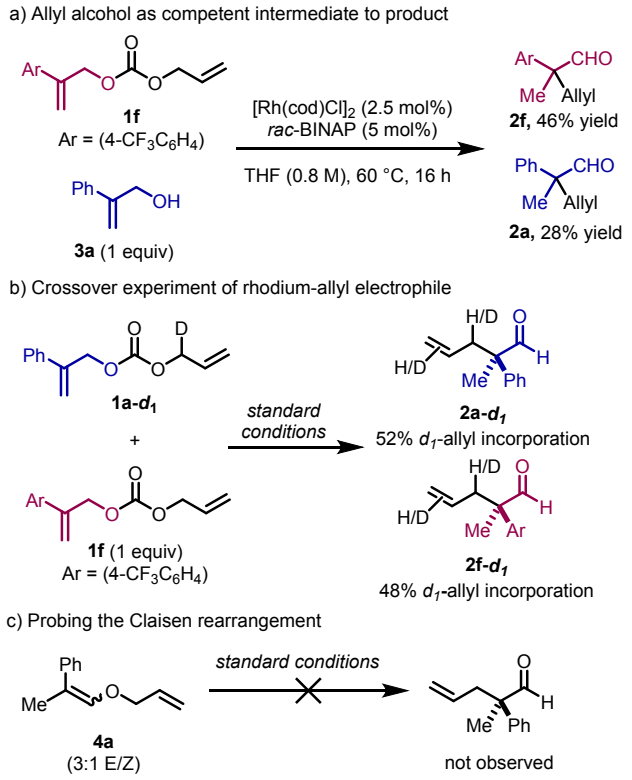


[a] Standard conditions: $[Rh(cod)Cl]_2$ (2.5 mol%, 4.9 mg), *rac*-BINAP (5 mol%, 13 mg) and allyl carbonate **1a** (0.40 mmol, 87 mg) in THF (0.50 mL), under argon atmosphere, heated at 60 °C for 14 hours. [b] Reaction stirred for 48 hours.

The high chemoselectivity of our protocol is best illustrated by the tolerance of functional groups such as ketones (Table 2, **2h** and **2p**), Michael acceptors (**2p**) and esters (**2i** and **2j**). Notably, our reaction displays good selectivity even in the presence of other enolizable centers (**2j**–**2k** and **2p**). By contrast, this type of selectivity would be hard to achieve by traditional synthetic routes. Heteroaromatic substrates afforded aldehydes bearing thiophene (**2l**), indole (**2m**) and furan (**2n**) moieties. Aliphatic allylic alcohols were converted to the corresponding aldehydes in moderate to good yields (**2o** and **2p**). Allyl carbonates with non-terminal alkenes, a mixture of E/Z, could also be isomerized, providing the desired products in moderate to excellent yields (**2q**–**2s**). Finally, a gram scale reaction of **1a**

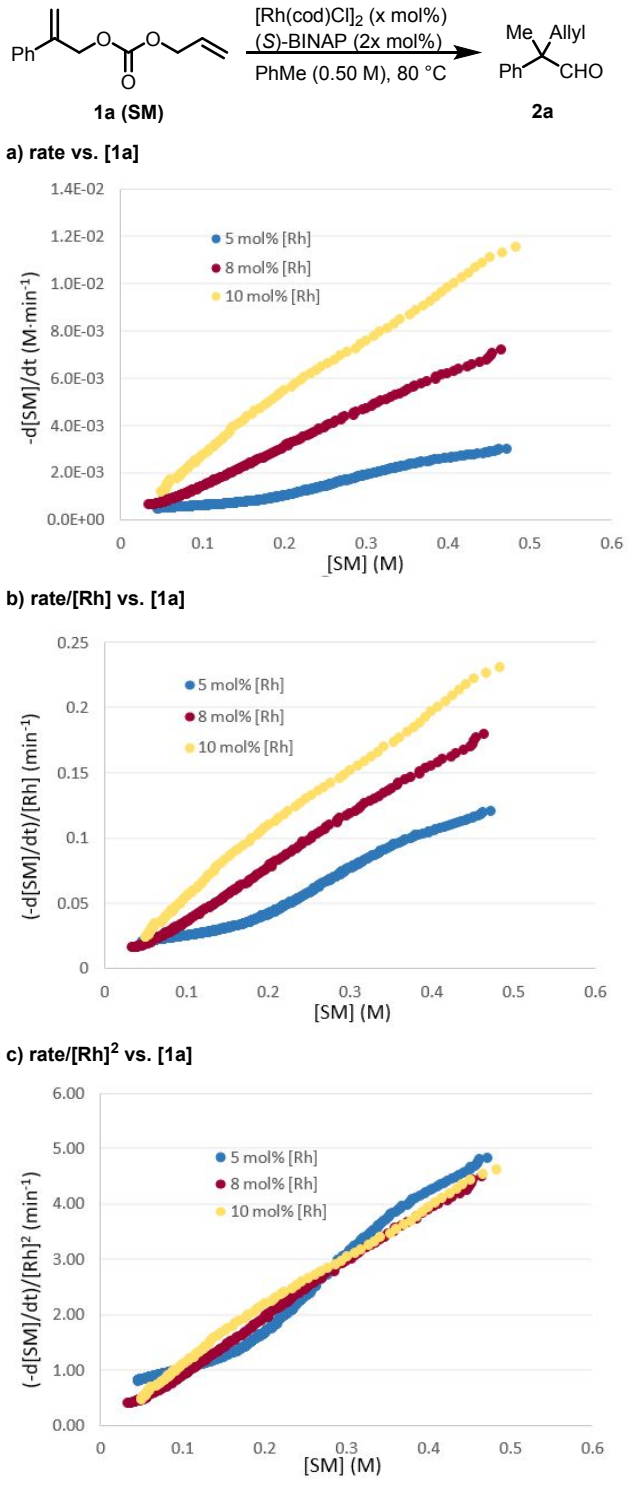
was accomplished with a reduced catalyst loading of 1.25 mol%, affording the product in 81% yield.

To gain further understanding of this unique catalytic process, control and cross-over experiments were conducted (Scheme 2). A competition experiment with allyl carbonate **1f** and allylic alcohol **3a** was conducted (Scheme 2a). Both allylated aldehydes were formed, demonstrating that the allylic alcohol is a competent intermediate en route to product. Next, a cross-over experiment between two different allyl carbonates was undertaken (Scheme 2b). Upon subjecting substrates **1a-d_1** and **1f** under the standard conditions, extensive crossover of the mono-deuterated allyl group was observed. To further investigate the selectivity between C− and O−alkylation following the isomerization, the corresponding allyl enol ether **4a** was synthesized (Scheme 2c). Subjecting the enol allyl ether **4a** to the standard conditions resulted in the recovery of the starting material, which indicates that the Claisen rearrangement of **4a** is not involved in the formation of the desired product.



Scheme 2. Competition and Control Experiments

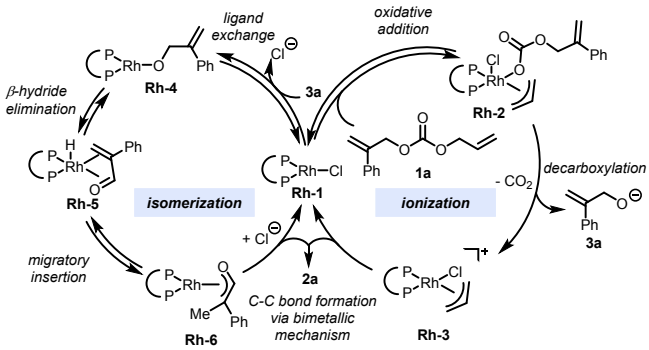
Next, we performed reaction progress kinetic analysis (RPKA) using React-IR spectroscopy to gain additional mechanistic information (Scheme 3).[13] Three experiments were conducted with different catalyst loadings to determine the order in catalyst. When normalizing the rates as a function of [Rh], we did not observe overlap of the curves, ruling out first order kinetics in catalyst (Scheme 3b). Good overlay of the curves was obtained when normalizing the rates assuming $[Rh]^2$ (Scheme 3c), which supports a mechanism that is second order in rhodium.[14] This observation suggests that two rhodium species may be involved in the rate-limiting step of the reaction. Moreover, the linear relationship obtained when plotting the rate against [**1a**] is in agreement with first order kinetics in substrate.



Scheme 3. Reaction Progress Kinetic Analysis

The second order kinetics suggests that the C–C bond formation step may operate via a rate-limiting bimetallic pathway (Scheme 4). It should be noted that the extensive crossovers observed in the competition experiments (Scheme 2a & b) are also consistent with this proposal. Upon formation of the rhodium(I)-BINAP complex **Rh-1**, the catalyst undergoes selective oxidative addition into the less hindered

allyl component of the carbonate **1a** leading to the formation of rhodium (III) complex **Rh-2**. As first order kinetics in substrate is observed, we propose the oxidative addition step to be reversible. Decarboxylation can then lead to the formation of Rh-allyl complex **Rh-3**, releasing the allylic alkoxide **3a**. The allylic alkoxide **3a** by-product is then proposed to undergo ligand exchange with another **Rh-1** species to form rhodium(I) alkoxide **Rh-4**. Following ligand exchange, β-hydride elimination can occur to generate the rhodium(I) complex **Rh-5** bearing a coordinating α,β-unsaturated aldehyde. Next, migratory insertion delivers rhodium(I) enolate **Rh-6**. The rhodium allyl species **Rh-3** and the rhodium enolate complex **Rh-6** can then provide aldehyde **2a**, regenerating two equivalents of the active **Rh-1** catalyst. This last step is likely to be rate-limiting as it requires two catalytic species to meet in solution. A simplified version of this mechanism gives rise to a theoretical rate law that is second order in [**Rh**] and first order in [**1a**], which is consistent with our experimental data (see Supporting Information).



Scheme 4. Proposed Catalytic Cycle

In conclusion, we have successfully developed a convenient method to make α-allylated quaternary aldehydes starting from easily accessible diallyl carbonates. This rhodium-catalyzed reaction involves the catalytic generation of a rhodium-enolate and an allyl electrophile which allows for an overall increase in chemo- and regioselectivity. A key element of the reaction is the selectivity of the catalyst to differentiate between the pro-nucleophilic and the pro-electrophilic elements of the unsymmetrical diallyl carbonates. RPKA studies uncovered a second order dependence in rhodium on the reaction rate; this piece of information will be valuable for the design of an enantioselective variant of this reaction. We anticipate this work will stimulate further development of other tandem reactions exploiting the isomerization of allylic alcohols to enols as a general and practical approach to obtain functionalized quaternary carbonyl compounds.

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, $^{1}H/^{13}C$ spectra, additional optimization data.This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

RPKA, Reaction Progress Kinetic Analysis.

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[10] The 2nd generation will be presented herein. For more experimental details on the 1rst generation, see Supporting Information.

[11] See ref 8d and: (a) Liu, T.-L.; Wei Ng, T.; Zhao, Y. Rhodium-Catalyzed Enantioselective Isomerization of Secondary Allylic Alcohols. *J. Am. Chem. Soc.* **2017**, *139*, 3643−3646; (b) Huang, R.-Z.; Lau, K. K.; Li, Z.; Liu, T.-L.; Zhao, Y. Rhodium-Catalyzed Enantioconvergent Isomerization of Homoallylic and Bishomoallylic Secondary Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 14647−14654; (c) Kress, S.; Johnson, T.; Weisshar, F.; Lautens, M. Synthetic and Mechanistic Studies on the Rhodium-Catalyzed Redox Isomerization of Cyclohexa-2,5-dienols. *ACS Catal.* **2016**, *6*, 747-750.

[12] We also attempted to develop an enantioselective variant of this reaction, but we were not successful in doing so. A chiral ligand screen is presented in the Supporting Information (Table S2).

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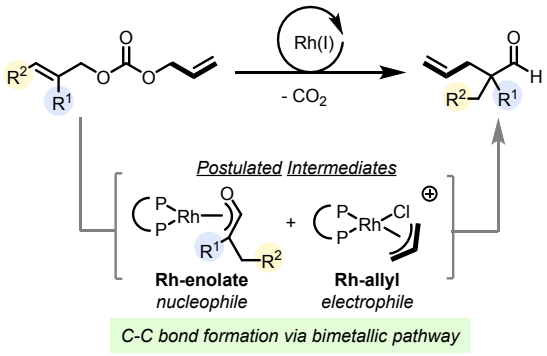
[14] Second order kinetics were also determined when using Burés graphical method analysis (see Supporting Information for details): Burés, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem. Int. Ed.* **2016**, *55*, 2028-2031.



C-C bond formation via bimetallic pathway