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Introducing unactivated acyclic internal aliphatic olefins into a cobalt catalyzed allylic selective dehydrogenative Heck reaction†

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Unactivated acyclic internal aliphatic olefins are often found to be unreactive in conventional alkenylation reactions. To address this problem, a cobalt catalyzed allylic selective dehydrogenative Heck reaction with internal aliphatic olefins has been developed. The method is highly regio- and stereoselective, the conditions are mild and a wide variety of functional groups can be tolerated. Remarkably, both internal and terminal aliphatic olefins can be employed, thereby significantly expanding the scope of alkenylation chemistry with aliphatic olefins.

Introduction

The selective incorporation of unactivated aliphatic olefins into arenes is a highly sought-after transformation in modern Heck chemistry.[1] The ubiquity and synthetic potential of aliphatic olefins and α-olefins have inspired significant developments in recent times.[2] An existing problem of this methodology, however, is the inertness of internal aliphatic olefins. This could be attributed to a number of factors, such as inappropriate coordination or sensitivity towards the enhanced steric environment in the carbometalation step.[3] To solve this problem, the discovery and development of new catalysts seems essential. Here we report a method that overcomes these limitations and successfully introduces internal aliphatic olefins in a highly regio- and stereoselective manner.
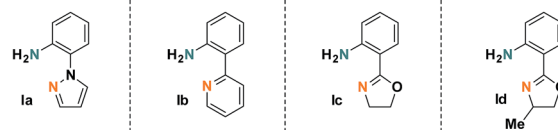
Our recent studies suggested that an inexpensive and readily available cobalt catalyst could facilitate an allylic selective Heck-type reaction with a variety of terminal aliphatic olefins.[4] The unorthodox allylic selectivity was attributed to a flexible framework consisting of a bis-chelating directing scaffold, which placed the metal suitably to generate the allylic product. However, an attempt to extend this reaction to internal aliphatic olefins remained unsuccessful, as competitive reductive elimination predominated.[5] We hypothesized that a structural modification of the 5,7-membered fused metallacycle intermediate (such as **IIb**) could suppress the annulation pathway. As a consequence, unbiased internal aliphatic olefins could be selectively included (Scheme 1B).

This hypothesis led to the synthesis and evaluation of several 1,5-bis-chelating systems with attached pyrazole, pyridine and dihydrooxazole moieties. Out of this selection of directing groups, 2-(4,5-dihydrooxazol-2-yl)aniline (**Ic**, Scheme 1A), first developed by the Yu group, showed promising reactivity with commercially available cobalt catalysts.[6] Optimization of the reaction parameters and inclusion of aliphatic acid additives considerably increased the efficiency of the method (Table 1). Under the optimized conditions, completely allylic selective alkenylated products could be obtained in high synthetic yields with very high diastereomeric ratios (Scheme 2).
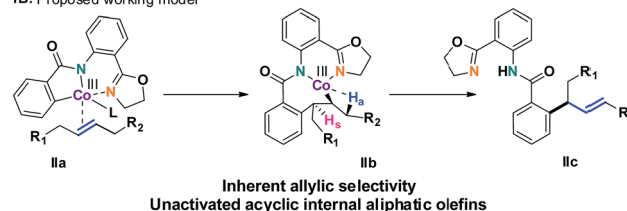
Results and discussion

We began to study the scope of the reaction with *trans*-4-octene as a model olefin. These olefins have historically proven to be difficult substrates for any Heck-type transformations and Fujiwara–Moritani reactions.[7] In the absence of electronic bias,

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Scheme 1 Evaluation of directing groups with internal aliphatic olefins.

Table 1 Optimization of several reaction parameters

| Entry	Catalyst	Oxidant	Solvent	Yield
1	Co(OAc)$_2$·4H$_2$O	Ag$_2$SO$_4$	DCE	19%
2	Co(OAc)$_2$·4H$_2$O	Ag$_2$SO$_4$	1,4-Dioxane	38%
3	Co(OAc)$_2$·4H$_2$O	Ag$_2$CO$_3$	1,4-Dioxane	35%
4	Co(OAc)$_2$·4H$_2$O	PhI(OAc)$_2$	1,4-Dioxane	19%
5	Co(OAc)$_2$·4H$_2$O	Ag$_2$SO$_4$	1,4-Dioxane	90%[a]
6	Co(acac)$_2$	Ag$_2$SO$_4$	1,4-Dioxane	51%
7	CoBr$_2$	Ag$_2$SO$_4$	1,4-Dioxane	56%

[a] With 1 equiv. isobutyric acid additive and 3 equiv. NaHCO$_3$ base.

Scheme 2 Introducing acyclic internal aliphatic olefins in dehydrogenative Heck chemistry.

the migratory insertion step is less facile and the methods often suffer from poor reaction rates. Even if the metal could bind with the olefin effectively, the carbometalation intermediate (**IIb**) might lead to a deleterious mixture of styrenyl/allylic products.[8] In the present system, however, the affiliation of the 1,5-chelating directing scaffold and the cobalt catalyst proved to be inherently allylic selective.[9,10] Although the origin of this selectivity is yet to be fully established, given the thermodynamic non-preference of allylic isomers (*vs.* styrenyl), this observation demanded a more detailed evaluation of the scope of the reaction.

Therefore, we tested different benzoic acid derivatives under standard conditions (Scheme 3). It was observed that the reaction was quite general, as both electron donating as well as electron withdrawing substituents could be tolerated at the *ortho*-, *meta*- or *para*-positions of the arene ring. Even multiple fluoro groups did not affect the efficiency of the method (**3b–3e** and **3q**). Among the synthesized compounds, entry **3c** was characterized through X-ray crystallography, thereby unambiguously assigning the *trans*-geometry to the α-branched internal allylarene product. Different functional groups such as –CN, –Cl and –OMe were well suited (**3n**, **3p** and **3q**; 75–80%). When both the *ortho*-positions were unsubstituted, some amount of diallylation (7–10%) was observed, which could be easily purified through column chromatography. For substrates with moderate yields (**3i** and **3l**), the unreacted starting materials were recovered in considerable amounts. Heteroaromatic benzoic acids such as thiophene (**3g**, 70%) and benzothiophene (**3j**, 60%) carboxylic acids were also found to be useful substrates. Interestingly, a chiral center was generated in all these cases;
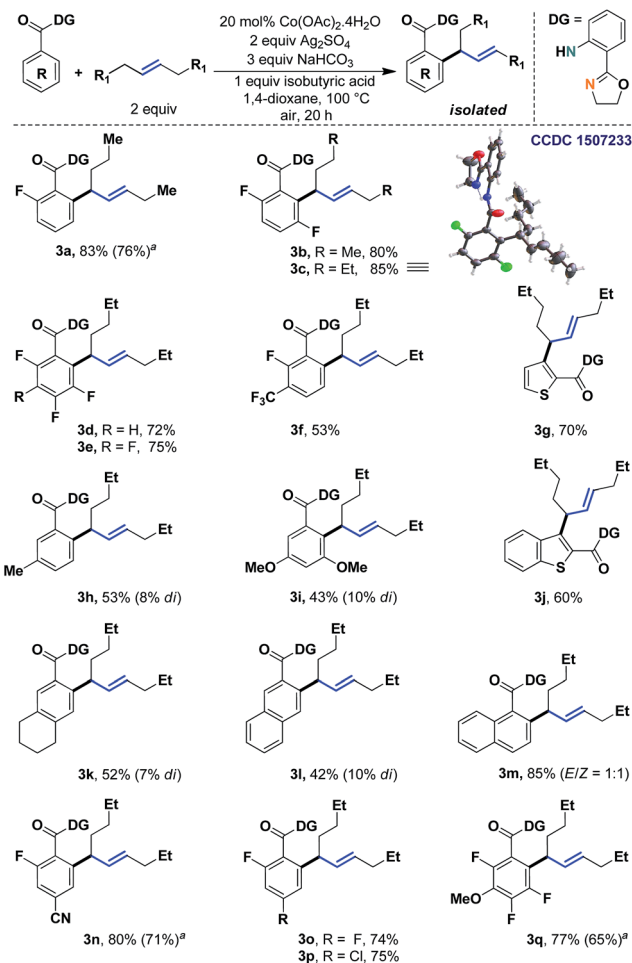
Scheme 3 Allylic selective alkenylation with unactivated acyclic internal aliphatic olefins. [a]Yields with 10 mol% Co.

thus future development of an asymmetric variant of the method could be envisaged.

The scope of the method was evaluated further with different internal aliphatic olefins (Scheme 4). As expected, a higher homologue, *trans*-5-decene, was found to be equally reactive (**4a**, 89%). Although we observed a slight erosion of efficiency with *trans*-3-hexene (**4b**), this might be attributed to the volatility of the olefin substrate. A free alcohol containing olefin could be successfully employed without oxidation of the alcohol functional group (**4g**, 65%). Other unsymmetrical internal olefins were also useful in this reaction (entries **4g–4l**). An internal allyl ester was particularly interesting, as regioselective allylation was observed in an 8 : 1 ratio (**4e**, 60%). Although in principle two allyl isomers are possible, the conjugation with the carbonyl group determined the geometry of the major allyl isomer. A similar reactivity pattern was observed with internal olefins derived from naturally occurring citronellol (**4k**) and nerol (**4l**), which had additional tri-substituted double bonds. Unfortunately, despite our best efforts, *cis*-olefins proved to be difficult substrates (**4c**, 48%). Even a prolonged reaction time failed to improve the synthetic yield to a considerable extent.

Scheme 4 Evaluation of unactivated acyclic internal aliphatic olefins. [a]Another isomer can be detected in minor amounts; [b]regioisomeric ratios are mentioned in parentheses.

Scheme 5 Allylic selectivity with terminal aliphatic olefins. [a]Yields with 10 mol% Co.

Nevertheless, considering the documented difficulties with internal aliphatic olefins, these studies seemed very encouraging.

To gain additional insight as to whether this reactivity was internally specific, we decided to assess terminal aliphatic olefins as well (Scheme 5). We were pleased to observe that a wide variety of terminal alkenes could be incorporated with excellent yields and complete allylic selectivity. Simple benzoic acids as well as heteroaromatic acids, without any bias, were useful substrates, thereby significantly expanding the scope of allylation with aliphatic olefins (**5a–5i**). Additionally, sequential allylation could be performed with equal ease (**5s–5u**).[11]

We next decided to study the comparative reactivity of different aliphatic olefins (Scheme 6). An intermolecular competition experiment revealed that 1-octene could react preferentially in a 14 : 1 ratio over *trans*-4-octene (**6a**, 60%). Similarly, a substrate with both terminal and internal olefins reacted exclusively at the terminal site, while the internal olefin remained completely unreacted (**6b**). Kinetic studies further showed that a *trans*-olefin reacts 2.5 times faster than the *cis*-

isomer, which partially explained the apparent lower reactivity of *cis*-olefins under the standard conditions.

A plausible mechanism has been depicted in Scheme 7. The reaction was thought to be initiated by an *in situ* generated Co(III) species under aerobic conditions. C–H activation (**C**), olefin coordination (**D**), and subsequent migratory insertion led
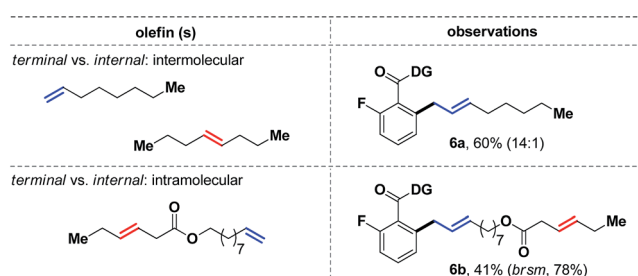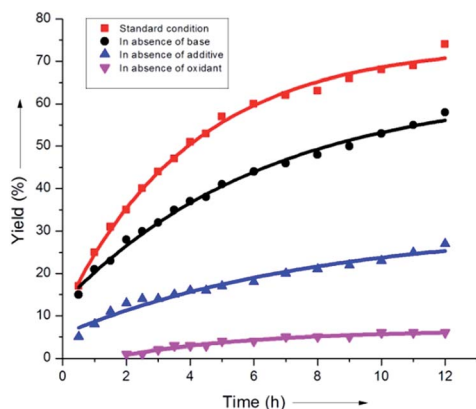

Scheme 6 Competition experiments with aliphatic olefins.

Scheme 7 Plausible mechanism for allylic selective alkenylation with internal aliphatic olefins.

Scheme 9 Determination of the kinetic isotope effect.

to a unique seven-membered intermediate (**E**), the stability of which was crucial for the progress of the reaction. In all probability, the geometry of this particular intermediate determined the regioselective outcome of the reaction.

It was found that the aliphatic acid additives had a profound influence on the rate enhancement. In sharp contrast, omitting NaHCO$_3$ slightly altered the rate of the reaction (Scheme 8). This could be justified by considering the superiority of the aliphatic carboxylate (^{i}PrCO$_2$Na) as the proton abstracting agent in the C–H activation step (**B**), thus clearly indicating that a concerted metalation–deprotonation or CMD-type pathway was operative.

Interestingly, labeling studies revealed a k_H/k_D value of 2.8, thereby suggesting C–H activation as the rate determining step (r.d.s.) of the overall transformation (Scheme 9). This observation was supported further by the fact that both internal and terminal olefins could react at nearly the same rate in parallel experiments (see ESI†).

Conclusions

In summary, we have developed a cobalt catalyzed allylic selective alkenylation with unactivated internal aliphatic olefins. The excellent regio- and stereoselectivity, broad scope, and high synthetic yields are some of the noteworthy features of the present method. Remarkably, a variety of acyclic internal aliphatic olefins were successfully incorporated. The development of a related asymmetric transformation and detailed mechanistic investigations are presently underway in our laboratory.

Acknowledgements

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