EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601230

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601230

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Regioselective Rhodium-Catalyzed Addition of β-Keto Esters, β-Keto Amides and 1,3-Diketones to Internal Alkynes

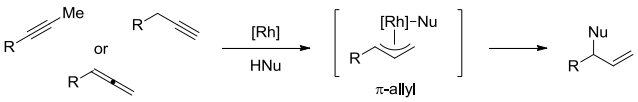
Thorsten M. Beck[a] and Bernhard Breit*[a]

Abstract: The first rhodium-catalyzed regioselective addition of 1,3-dicarbonyl compounds, including β-keto esters, β-keto amides and 1,3-diketones, to internal alkynes furnishing branched allylic compounds is reported. By applying Rh(I)/DPEphos/TFA as the catalytic system, aliphatic as well as aromatic internal methyl-substituted alkynes act as suitable substrates to yield valuable branched α-allylated 1,3-dicarbonyl compounds in good to excellent yields with perfect regioselectivity. A simple basic saponification-decarboxylation procedure accesses valuable γ,δ-unsaturated ketones. The reaction shows a broad functional group tolerance and numerous structural variations on both reaction partners highlight the synthetic potential and flexibility of this method.

Introduction

The selective formation of allylic C-heteroatom and C-C bonds is of great value to contemporary organic synthesis and enormous progress has been made during the last decades towards this goal. Of particular synthetic value is the transition metal-catalyzed allylic substitution – the Tsuji-Trost reaction – which allows the construction of complex target structures with high levels of chemo-, regio- and stereoselectivity.[1-5] The concomitant installation of a new stereocenter in allylic position with formation of an alkene moiety enabling subsequent skeleton expansion and functionalization is of particular synthetic utility. Drawbacks of the allylic substitution are the need to preinstall an allylic leaving group as well as the intrinsic lack of atom economy associated with the nature of the leaving group lost during the substitution reaction.[6]

As an atom-economic alternative, we recently reported on the rhodium-catalyzed addition of a series of pronucleophiles to allenes and alkynes furnishing branched allylic products through C-O, C-S, C-N and C-C bond formation (Scheme 1).[7] Mechanistic studies have revealed that these transformations pass a π- and/or σ-allyl intermediate which is attacked by the corresponding nucleophile.[7,8]

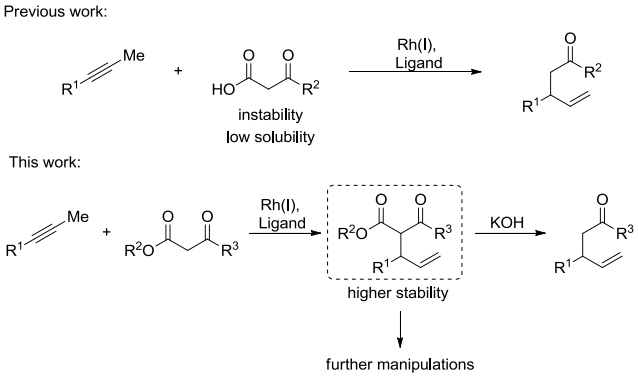


Scheme 1. Rhodium-catalyzed addition of pronucleophiles to terminal and internal alkynes and allenes.

Previous results have shown that terminal allenes[9] display higher reactivity in many cases, which so far allows the reaction with a broader range of pronucleophiles. On the other hand, the isomeric terminal alkynes and internal methyl alkynes[10] are much easier accessible substrates and thus synthetically more appealing starting materials.

Of particular synthetic importance is the formation of allylic C-C bonds. However, with alkynes as starting materials, the only successful examples have been reported employing 1,3-diketones[11] and β-keto acids[12] as carbon pronucleophiles. A decarboxylative allylation reaction provided the corresponding γ,δ-unsaturated ketones as valuable building blocks.[13] Drawbacks of this reaction were the instability and low solubility of the β-keto acid substrates and the restriction towards methyl-alkynes bearing an sp^2-carbon substituent such as aryl, alkenyl and cyclopropyl.

In order to extend the atom-economic addition of carbon-pronucleophiles to internal alkynes, we herein report on a broadly applicable method for the addition of β-keto esters, amides and 1,3-diketones to methyl-substituted internal alkynes bearing both aromatic and aliphatic substituents. Furthermore, follow-up chemistry allowing for the efficient synthesis of γ,δ-unsaturated ketones as well as transformation of the β-keto ester function into several heterocyclic systems demonstrates the synthetic utility of this method.



Scheme 2. Strategies for the Rhodium-catalyzed construction of γ,δ-unsaturated ketones.

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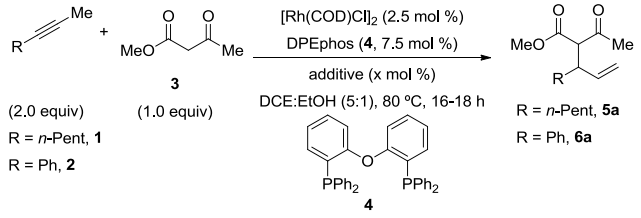
Results and Discussion

Our study commenced employing 2-octyne (**1**) and methyl acetoacetate (**3**) as model substrates. In the presence of 2.5 mol % $[Rh(COD)Cl]_2$ and 7.5 mol % DPEphos (**4**) in a previously optimized solvent mixture consisting of DCE and ethanol (5:1) at 80 °C, the desired addition product **5a** could be obtained in 14% isolated yield and 1:1.6 d.r. (Table 1, entry 1).

Table 1. Screening of additives and optimization of reaction conditions[14,15]



entry	R =	additive	x (mol %)	yield (%)[a]	d.r.[b]
1	*n*-Pent	no	0	14	1:1.6
2	*n*-Pent	*p*TSA	20	27	1:1
3	*n*-Pent	$PhMe_2CCOOH$	20	38	1:1
4	*n*-Pent	PPTS	20	80	1:1.6
5	*n*-Pent	*p*-$CF_3C_6H_4COOH$	50	87	1:1
6	Ph	*p*-$CF_3C_6H_4COOH$	50	20	1:1.1
7	*n*-Pent	TFA	20	99	1:1.2
8	Ph	TFA	20	99	1:1.4
9[c]	***n*-Pent**	**TFA**	**20**	**95**	**1:1**
10[c]	**Ph**	**TFA**	**20**	**99**	**1:1.4**

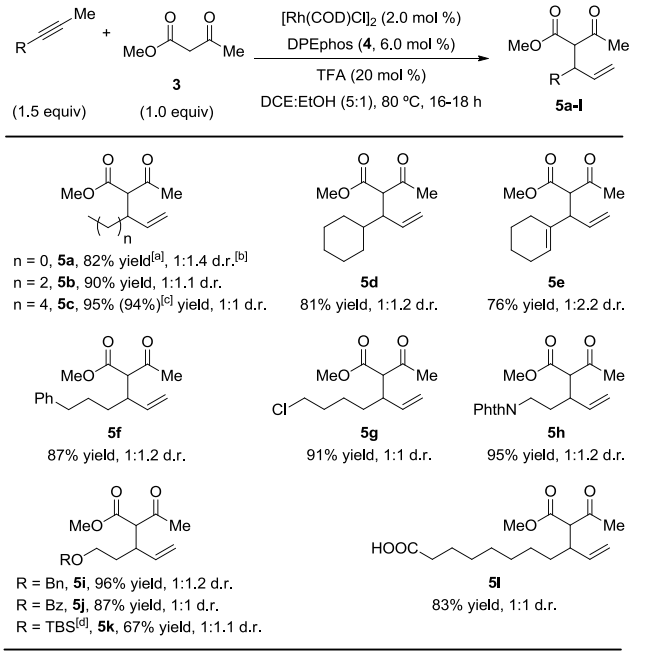
[a] Isolated yield of the branched products. [b] The diastereomeric ratio (d.r.) was determined by ^1H NMR analysis. [c] Reaction performed with reduced amount of alkyne (1.5 equiv), $[Rh(COD)Cl]_2$ (2.0 mol %) and DPEphos (6.0 mol %). *p*TSA = *p*-toluenesulfonic acid, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid.

Previous studies had shown that the addition of a Brønsted acid as a cocatalyst enhances the formation of a π-/σ-allyl rhodium intermediate thus promoting the reaction. Indeed, addition of several different sulfonic and carboxylic acid additives increased the yield of the allylic addition product significantly with trifluoroacetic acid being best. With both 2-octyne as well as the aromatic 1-phenyl-1-propyne basically quantitative yields of the desired addition products were obtained (Table 1, entries 7 and 8). The amount of alkyne substrate and rhodium catalyst could be lowered to 1.5 equivalents and 2 mol %, respectively without a detrimental effect on yields (entries 9 and 10).[14]

In all cases, neither a vinylic nor a linear side product was observed under these conditions and the branched allylic addition product was the only regioisomer notable.

With these optimized conditions in hands the scope of this reaction was explored. In a first reactivity assay, we looked at the scope of aliphatic internal methyl alkynes (Table 2).

Table 2. Scope of aliphatic alkynes with methyl acetoacetate (**3**).

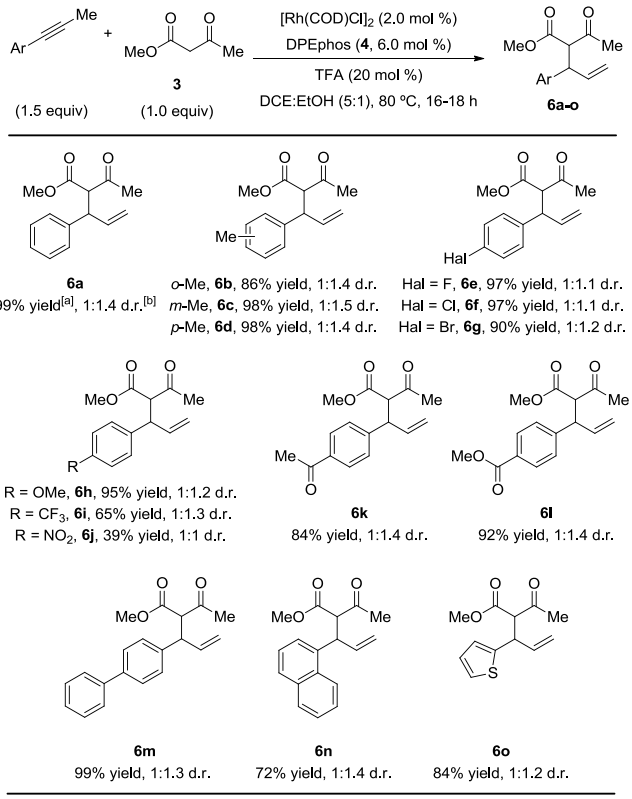


[a] All yields are isolated yields. [b] The diastereomeric ratio (d.r.) was determined by ^1H NMR analysis. [c] This reaction was additionally performed in a 10.0 mmol scale, half catalyst loading ($[Rh(COD)Cl]_2$ (1.0 mol %), DPEphos (3.0 mol %)), and gave **5c** in 93% isolated yield and 1:1.2 d.r. [d]. Reaction performed with conditions from table 1, entry 5: alkyne (2.0 equiv), $[Rh(COD)Cl]_2$ (2.5 mol %), DPEphos (7.5 mol %), *p*-$CF_3C_6H_4COOH$ (50 mol %).

Linear aliphatic internal alkynes devoid of any functional group were well tolerated and gave yields of 82% to 95% (**5a**–**5c**) along with cyclohexyl-, alkenyl- and phenyl-propyl-substituted alkynes and yields of 76% to 87% (**5d**–**5f**). Additionally, the standard reaction was performed on a 10.0 mmol scale and yielded 93% of **5c** with only half catalyst loading of 1.0 mol % $[Rh(COD)Cl]_2$ and 3.0 mol % DPEphos. To our delight, even a prehalogenated alkyne was applicable (91% yield, **5g**). Also, substrates bearing functional groups including a phthalimidoyl function (**5h**), a benzyl ether (**5i**), a benzoate group (**5j**) and a silyl ether (**5k**) behaved well. Even the presence of a free carboxylic acid was to yield **5l** in 83%. In all cases, the diastereomeric ratios were moderate up to 1:2.2 d.r.

Additionally, aromatic internal methyl alkynes were excellent substrates for the title reaction (Table 3).

Table 3. Scope of aromatic alkynes with methyl acetoacetate (**3**).

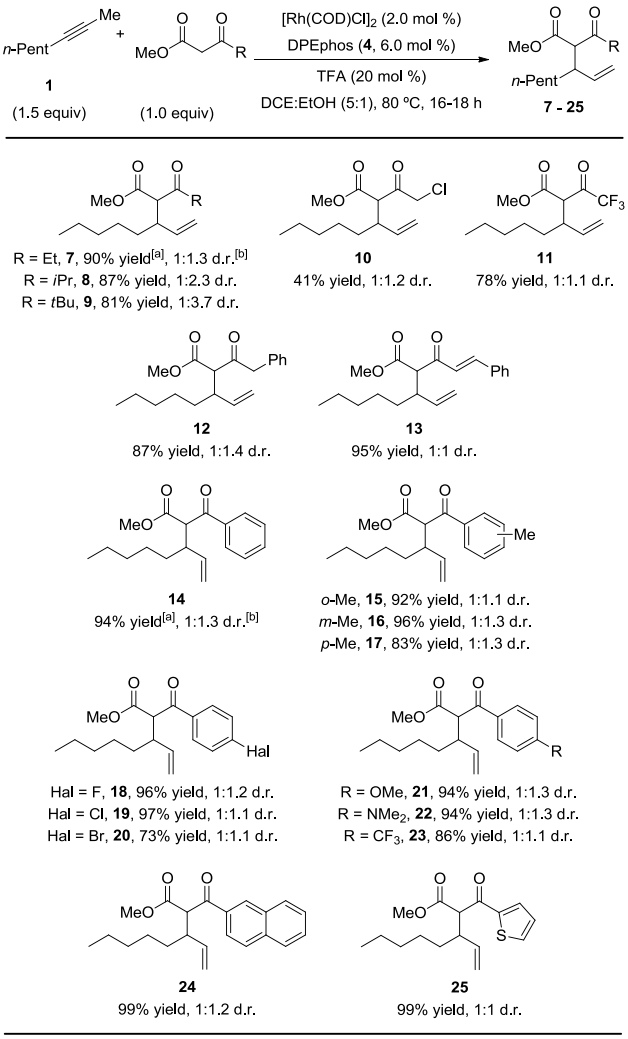


[a] All yields are isolated yields. [b] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis.

Benchmarking the excellent result of 99% yield of **6a** with unsubstituted 1-phenyl-1-propyne (**2**), a wide range of different substituents on the aryl moiety are tolerated (Table 3). A methyl substituent in *ortho*-position has only a small impact on the yield (86%, **6b**), whereas *meta*- and *para*-positions were well tolerated (98%, **6c** + **6d**). In *para*-position, halogenated 1-aryl-1-propynes (**6e**–**6g**) as well as an electron-donating methoxy group (**6h**) reacted smoothly in excellent yields. Conversely, strongly electron-withdrawing groups led to diminished yields (**6i** + **6j**). However, an acetyl or ester moiety are well tolerated to afford the corresponding products **6k** and **6l** in good yields. Bulkier 4-biphenyl (**6m**), 1-naphthyl (**6n**) and 2-thiophenyl (**6o**) substituents also behaved well in this reaction and furnished the desired addition products in good to excellent yields. In all cases, the diastereomeric ratios were moderate.

Next, the reaction could be applied to a large variety of β-keto esters (Tables 4 + 5).

Table 4. Scope of β-keto esters: variation on keto side.



[a] All yields are isolated yields. [b] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis.

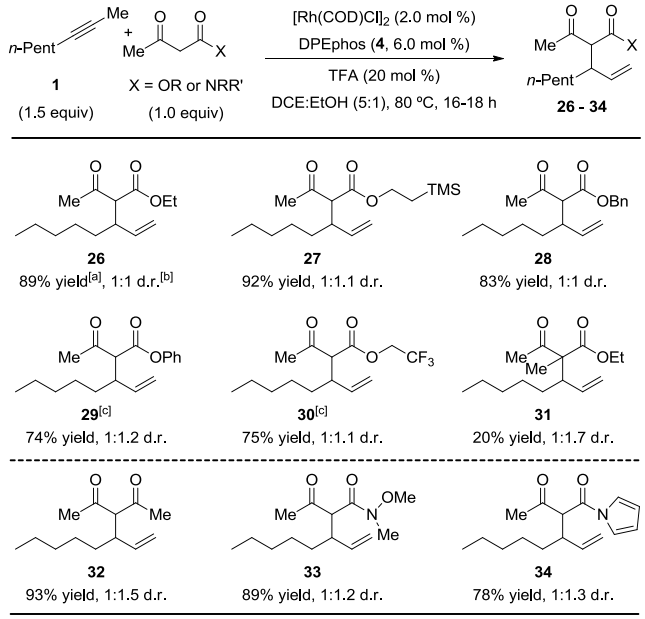
In a series of increasing steric demand on the keto side of the β-keto esters going from an ethyl via an isopropyl to a *tert*-butyl substituent, only a slight decrease in yield (from 90% to 81%) was noted while the diastereomeric ratio slightly increased (Table 4, **7**–**9**). In case of a chloromethylene substituent, the yield dropped to 41% (**10**), while a substrate having a CF_3 substituent behaved well (**11**). Even more challenging substrates such as the rather α-acidic benzyl group were well tolerated (**12**). Furthermore, a styrenyl substituent could be introduced (**13**) setting the stage for a subsequent ring-closing metathesis reaction towards cyclopentenones.[16]

Also, aryl-substituted β-keto esters were excellent substrates. A methyl substituent on the aryl substituent is well tolerated in *ortho*-, *meta*- and *para*-position (**15**–**17**).

Furthermore, tolerated functional groups in *para*-positions were halogens (F, Cl and Br) as well as electron-donating (OMe, NMe_2) and electron-withdrawing (CF_3) substituents. Finally, bulkier 2-naphthyl (**24**) and 2-thiophenyl (**25**) substituents also behaved well in this reaction and achieved the desired addition products in excellent yields of 99%.

The third possible site of variation in this reaction setup is the ester function of the β-keto esters (Table 5).

Table 5. Scope of β-keto esters: variation on ester side and β-keto amides.



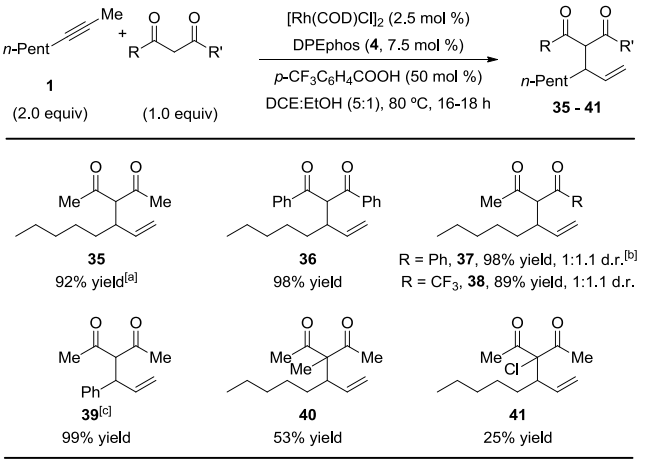
[a] All yields are isolated yields. [b] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis. [c] Reaction performed in pure DCE.

Variation on the ester side of the β-keto esters led to usually good yields (Table 5). Ethyl, (trimethylsiloxy)ethyl and benzyl acetoacetates proceed well in this reaction to give good yields (**26**–**28**). By using phenyl or trifluoroethyl acetoacetate (**29** + **30**), the solvent of choice is DCE without an ethanol additive to avoid partial transesterification to the corresponding product **26**. A methyl substituent in α-position led to a yield of 20%, showing up the limitations of too bulky nucleophiles (**31**).

We were pleased to find β-keto amides as yet another suitable nucleophile for the rhodium-catalyzed addition to internal methyl alkynes. Furthermore, all tested β-keto amides provided the addition products in satisfying yields (**32**–**34**).

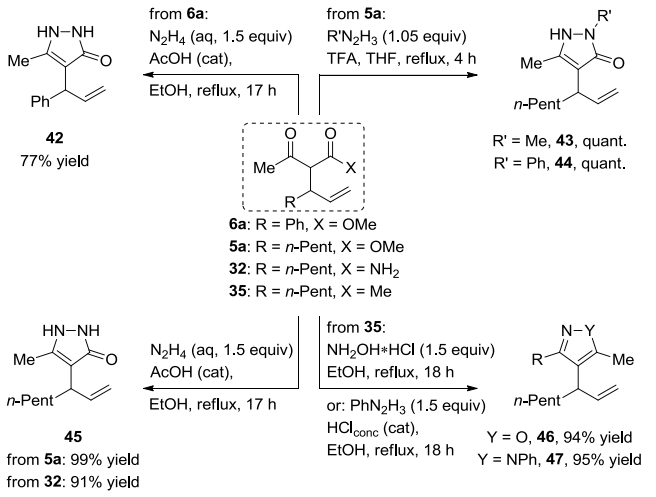
Since β-keto esters and β-keto amides proved to be outstanding nucleophiles in the rhodium-catalyzed addition to internal methyl alkynes, more reactive 1,3-diketones were subjected to the catalysis. To our surprise, the outcome under optimized conditions led to low yields, however, we resubjected these nucleophiles under previously used conditions for the addition to terminal alkynes (Table 6).[11]

Table 6. Scope of 1,3-diketones with 2-octyne (**1**).



[a] All yields are isolated yields. [b] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis. [c] Reaction performed using 1-phenyl-1-propyne (**2**, 2.0 equiv).

The reaction could be applied to simple acetylacetone to yield **35** in 92% (Table 6). The addition of symmetric bisbenzoyl methane gave **36** in 98% yield, whereas asymmetric 1,3-diketones led to the products **37** and **38** in 98% and 89% with moderate diastereoselectivity. Using the second alkyne, 1-phenyl-1-propyne (**2**), product **39** was isolated in 99% yield. Finally, more bulky α-substituted acetylacetones were explored to yield **40** (57%) and **41** (25%).



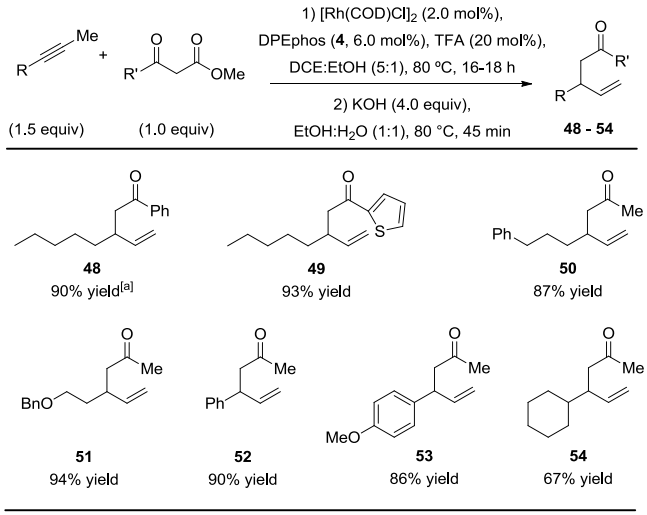
Scheme 3. Application in heterocyclic synthesis: condensation to pyrazolones, pyrazoles and oxazoles.

The resulting branched α-allylated 1,3-dicarbonyl intermediates are useful starting materials for heterocycle synthesis (Scheme 3). Condensation of β-keto esters with hydrazines furnished pyrazolones, which are privileged medicinal scaffolds that enjoy massive attention.[17]

Hence, reaction of **6a** with hydrazine provided pyrazolone **42** in 77% yield (Scheme 3). Correspondingly, reaction with methyl or phenyl hydrazine gave pyrazolones **43** and **44** in quantitative yields. It was also possible to vary the substrate for condensation: both, α-allylated β-keto ester **5a** and amid **32** led to **45** in excellent yields. Finally, reaction of α-allylated 1,3-diketone **35** with hydroxylamine led to oxazole **46** or using hydrazine led to pyrazole **47**. Oxazoles and pyrazoles are also of enormous medicinal interest.[18,19]

The received branched α-allylated β-keto esters can also be subjected to a simple basic saponification followed by decarboxylation to furnish γ,δ-unsaturated ketones (Table 7). γ,δ-unsaturated ketones are important intermediates for the synthesis of many biologically active molecules.[13] Our access represents a synthetic alternative to a methyl-ketone-enolate allylation reaction or a Claisen/Carroll-type rearrangement.[20]

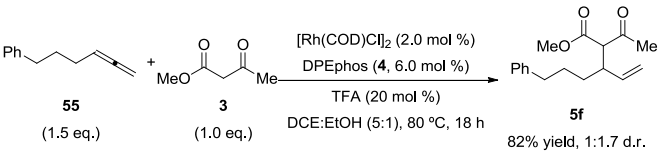
Table 7. Rhodium-catalyzed addition of β-keto esters to internal methyl alkynes followed by basic saponification/decarboxylation to form γ,δ-unsaturated ketones.



[a] All yields are isolated yields over two steps.

The tandem reaction of rhodium-catalyzed addition followed by basic saponification/decarboxylation proceeded smoothly with potassium hydroxide in ethanol and water (1:1), and the resulting γ,δ-unsaturated ketones were obtained in good to excellent yields (Table 7). Simple unfunctionalized alkynes and functional groups, such as ethers as well as aryl substituents on the β-keto esters, were well tolerated (**48**–**54**).

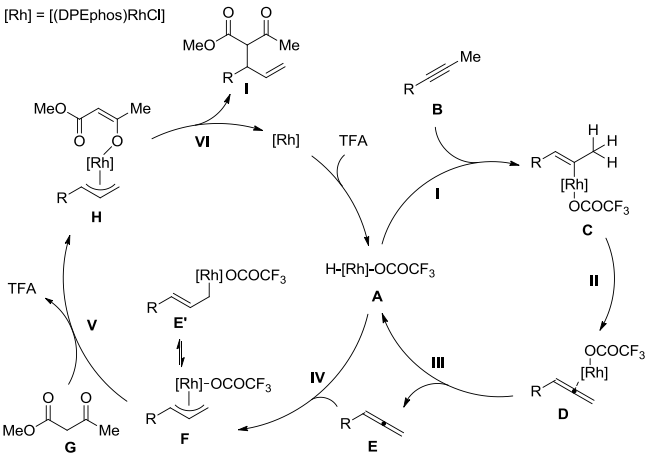
In order to attain first insights into the reaction mechanism, the following control experiment was performed (Scheme 4).



Scheme 4. Control experiment: rhodium-catalyzed addition of methyl acetoacetate (**3**) to *allene* **55**.

The rhodium-catalyzed addition of methyl acetoacetate (**3**) to the terminal *allene* **55** provided the product **5f** in a good yield of 82% and 1:1.7 d.r. (Scheme 4). This indicates that the allene or its rhodium-complex is likely to be an intermediate during the course of this reaction.

Based on this control experiment and on our previous investigations, we propose the following catalytic cycle (Scheme 5).[7,8,21]



Scheme 5. Proposed mechanism of the rhodium-catalyzed addition of β-keto esters to internal alkynes.

The first part of the proposed mechanism contains the rhodium-catalyzed isomerization of an internal methyl alkyne **B** to an allene **E** via formation of a Rh-vinyl species **C** (step **I**, Scheme 5). Subsequent β-hydride elimination (step **II**) furnishes the allene **E** via its rhodium complex **D** (step **III**).[22] In the second cycle, the rhodium catalyst can undergo oxidative addition to form rhodium(III) hydride **A**. Hydrometallation of allene **E** furnishes the π-allyl complex **F** (step **IV**), which is presumably in equilibrium with σ- allyl complex **F'**. Anion exchange of **F** with β-keto ester **G** would provide complex **H** (step **V**). Reductive elimination releases the addition product **I** and regenerates the rhodium(I) catalyst (step **VI**).[23]

Conclusions

To conclude, starting from simple readily available alkynes and 1,3-dicarbonyl compounds, e.g. β-keto esters, β-keto amides and 1,3-diketones, we have developed a highly regioselective rhodium-catalyzed C-C bond forming reaction furnishing valuable branched α-allylated 1,3-dicarbonyl compounds in good to excellent yields. The utility of the obtained products was demonstrated through one-step transformations to pyrazolones, oxazoles and pyrazoles, which are privileged medicinal scaffolds of interest. Furthermore, simple basic saponification followed by decarboxylation provided γ,δ-unsaturated ketones, products of a formal methyl-ketone-enolate allylation or a Claisen/Carroll-type rearrangement. Further attempts regarding extension of this method to the formation of quaternary centers, other (carbon-) nucleophiles as well as the development of an asymmetric catalytic variant are ongoing in our laboratories.

Experimental Section

General procedure A for the addition of a 1,3-dicarbonyl compound to a terminal alkyne

A flame-dried 10 ml Young tube was charged with $[Rh(COD)Cl]_2$ (4.9 mg, 10 µmol, 2.0 mol %) and DPEphos (16.2 mg, 30 µmol, 6.0 mol %). The tube was evacuated and backfilled with argon, before pre-mixed solvent of DCE and EtOH (5:1, 1.25 ml) was added. Then the alkyne (0.75 mmol, 1.5 eq.), TFA (8.0 µl, 12 mg, 0.1 mmol, 20 mol %), and the 1,3-dicarbonyl compound (0.5 mmol. 1.0 eq.) were added. The tube was sealed and heated to 80 °C for 16 hours. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel.

General procedure B for the addition of a 1,3-dicarbonyl compound to a terminal alkyne

A flame-dried 10 ml Young tube was charged with $[Rh(COD)Cl]_2$ (6.2 mg, 12.5 µmol, 2.5 mol %), DPEphos (20.2 mg, 37.5 µmol, 7.5 mol %) and *p*-$CF_3C_6H_4COOH$ (47.5 mg, 0.25 mmol, 50 mol %). The tube was evacuated and backfilled with argon, before pre-mixed solvent of DCE and EtOH (5:1, 1.25 ml) was added. Then the alkyne (1.0 mmol, 2.0 eq.) and the 1,3-dicarbonyl compound (0.5 mmol. 1.0 eq.) were added. The tube was sealed and heated to 80 °C for 16 hours. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel.

Acknowledgements

This work was supported by the DFG and the Fond of the Chemical Industry. We thank Umicore, BASF and Wacker for generous gifts of chemicals. Anne Aßmann (University Freiburg) is acknowledged for her motivated and skillful technical assistance.

Keywords: rhodium • 1,3-dicarbonyl compounds • alkynes • regioselective addition • γ,δ-unsaturated ketones

[1] For selected reviews on transition metal catalyzed allylic substitution, see: a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395-422. b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921-2944. c) J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140-145. d) Z. Lu, S. Ma, *Angew. Chem.* **2007**, *120*, 264-303; *Angew. Chem. Int. Ed.* **2007**, *47*, 258-297. e) G. Helmchen, A. Dahnz, P. Dubon, M. Schelwies, R. Weihofen, *Chem. Commun.* **2007**, 675-691.

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[22] The β-hydride elimination towards the terminal allene is presumably favored by the increased probability to eliminate one out of three C-H bonds, and by sterical reasons, forming the more stable rhodium complex.

[23] Products resulting from a reductive elimination to form a C-O bond have not been observed.

Entry for the Table of Contents

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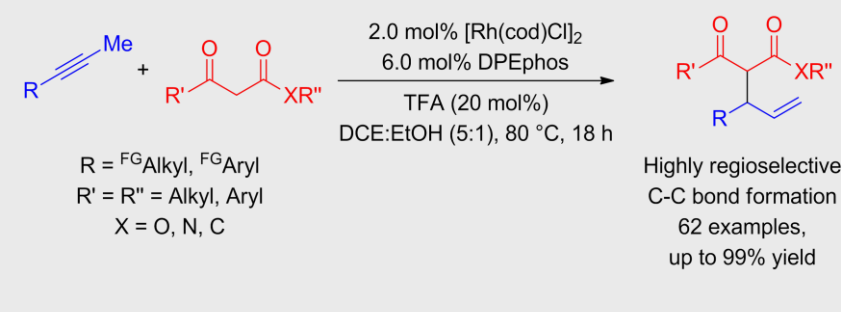

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Title

Short text for the Table of Contents (2):

An unprecedented rhodium-catalyzed regioselective addition of 1,3-dicarbonyl compounds, including β-keto esters, β-keto amides and 1,3-diketones, to internal alkynes furnishing branched allylic compounds is reported. The reaction shows a broad functional group tolerance and numerous structural variations on both reaction partners highlight the synthetic potential and flexibility of this method.