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RESEARCH ARTICLE

Switch in Selectivity for the Formal Hydroalkylation of 1,3-Dienes and Enynes with Simple Hydrazones

Leiyang Lv,[‡[a]] Lin Yu,[‡[a]] Zihang Qiu[[a]] and Chao-Jun Li*[[a]]

Dedication ((optional))

Abstract: Controlling reaction selectivity is a permanent pursuit for chemists. In particular, regio-selective catalysis, which exploits and/or overcomes innate steric and electronic bias to deliver diverse regio-enriched products from the same starting materials, represents a powerful tool for divergent synthesis. Recently, our group reported the 1,2-Markovnikov hydroalkylation of 1,3-dienes with simple hydrazones to generate branched allylic compounds when a nickel catalyst was used. As part of the effort, herein we show that a complete switch of Markovnikov to anti-Markovnikov directionality is obtained by slightly changing to a ruthenium catalyst, thus providing a direct and efficient access to the homoallylic products exclusively. Isotopic substitution experiments indicate that no reversible hydro-metallation across the metal-π-allyl system occurred under ruthenium catalysis. Moreover, this protocol is also applicable to the regio-specific hydro-alkylation of the distal C=C bond of 1,3-enynes.

Introduction

Engineering reaction selectivity rationally and predictably remains a formidable challenge to synthetic chemists.[1] Catalyst-controlled selective transformation represents a promising tool for divergent synthesis.[2] The power of using catalysis to attain exquisitely selective transformations is elegantly exploited by Nature, which can convert the identical starting materials into a variety of diversified products by enzymes. Inspired by the extraordinary selectivity of biocatalysis, several strategies have been devoted to gain an analogous level of regio-enriched products over facile innate reactivity.[3] Examples include (a) installation of different protecting or directing groups[4] to overcome the inherent steric and electronic biased factors, (b) modification of reaction parameters, such as solvent[5], temperature[6], additives[7], etc. and (c) design and manipulation of the catalyst system.[8] As Trost has asserted, engineering a catalyst that completely overrides inherent regio- or chemoselectivity to give exclusively the desired product requires creativity and insight.[9] To this end, transition metal-catalyzed selective transformations have gained preferred attention due to their versatility, broad applicability, and especially predictability.[10] The appropriate combination of metal catalysts and clever selection of ligands serve as an ideal platform for designing and developing selective catalysis, especially from the same simple starting materials.[11]

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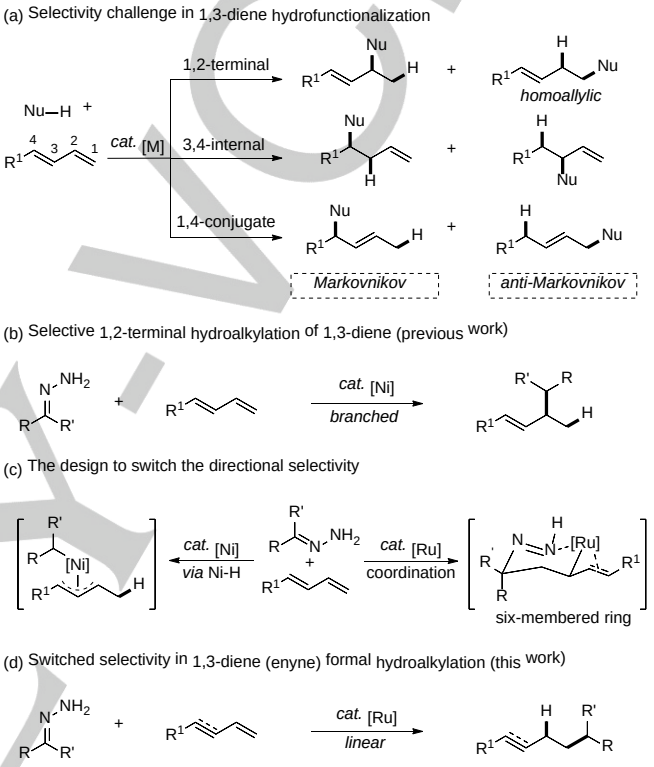

Scheme 1. Selectivity challenge in the transition-metal-catalyzed hydrofunctionalization of 1,3-dienes and strategy to switch the 1,2-terminal directional selectivity.

1,3-Dienes represents an exceptionally attractive platform for selective functionalization, because labile coordination and insertion modes are accessible in the presence of transition metal.[12] In other words, at least six different isomers can be potentially formed during the addition of Nu-H addition across a terminal diene, and the selectivity of the newly formed bonds depends on the Markovnikov or anti-Markovnikov directionality with internal, terminal 1,2-addition or conjugate 1,4-addition (Scheme 1a).[13-16] We[17] and Zhou's lab[18] recently independently communicated an nickel-catalyzed 1,2-Markovnikov hydroalkylation[19] of 1,3-dienes with umpolung carbonyls to generate branched allylic compounds (Scheme 1b). In these reactions, the nickel hydride species is generated, which reacts with the diene to generate an electrophilic nickel-π-allyl intermediate (hydride adds preferentially to the less steric hindered terminal olefinic carbon) (Scheme 1c, left). Based on the literature report[20] and our previous work[21], instead of generating metal hydride species, the ruthenium catalyst[22] favors the coordination of hydrazone and unsaturated partner and assists the inner-sphere rearrangement of coordinated complexes to form a stable six-membered ring intermediate. Inspired by this, we hypothesized that if

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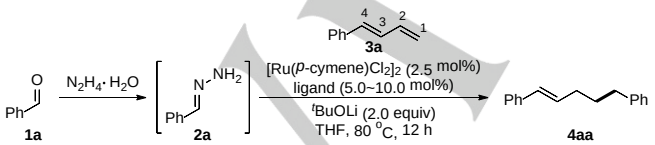
1,3-diene was used as the unsaturated partner, the readily formed six-membered ring system might allow for the anti-Markovnikov addition directionality (Scheme 1c, right). Namely, outer-sphere addition gave the branched Markovnikov product whereas inner-sphere carboruthenation gave the linear anti-Markovnikov product. Besides, this conformation controlled strategy might also help to prevent the undesired allylic isomerization of the remaining C=C bond. With this design in mind, herein we wish to report that changing the metal catalyst from nickel to ruthenium, a complete switch of a Markovnikov to anti-Markovnikov directionality was obtained from the same simple starting materials (hydrazones and 1,3-dienes), thus affording the homoallylic products exclusively (Scheme 1d). Moreover, the ruthenium catalysis is applicable to the regio-specific formal hydro-alkylation of the distal C=C bond of 1,3-enynes.[23] The studies on simple hydrazone chemistry also contribute to a departure from pre-metalated reagents in metal-catalyzed C-C bond formation.[24]

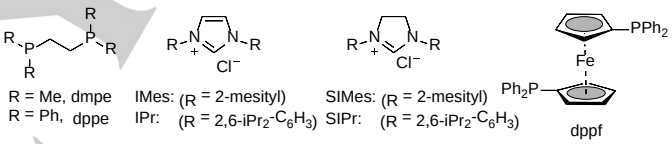
Results and Discussion

We started our study by evaluating the reaction between phenyl hydrazone **2a** (generated from benzaldehyde **1a** and hydrazine, water and solvent were removed before use without further purification) and phenyl butadiene **3a** in the presence of [Ru(*p*-cymene)Cl_2]$_2$, PMe_3 and ^{t}BuOLi in THF (tetrahydrofuran) at 80 °C for 12 h (Table 1). Gratifyingly, the 1,2- and anti-Markovnikov addition product **3a** was formed in 23% yield exclusively (entry 1). Encouraged by this result and given the vital role of ligands in transition-metal-catalyzed transformations, we next interrogated a series of commercially available ligands to improve the reaction efficiency. Notably, a 85% yield of the desired product was obtained when bi-dentate and electron-rich phosphine ligand dmpe [1,2-bis(dimethylphosphino)ethane] was used (entry 4), while the other phosphine-, nitrogen-containing and/or NHC ligands were found to be inferior for this transformation, leaving most of the starting material 1,3-diene unreacted (entries 2-12). Further investigation of several common ruthenium (II) catalysts showed that comparative selectivity and yields could be achieved (entries 13-15). Enquiry of bases revealed that ^{t}BuOLi gave the best results (entries 16-19). The absence of reactivity with ^{t}BuOK was ascribed to the competing Wolff–Kishner reduction of hydrazone under more basic conditions (entry 18). As control experiments, no desired product was generated in the absence of ruthenium catalyst, base or ligand (entries 20-22).

Table 1. Optimization of the reaction conditions.[a]



entry	catalyst	ligand	base	**4aa** (%)[b]
1	[Ru(*p*-cymene)Cl_2]$_2$	PMe_3	^{t}BuOLi	23
2	[Ru(*p*-cymene)Cl_2]$_2$	PPh_3	^{t}BuOLi	trace
3	[Ru(*p*-cymene)Cl_2]$_2$	PCy_3	^{t}BuOLi	trace
4	[Ru(*p*-cymene)Cl_2]$_2$	dmpe	^{t}BuOLi	85 (81)
5	[Ru(*p*-cymene)Cl_2]$_2$	dppe	^{t}BuOLi	trace
6	[Ru(*p*-cymene)Cl_2]$_2$	dppf	^{t}BuOLi	trace
7	[Ru(*p*-cymene)Cl_2]$_2$	2,2′-bipyridyl	^{t}BuOLi	7
8	[Ru(*p*-cymene)Cl_2]$_2$	1,10-phen-anthrolinlone	^{t}BuOLi	trace
9	[Ru(*p*-cymene)Cl_2]$_2$	IMes•HCl	^{t}BuOLi	26
10	[Ru(*p*-cymene)Cl_2]$_2$	SIMes•HCl	^{t}BuOLi	trace
11	[Ru(*p*-cymene)Cl_2]$_2$	IPr•HCl	^{t}BuOLi	11
12	[Ru(*p*-cymene)Cl_2]$_2$	SIPr•HCl	^{t}BuOLi	trace
13	[Ru(C_6Me_6)Cl_2]$_2$	dmpe	^{t}BuOLi	85
14	Cp*Ru(cod)Cl	dmpe	^{t}BuOLi	84
15	$Ru(PPh_3)_4Cl_2$	dmpe	^{t}BuOLi	84
16	[Ru(*p*-cymene)Cl_2]$_2$	dmpe	K_3PO_4	47
17	[Ru(*p*-cymene)Cl_2]$_2$	dmpe	KOH	78
18	[Ru(*p*-cymene)Cl_2]$_2$	dmpe	^{t}BuOK	trace
19	[Ru(*p*-cymene)Cl_2]$_2$	dmpe	DBU	N.D.
20	-	dmpe	^{t}BuOLi	N.D.
21	[Ru(*p*-cymene)Cl_2]$_2$	-	^{t}BuOLi	N.D.
22	[Ru(*p*-cymene)Cl_2]$_2$	dmpe	-	N.D.



[a] Reaction conditions: phenyl butadiene **3a** (0.2 mmol), phenyl hydrazone **2a** (0.6 mmol, generated from benzaldehyde and hydrazine), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), ligand (5 mol% for monodentate, 10 mol% for bidentate) and ^{t}BuOLi (0.4 mmol) in THF (0.3 mL) at 80 °C for 12 h under N_2 unless otherwise noted. [b] The yield of **4aa** was determined by ^{1}H NMR using mesitylene as an internal standard (isolated yield of **4aa** in parenthesis). N. D. = not detected. DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene. Cp* = pentamethylcyclopentadiene.

With the optimized reaction conditions established, we first examined the scope of the transformation with respect to the hydrazones. As shown in Table 2, a series of aryl hydrazones bearing electron-donating and electron-withdrawing substituents were amenable in this transformation, providing the corresponding products **4ab-ap** in moderate to good yields (64-88%). Hydrazone derived from mesitaldehyde gave a lower yield (**4aq**, 41%), indicating that the reaction efficiency was hampered by the increased steric hindrance. Notably, substrates bearing ferrocene and boronic ester underwent the reaction and afforded the desired products **4ar** and **4as** in 36% and 41% yields, respectively. Heterocyclic hydrazones including furan, thiophene, pyridine and carbazole also reacted smoothly (**4av-ax**) without any interference from the coordinating hetero-atoms. Hydrazones derived from ketones and aliphatic aldehydes were found to be a less effective substrate in this protocol, owing to the rapid dimerization to form azines. To highlight the practicability of this protocol, 3.0 mmol scale reaction was carried out, giving the product **4ae** in 76% yield (0.75 g). Subsequently, we continued to explore the generality of this regioselective addition

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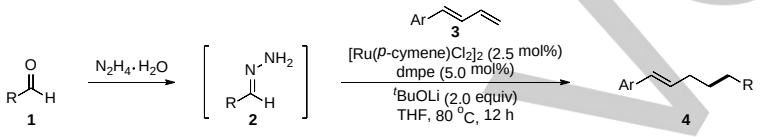
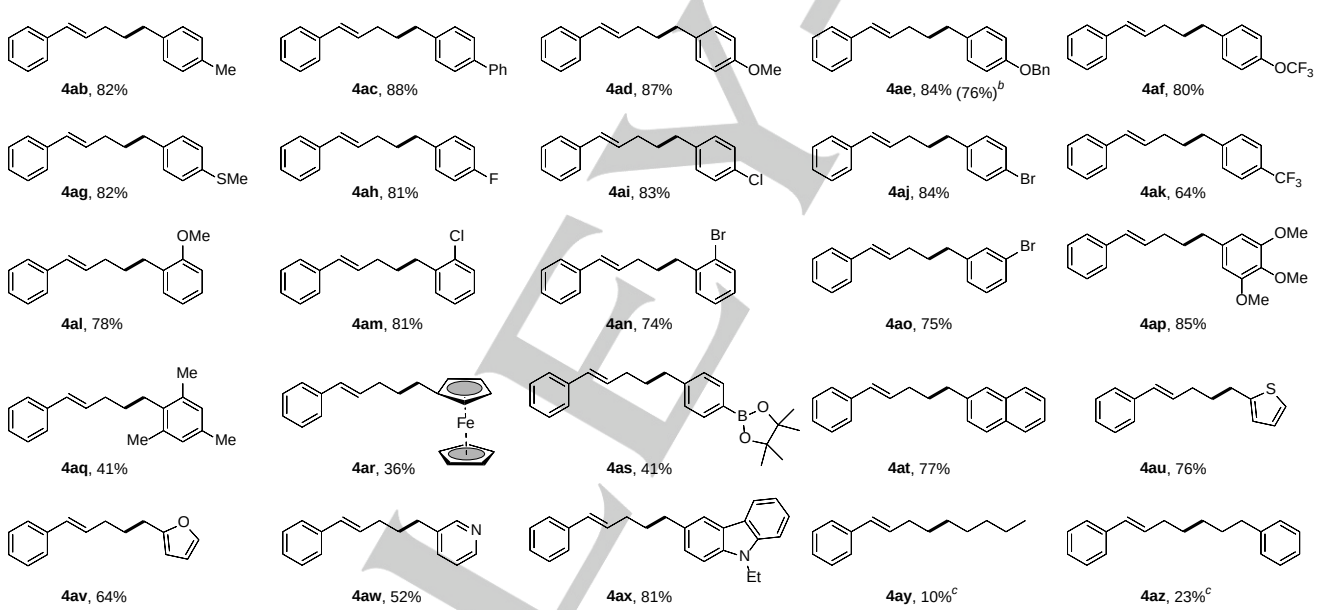
reaction towards 1,3-dienes under the standard reaction conditions. The presence of an electron-withdrawing group on the aromatic moiety of dienes appeared to be more beneficial than the presence of an electron-donating group (**4ba-bl**). Dienes with polycyclic (hetero-) aromatic substituents were also competent substrates, delivering the corresponding products **4bj-bl** in good to excellent yields (75-85%). Buta-1,3-diene-1,1-diyldibenzene **3m** was a suitable substrate in this reaction, while substitution on other position were not accommodated. Notably, this method could be readily extended to the functionalization of pharmaceutically relevant α-Tocopherol derivative **3n**.

Encouraged by these results, we speculated the possibility to extend the method to the hydrofunctionalization of 1,3-enynes (Table 3). To our delight, the regio-specific 1,2- and anti-Markovnikov addition activity to the alkene moiety were obtained, without any complication from the alkyne part. The general applicability of this protocol was well illustrated by the tolerance of an array of functional groups, such as methyl, phenyl, methoxy, benzyloxy, trifluoromethoxy, methylthio, *N*,*N*-dimethyl, trifluoromethyl, fluoride, chloride, bromide and methylenedioxyl attached onto hydrazone (**6aa-aaa**, 49-99%). Various hetero-aromatic hydrazones were evaluated and all worked efficiently, giving the desired products (**6aab-aak**) in good yields. It is noteworthy that hydrazones derived from aliphatic aldehydes and ketones could also be used as suitable substrates, thus affording the desired products **6aal-aaq** in 21-94% yields.

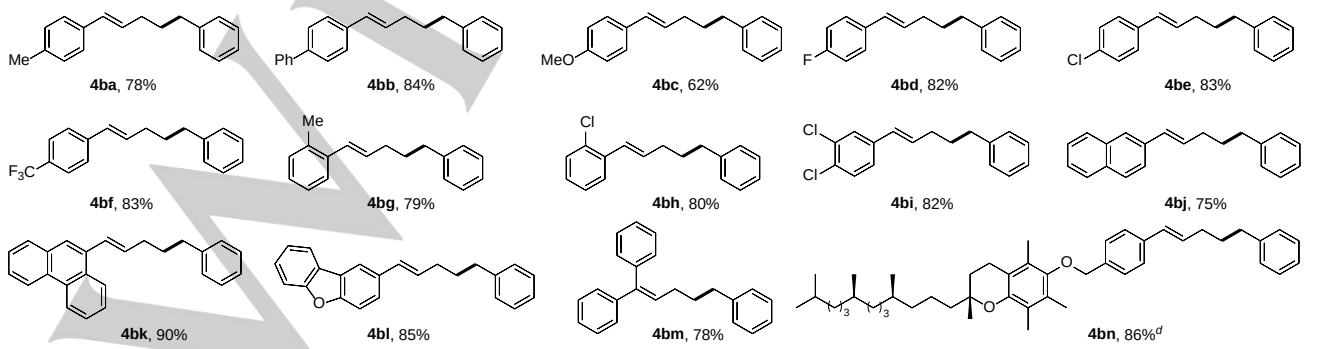
Table 2. Scope of hydrazones and 1,3-dienes.[a]



(a) Scope of hydrazones



(b) Scope of 1,3-dienes



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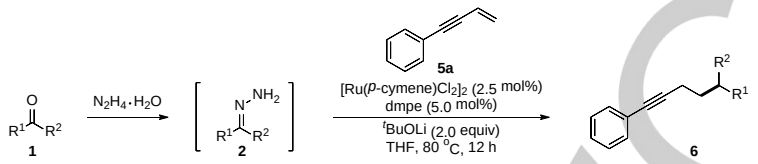
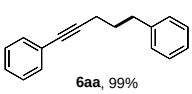
[a] Reaction conditions: 1,3-diene **3** (0.2 mmol), hydrazone **2** (0.6 mmol, generated from aldehyde and hydrazine), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), dmpe (5 mol%) and ^{t}BuOLi (0.4 mmol) in THF (0.3 mL) at 80 °C for 12 h under N_2. Reported yields were the isolated ones unless otherwise noted. [b] The yield in parenthesis was obtained in 3.0 mmol scale based on 1,3-diene. [c] The yield was determined by ^{1}H NMR analysis of the crude mixtures. [d] The reaction was performed on 0.1 mmol scale.

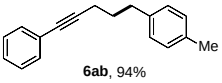
Table 3. Scope of hydrazones with 1,3-enynes.[a]



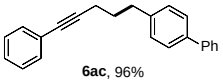
(a) Aromatic hydrazones



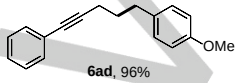
6aa, 99%



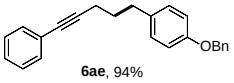
6ab, 94%



6ac, 96%



6ad, 96%



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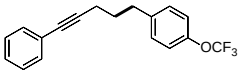
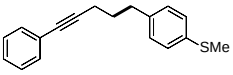
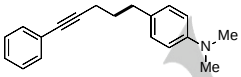


6af, 95%



6ag, 93%



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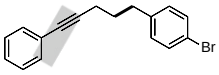

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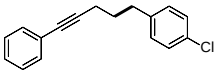

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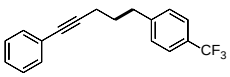

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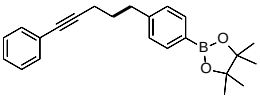

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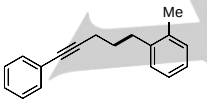
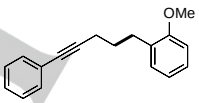


6am, 85%



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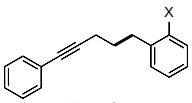
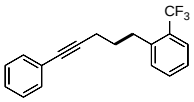


X = F, **6ao**, 89%
X = Cl, **6ap**, 87%
X = Br, **6aq**, 88%



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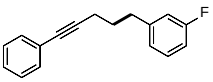

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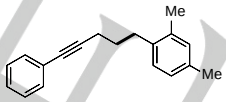

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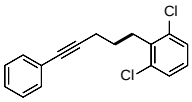

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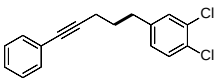

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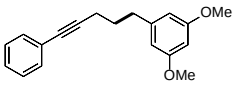

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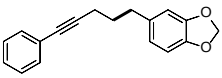

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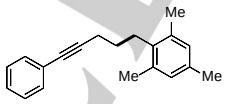

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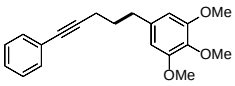
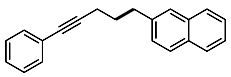
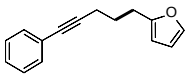


6az, 94%

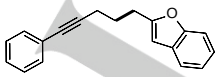


6aaa, 95%

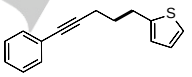
(b) Hetero-aromatic hydrazones



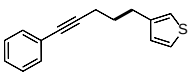
6aab, 78%



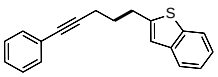
6aac, 81%



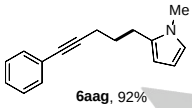
6aad, 92%



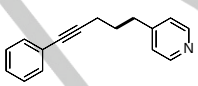
6aae, 89%



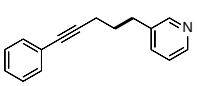
6aaf, 84%



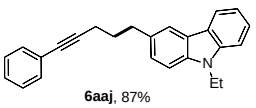
6aag, 92%



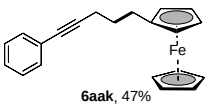
6aah, 82%



6aai, 87%

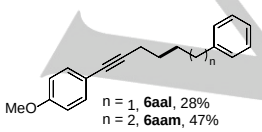


6aaj, 87%

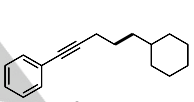


6aak, 47%

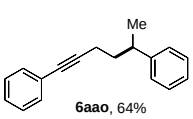
(c) Aliphatic hydrazones from aldehydes and ketones



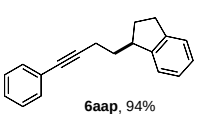
n = 1, **6aal**, 28%
n = 2, **6aam**, 47%



6aan, 21%



6aao, 64%



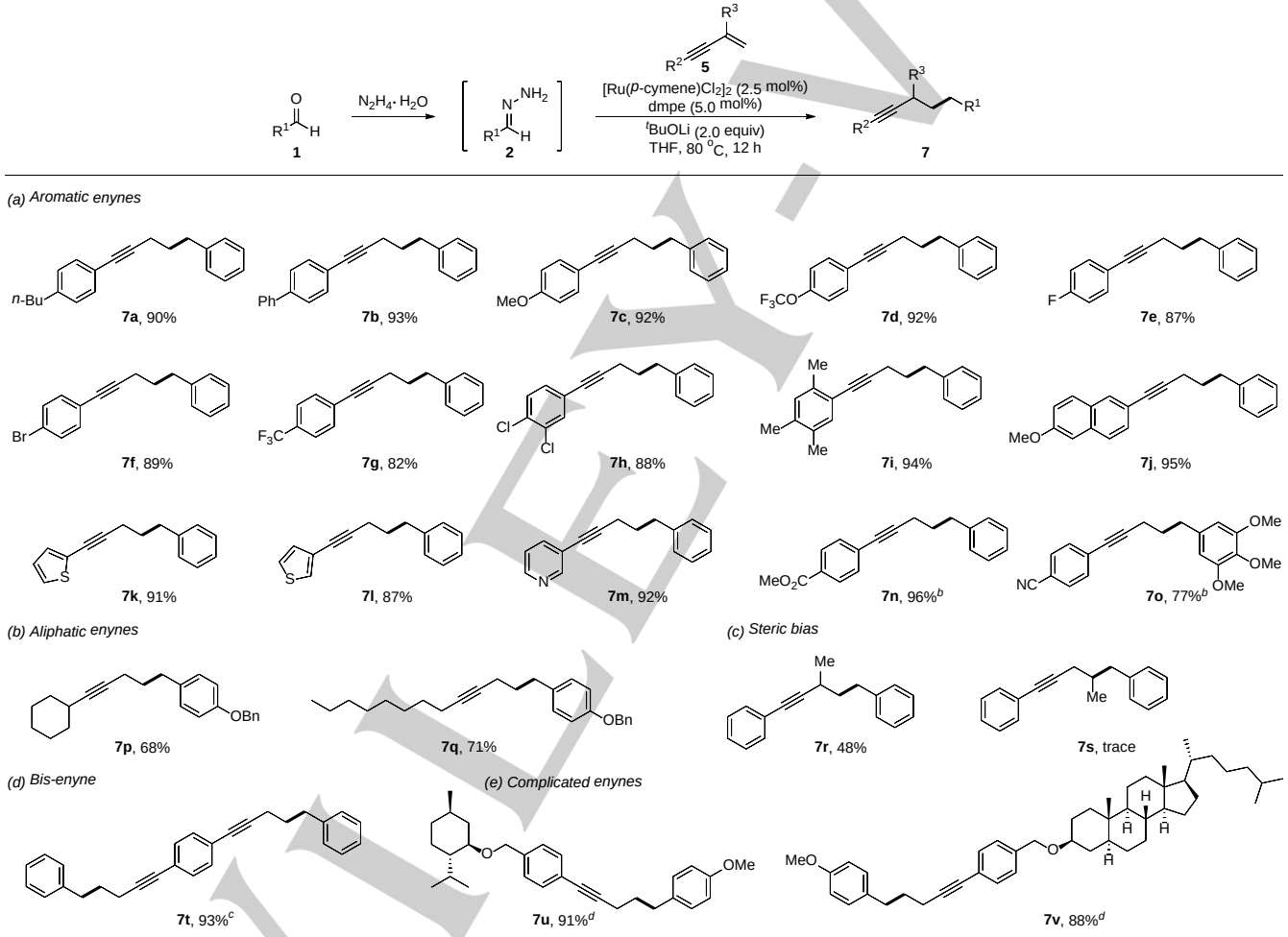
6aap, 94%

6aaq, 86%

[a] Reaction conditions: 1,3-enyne **5a** (0.2 mmol), hydrazone **2** (0.4 mmol, generated from aldehyde/ketone and hydrazine), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), dmpe (5 mol%) and ^{t}BuOLi (0.4 mmol) in THF (0.6 mL) at 80 °C for 12 h under N_2. Reported yields were the isolated ones.

The potential of the present regioselective catalysis was demonstrated by further elaboration of the enyne partners. As illustrated in Table 4, a broad range of structurally diverse enynes bearing either electron-donating or electron-withdrawing functional groups at the *para*-, *meta*-, and *ortho*- positions of the phenyl moiety were all converted into the desired products (**7a-j**) smoothly. In addition, hetero-aromatic such as thienyl and/or pyridyl substituted enynes could be applied in the transformation with very good efficiency (**7k-m**, 87-92%). Functionalities assembled onto the substrates, such as ester and nitrile, were well tolerated, enabling further functionalization of the generated products (**7n** and **7o**). More importantly, the scope is not restricted to aromatic enynes, alkyl enynes, such as cyclohexyl and octyl substituted ones, were also exemplified as suitable substrates for this catalytic system (**7p** and **7q**). The steric bias onto the alkene moiety resulted in reduced reactivity of enynes, as previously observed in the dienes functionalization. The yield was decreased to 48% (**7r**) when 2-methyl group was installed onto the olefinic part, while only trace amount of desired product **7s** was observed when internal enyne tested. Interestingly, the diyne product **7t** was obtained exclusively in 93% yield in the case of bis-enyne tested. Moreover, relatively complicated enynes, derived from L-menthol and cholesterol, were accommodated as well in this reaction (**7u** and **7v**).

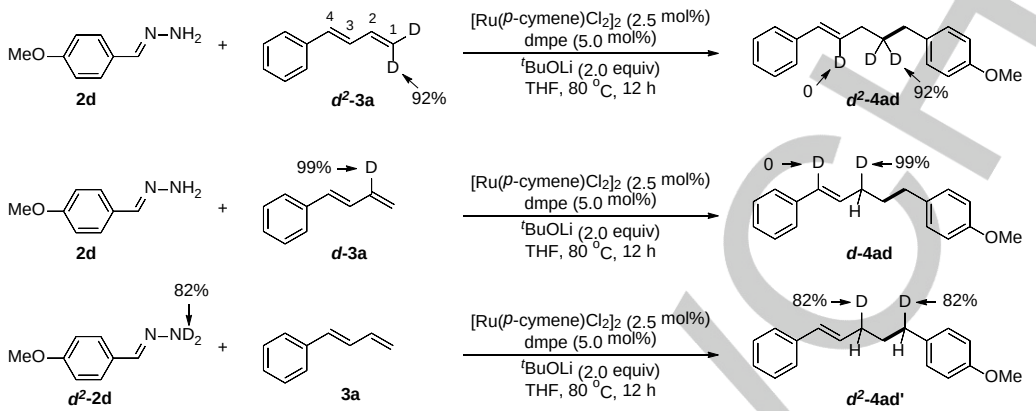
Table 4. Scope of 1,3-enynes with hydrazones.[a]



[a] Reaction conditions: 1,3-enyne **5** (0.2 mmol), hydrazone **2** (0.4 mmol, generated from aldehyde and hydrazine), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), dmpe (5 mol%) and ^{t}BuOLi (0.4 mmol) in THF (0.6 mL) at 80 °C for 12 h under N_2 unless otherwise noted. Reported yields were the isolated ones. [b] K_3PO_4 was used instead of ^{t}BuOLi. [c] Bis-enyne (0.1 mmol), phenyl hydrazone **2a** (0.5 mmol), other reaction conditions were similar. [d] The reaction was performed on 0.1 mmol scale.

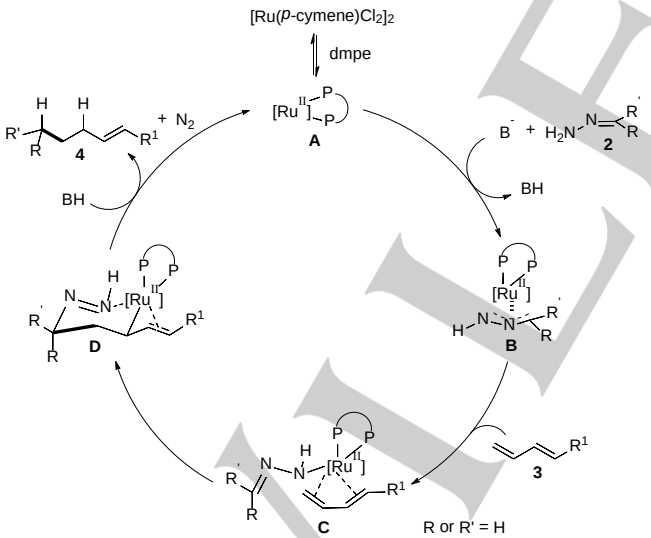
In order to gain some information about this transformation, deuterium-labeled substrates ***d*^{2}-3a** and ***d*-3a** were reacted under the standard conditions. We found that the formed products ***d*^{2}-4ad** and ***d*-4ad** with deuteration solely at the 1- and 2-position, respectively (Scheme 2, Eqs a and b). These results indicated that there were no reversible hydro-metallation across the metal-π-allyl system, since we would observe deuterium scrambling at the 3- or 4- position, which was detected in our previously recorded nickel-catalyzed Markovnikov hydroalkylation. To examine this hypothesis further, ***d*^{2}-2d** was employed under standard reaction conditions, in which product ***d*^{2}-4ad′**

was obtained while no deuterium migration was detected (Scheme 2, Eq c).



Scheme 2. Isotope-labeling experiments

Based on these results and previous studies[17,18,20-22], the following reaction mechanism was proposed (Scheme 3). The catalytic active species **A** is generated from precatalyst [Ru(*p*-cymene)Cl_2]$_2$ upon ligand dissociation/association with dmpe. Then hydrazone **2** and 1,3-diene **3** coordinates to the metal center to form intermediate **C**, which undergoes inner-sphere rearrangement to form a new carbon-carbon bond and the six-memebered ring intermediate **D** in the meantime. Subsequently, decomposition of this species by N_2 extrusion and protodemetalation releases product **4**, and completes the catalytic cycle.



Scheme 3. Proposed reaction mechanism

Conclusion

In conclusion, we have developed a highly selective protocol for the 1,2-anti-Markovnikov formal hydroalkylation of both 1,3-dienes and 1,3-enynes with umpolung carbonyls. This methodology provided a straightforward and efficient access to a variety of valuable homoallylic alkenes and alkynes (> 100 examples), which were versatile intermediates in chemical synthesis. The conformation (six-membered ring) controlled strategy might account for the regio-specific 1,2-anti-Markovnikov addition selectivity. Our study contributes to the art of tuning metal catalyst to engineer the reaction selectivity from the same starting materials to construct different products and also a departure from pre-metalated reagents in metal-catalyzed C-C bond formation.

Acknowledgements

We are grateful to the Canada Research Chair Foundation (to C.-J. Li), the Canadian Foundation for Innovation, FRQNT Centre in Green Chemistry and Catalysis, the Natural Science and Engineering Research Council of Canada and Killam Research Fellow of the Canadian Council of Arts for support of our research. We are also indebted to Dr. Haining Wang for constructive discussion on the mechanism.

Keywords: directional selectivity • 1,3-diene • hydrazone • hydroalkylation • ruthenium catalysis

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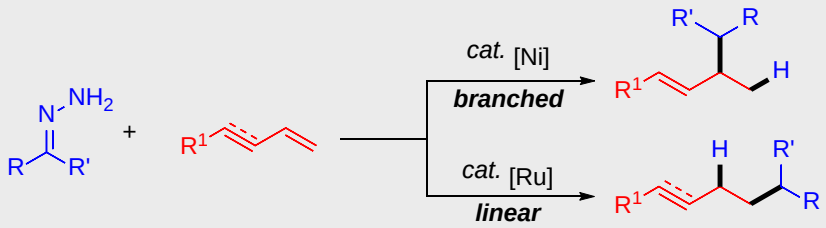

Rodeo ruthenium: Different directional selectivity can be obtained from the same starting materials by using different catalytic systems. The nickel-catalyzed hydroalkylation of hydrazones with 1,3-dienes yielded 1,2-Markovnikov products, whereas the ruthenium-catalyzed version led to 1,2-*anti*-Markovnikov directionality.

*Leiyang Lv,[‡] Lin Yu,[‡] Zihang Qiu and Chao-Jun Li**

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Title: Switch in Selectivity for the Formal Hydroalkylation of 1,3-Dienes and Enynes with Simple Hydrazones