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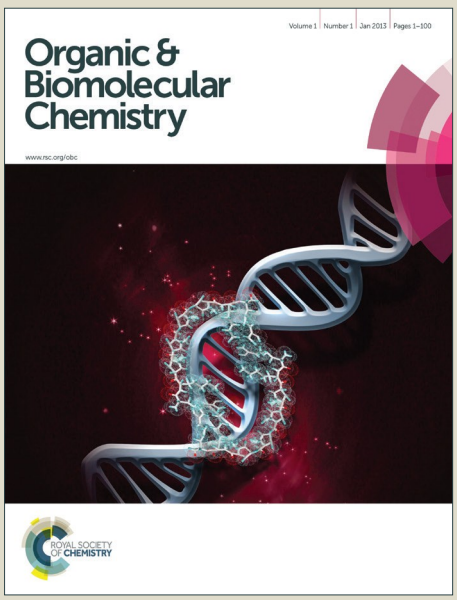





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# Copper-Free Arylation of 3,3-Disubstituted Allylic Halides with Triazene-Softened Aryl Grignard Reagents

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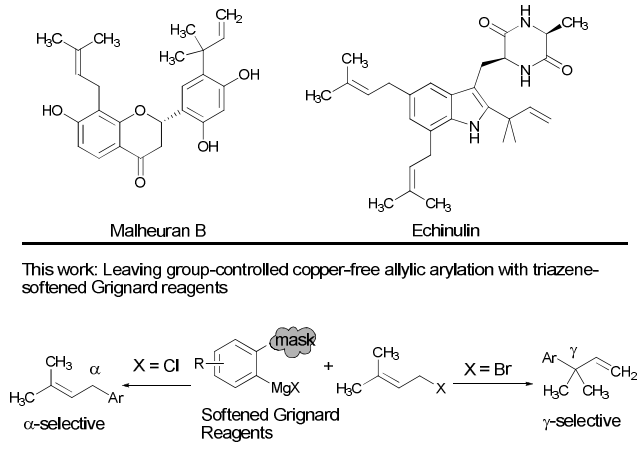
A copper-free allylic arylation reaction between 3,3-disubstituted allylic halides and triazene-softened aryl Grignard reagents has been developed. This protocol presents a direct and efficient way to construct both α- or γ- isomers with high regioselectivity under environmentally benign conditions. Various functional groups can be tolerated in the reaction and the products are of high value for multiple synthetic applications. The α- and γ- isomers can be converted to the corresponding 3H-indole and indole derivatives in multigram scale respectively.

## Introduction

Prenylated and reverse prenylated arenes are found in many biological and pharmacological active compounds, such as prenylated flavanone malheuran B[1] and indole alkaloid echinulin[2] (Scheme 1). Thus, the development of efficient methods to construct both normal prenylated and reverse prenylated arenes under simple condition is very appealing. Recently, Organ et al has developed a well-tailored NHC-based catalyst for the linear-selective (normal prenylated) Suzuki-Miyaura cross-coupling of 3,3-disubstituted allylboronates with aryl halides.[3] Buchwald et al also reports a palladium-catalyzed Negishi cross-coupling of allylzinc halides with aryl and vinyl electrophiles for completely linear-selective prenylation.[4] The γ-selective coupling of 3,3-disubstituted allylboronates to provide a sterically hindered quaternary center remains a formidable challenge. To address this challenge, Buchwald et al reports an orthogonal set of ligand-controlled palladium-catalyzed Suzuki-Miyaura cross-coupling of allylboronates and aryl halides for the highly selective preparation of either α- or γ-isomer (Scheme 1).[5]

Comparing with transition-metal catalyzed cross-coupling reaction between aryl halides and allylic metal reagents, the direct substitution of nucleophiles such as Grignard reagents with allylic substrates represents a powerful alternative method for C-C bond formation.[6] An important issue of this type of allylic substitution is the control of the regioselectivity in the reaction of unsymmetrically substituted allylic substrates. Copper-catalyzed allylic substitution reaction between a Grignard reagent and an allylic substrate has been investigated by Breit, Sawamura, Kobayashi et al[7] and demonstrated that the method is efficient for preparation of allylic products with good regioselectivity and even good enantioselectivity.[8] However, the reported allylic substitutions with Grignard reagents are still limited: 1) the nucleophiles are limited in alkyl Grignard reagents, only few cases succeed in cinnamyl-type substrates when using aryl Grignard reagents;[9] 2) the electrophiles are limited in 3-monosubstituted allylic system. 3,3-Disubstituted allylic systems are scarce, only few examples succeed when using 3,3-disubstituted allylic system as electrophiles in the formation of quaternary carbon center;[10] 3) the reaction with good selectivity needed to be catalyzed by transition metals predominantly catalyzed by Cu(I) salts.




***Scheme 1.*** Prenylated nature products (malheuran B and echinulin) and our proposed regioselective prenylation of prenyl halides with "softened" Grignard reagents.

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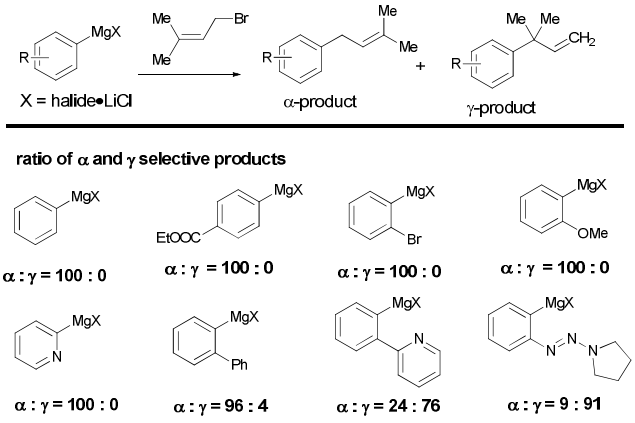
## Results and Discussion

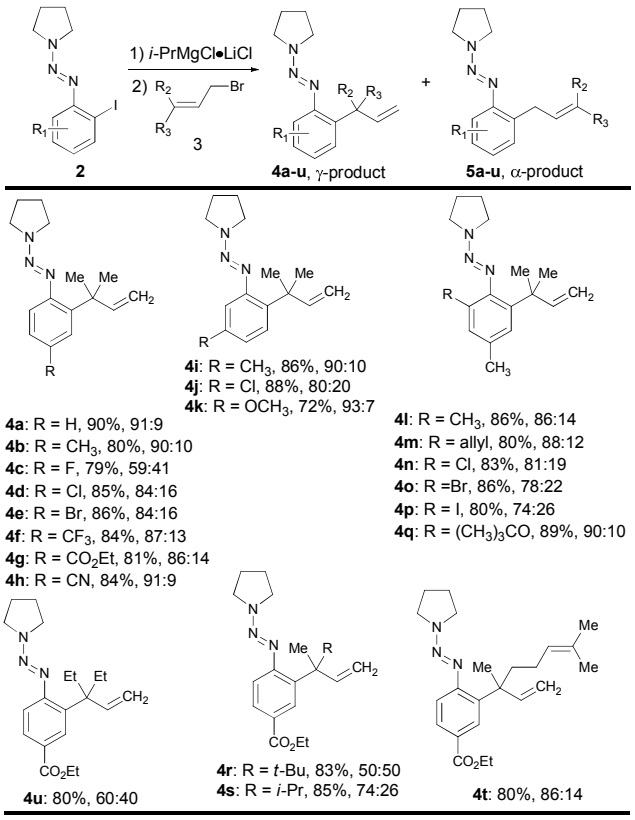
In the pursuit of more environmentally benign reaction, uncatalyzed allylic substitution with aryl Grignard[11] is very important since the method for the preparation of functionalized aromatic Grignard reagents are well established.[12] The controlled reaction of aromatic Grignard reagents with 3,3-disubstituted allylic system will be the most direct and powerful methods for introducing prenyl and prenyl-related side chains into aromatic systems.Normally, the addition reaction of hard nucleophiles such as aryl Grignard reagents with prenyl bromide would provide entirely α-selective products (selective attack at the primary carbon will be much faster than allylic attack at the tertiary carbon atom). It was demonstrated by the reaction of phenyl Grignard reagent or functionalized Grignard reagent of *para*-(ethoxycarbonyl)phenyl magnesium with prenyl bromide to afford α-selective products completely (Figure 1). In order to establish a method for the formation of γ-selective product, we imagined that if we could soften the "hardness" of aryl Grignard reagents, the selectivity might be a dramatic reversal (Scheme 2).




***Scheme 2.*** Regioselectivity of arylation between mask softened aryl Grignard reagents and prenyl bromide. X = Br·LiCl or I·LiCl.

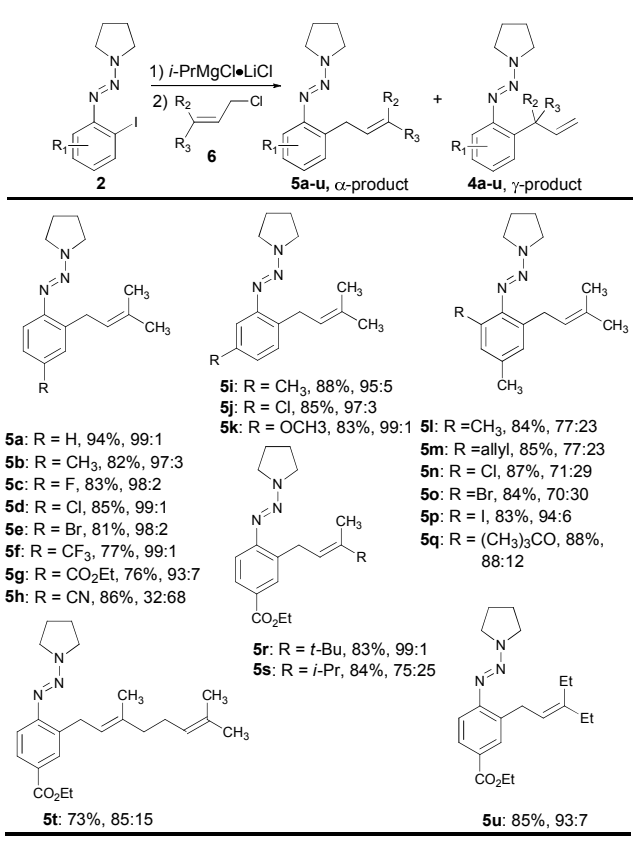
We commenced our study by looking for a "mask" for the magnesium of aryl Grignard reagents which could soften their "hardness". Since the phenyl and *para*-(ethoxycarbonyl)phenyl magnesium reagents are naked, we tried the reaction between *ortho*-substituted phenyl magnesium reagents and prenyl bromide. Unfortunately, both *ortho*-Br and *ortho*-$OCH_3$ substituted phenyl magnesium reagents provided the completely α-selective products. To our delight, when *ortho*-Ph substituted phenyl magnesium reagent was used, the γ-selective product was identified from $^1$HNMR (the ratio of γ:α= 4:96). When *ortho*-Py substituted magnesium reagent was applied, the ratio of γ:α increased to 76:24 (Figure 1). Gratifyingly, the ratio of γ:α increased to 91:9 when *ortho*-triazenyl phenyl magnesium reagent[13] was used. In order to improve the selectivity, the temperature effect was screened and the reaction of *ortho*-triazenyl phenyl magnesium reagent with prenyl bromide performed the best result at -40 °C. The copper catalyst was also tested, but the same results were obtained as without catalyst (see supporting information). Finally, the weaker leaving groups such as OCOPh, OCOBu-*t* were also applied to react with triazenyl aryl Grignard reagent, however, no reaction occurred.

With the optimal conditions in hand, we further explored the reaction between other functionalized triazenyl-aryl Grignard reagents and 3,3-disubstituted allylic bromides to examine the scope and limitation of the current prenylation reaction. A variety of triazenyl-aryl iodides, bearing electron-donating or withdrawing substituents (**4a-q**, Scheme 3), could be efficiently converted to their corresponding branched products (γ-products) with high regioselectivity (the ratio of γ:α up to 91:9). Both the electronic and steric effects are important issues for the regioselectivity. Electron-donating substituents give higher γ selectivity than withdrawing ones (**4i-k**). Steric bulk of the *ortho*-substituents (comparing to triazenyl group) on aryl triazene produce negative effect on the γ selectivity (**4a**, **4l** and **4m**; **4n-p**). The substituents on electrophiles of 3,3-disubstituted allylic bromides also affect the regioselectivity significantly (**4r-u**). The bulkier of 3-substituted group on 3,3-disubstituted allylic bromides, the lower of γ selectivity was observed. For example, when geranyl bromide was used as electrophile, the ratio of γ:α is 86:14 (**4t**). The ratio of γ:α decreased to 74:26 when a slightly bulkier substrate (*E*)-1-chloro-3,4-dimethylpent-2-ene was tested (**4s**). While (*E*)-1-chloro-3,4,4-trimethylpent-2-ene, which bearing the bulkiest *t*-Bu group, give γ product and α product in 50:50 ratio (**4r**).



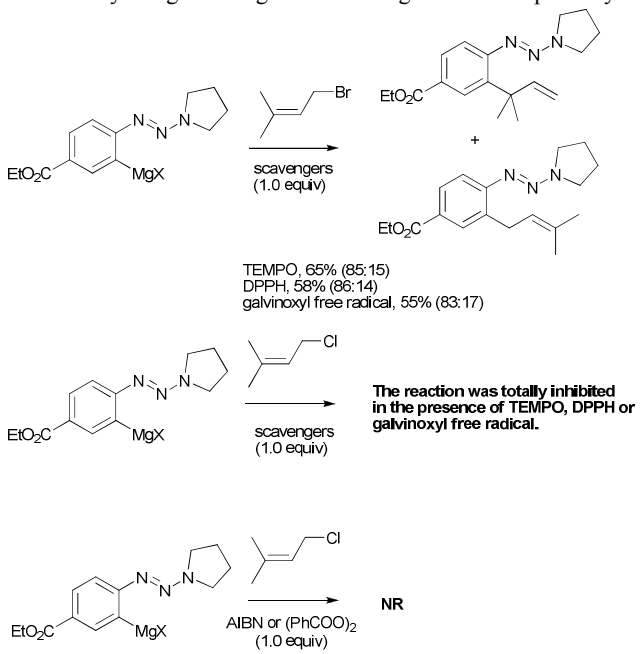

***Scheme 3.*** Substrate scope of triazenyl-aryl Grignards and 3,3-disubstituted allylic bormides. Reaction conditions: triazenyl-aryl iodide (1.0 mmol), *i*PrMgCl·LiCl (1.3 mmol), 3,3-disubstituted allylic bormide (3.0 mmol), -40 °C, 24h. Yields are of isolated products, see Supporting Information for details. The ratio of γ:α was determined by $^1$HNMR spectroscopy of the crude reaction mixture after removing the excess 3,3-disubstituted allylic bormides reagents by short silica column.

Since we have studied the allylic arylation of 3,3-disubstituted allylic bromide with triazene "softened" aryl Grignard reagents and found transition-metal-free procedures lead to well γ selectivity (the ratio of γ:α up to 91:9). Then we turn our attention to the α-selectivity of the allylic arylation of the triazenyl Grignard reagents. The significant issues in the control of regiochemistry are the leaving group and catalyst in the 3,3-disubstituted allylic substrate. Using chloride as a leaving group, Fürstner[8d] and Bäckvall[7a] developed allylic arylation reaction between geranyl chloride and PhMgBr affording great α selectivity catalyzed by iron and Cu(I) independently. Interestingly, when we treated the triazenyl aryl Grignard reagent with geranyl chloride at -30 °C, the product **5t** with high α selectivity (α:γ up to 85:15 ) was obtained. A range of triazenyl aryl Grignard reagents participated in the reaction with 3,3-disubstituted allylic chlorides and produced their corresponding products in high α selectivities (the ratio of α : γ up to 99:1) (**5a-u**, Scheme 4). Functional groups, such as ester (**5g**, **5r-u**), odide (**5p**), ketone (**5q**) and cyanide (**5h**), are tolerated in this reaction.




***Scheme 4.*** Substrate scope of triazenyl-aryl Grignards and 3,3-disubstituted allylic chlorides. Reaction conditions: tyiazenyl-aryl iodide (1.0 mmol), *i*PrMgCl·LiCl (1.3 mmol), 3,3-disubstituted allylic chlorides (3.0 mmol), -30 °C, 24h. Yields are of isolated product, see Supporting Information for details. The ratio of α:γ was determined by $^1$HNMR spectroscopy of the crude reaction mixture after removing the excess 3,3-disubstituted allylic chlorides reagents by short silica column.

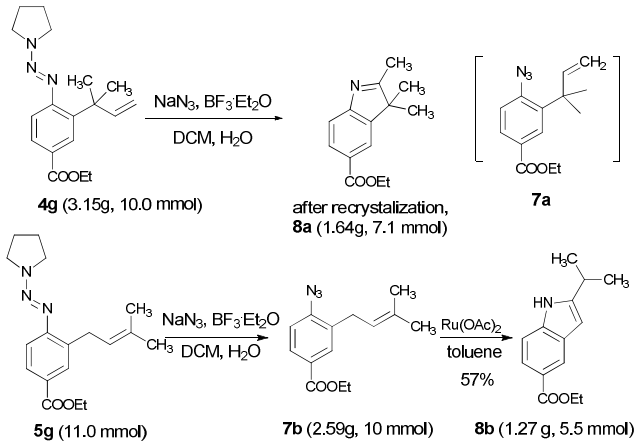
In order to explore the reaction mechanism for the regiospecific preparation of triazene-related prenylated and reverse prenylated arenes, the control experiments were carried out in the presence of different radical scavengers. When classical radical scavengers such as 2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO), di(phenyl)-(2,4,6-trinitrophenyl)iminoazanium (DPPH) and 2,6-di-*tert*-butyl-*α*-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy (galvinoxyl free radical), were added to the reaction system of *ortho*-triazenyl phenyl magnesium reagent and prenyl bromide respectively, the yield of the reaction was lowed to 55-65% but the ratio of γ: α was not affected (Scheme 5). When these radical scavengers were added to the reaction system of *ortho*-triazenyl phenyl magnesium reagent and prenyl chloride, the reaction was totally inhibited and no desired prenylated or reverse prenylated was obtained. When 100% of radical initiators such as AIBN or $(PhCOO)_2$ were used, also no reaction was observed. These results strongly suggests that the copper-free allylic arylation reaction between 3,3-disubstituted allylic chlorides and triazene-softened aryl Grignard reagents probably proceeds *via* a radical pathway. However, the reaction between 3,3-disubstituted allylic bromides and triazene-softened aryl Grignard reagents favors organometallic pathway.




***Scheme 5.*** Control experiments of triazenyl-aryl Grignards and 3,3-disubstituted allylic halides in the presence of different radical scavengers. TEMPO = 2,2,6,6-tetramethyl-piperidin-1-yl) oxyl, DPPH = di(phenyl)-(2,4,6-trinitrophenyl)iminoazanium, galvinoxyl free radical = 2,6-di-*tert*-butyl-*α*-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy.

To explore the possibility by using prenylated and reverse prenylated aryl triazenes as building blocks for the synthesis of heterocyclic compounds, we treated branch prenylated product **4g** with $NaN_3$ in the presence of Lewis acid $BF_3{\cdot}OEt_2$. Instead of the formation of anticipated azide compound **7a**, the unexpected 2,3,3-trimethyl-3*H*-indole **8a**, a useful precursor for the synthesis of cyanine dye, was isolated. The present protocol is exceptionally practical, as shown in Scheme 6, the reaction can be efficiently processed on a multigram scale and the desired product can be obtained in 71% yield after simple recrystallization. Interestingly, when linear prenylated product **5g** was treated with $NaN_3$ in the presence of Lewis acid $BF_3{\cdot}OEt_2$,

the desired azide **7b** was obtained in 91% yield. After heating azide **7b** on a multigram scale under the catalyst of $Rh_2(OAc)_4$ (5 mol %) according to the procedure from Driver, [14] the desired indole derivate **8b** was obtained in 57% yield.




***Scheme 6.*** Multigram scale synthesis of 2,3,3-trimethyl-3*H*-indole **7a** and indole derivate **7b** from their corresponding triazenyl prenylated arenes.

## Conclusions

In summary, we have developed a controllable copper-free allylic arylation reaction of 3,3-disubstituted allylic halides with triazene-softened aryl Grignard reagents to provide an efficient route to prenylated and reverse prenylated arenes with high regioselectivity by just switching the leaving group. This method represents great functional groups tolerance and environmentally benign advantage. Also, the obtained products are of great value for multiple synthetic applications. The branched and linear products can be transformed to the corresponding 3*H*-indole and indole derivatives in multigram scale respectively. Further studies of the mechanism and utility of these processes are in progress in our laboratory.

## Acknowledgements

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