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Synthesis of tertiary 1,3-butadien-2-ylcarbinols from chromium-catalyzed addition of (4-bromobut-2-ynyl)trimethylsilane to ketones

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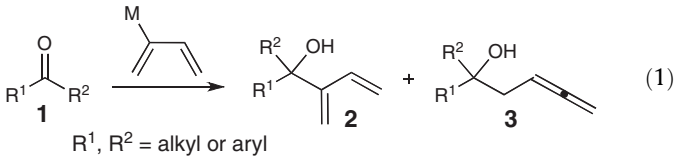
ABSTRACT

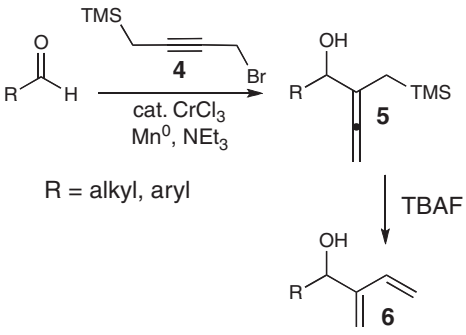
The synthesis of 1,3-butadien-2-ylcarbinols containing a tertiary alcohol is achieved by desilylation of (trimethylsilyl)methylallenic alcohols. The latter are obtained via a chromium-catalyzed addition of (4-bromobut-2-ynyl)trimethylsilane to aliphatic or aromatic ketones. The desired adducts are obtained in yields ranging from 21% to 67% for this two-step, one-pot process.

1,3-Butadien-2-ylcarbinols are valuable moieties that can be used in the synthesis of more complex organic molecules.[1] Several strategies for the synthesis of 1,3-butadien-2-ylcarbinols from additions to aldehydes to afford secondary alcohols have been developed.[2] However, methodologies for the synthesis of tertiary 1,3-butadien-2-ylcarbinols **2** from ketones are scarce, regardless of their significance. Although the addition of a nucleophilic organometallic reagent to a carbonyl group is a common approach for the formation of new carbon–carbon bonds,[3] aldehydes are used for this purpose much more regularly than ketones,[4] presumably due to the lower electrophilicity of ketones toward nucleophilic additions which also increases the possibility of competitive proton transfer. Among the examples of organometallic additions to ketones (**1**), the use of magnesium[5] and lithium[6] reagents derived from organostannanes for the synthesis of **2** can be highlighted (equiv 1). Unfortunately, these early methods present low regioselectivity and afford mixtures of the desired diene and the corresponding homoallenic alcohol **3**.



(1)

Due to this difficulty, alternative strategies have been developed. Tertiary 1,3-butadien-2-ylcarbinols can be obtained by thermal ring opening of cyclobutenyl alcohols.[7] Although this method provides the desired alcohols with good yields, the required starting materials are not readily available and the substrate scope is limited. More recently, Alcaraz et al. reported the homologation of chiral epoxy bromides with dimethylsulfonium methylide for the synthesis of **2**.[8] This method provides alkyl or alkyl/aryl 1,3-butadien-2-ylcarbinols with good yields. Nevertheless, the substrates are not commercially available.



(2)

In an effort to overcome some of the drawbacks presented by the existing procedures, we recently reported the synthesis of 2° 1,3-butadien-2-ylcarbinols by the chromium-catalyzed addition of (4-bromobut-2-ynyl)trimethylsilane (**4**) to aldehydes followed by desilylation of the resulting (silylmethyl)allenic alcohols (**5**) to provide dienes **6** (equiv 2).[9] This reaction proceeds well with a variety of aldehydes including alkyl, aryl, electron-rich, or electron-poor and the corresponding adducts were obtained with good yields. Encouraged by these results with aldehydes, we aimed for the extension of this methodology to ketone electrophiles. Even though chromium-catalyzed additions to ketones are not common,[10] it was envisioned that the allenylation of ketones and the subsequent desilylation of the tertiary allenic alcohol could provide a useful approach for the regioselective synthesis of dienes **2**.

The reactivity of ketones toward the chromium-catalyzed allenylation was explored. 4-Phenylbutan-2-one **1a** was combined with 1.1 equiv of **4** in the presence of a catalytic amount of $CrCl_3$ and 2 equiv each of Mn^0 and TMSCl in THF. After quenching with 1 M HCl, the deprotected 3° allenic alcohol **5a** was obtained in 51% conversion (Table 1, entry 1). No regioisomers, such as the corresponding propargylic alcohol **7**, were observed. This is complementary to

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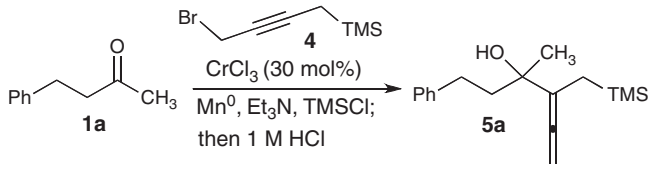
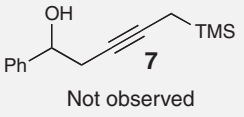
Table 1
Optimization of the allenylation reaction[a]



Entry	**4** (equiv)	Conversion[b] (%)	
1	1.1	51	
2	2.2	61	
3	3.0	80	
4	4.0	50	



Not observed

[a] $CrCl_3$ (30 mol %), Mn^0 (2 equiv), TMSCl (2 equiv), rt, 24 h. Then 1 M HCl, rt, 30 min.
[b] Determined by ^1H NMR.

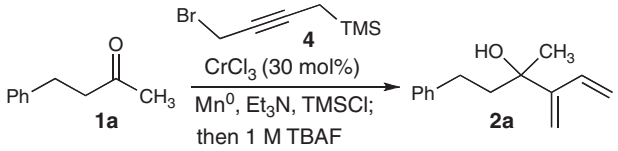
prior methods in which the formation of the propargylic alcohol **7** is favored.[11] Increasing the equivalents of **4** results in an increase in conversion (entries 1–3) until 4 equiv is reached, at which point a notable decrease in conversion is observed (entry 4).

The desired 1,3-butadien-2-ylcarbinol **2a** was prepared in situ from the unpurified allene **5a** by direct treatment with TBAF. Use of 2 equiv of TBAF resulted in only 25% conversion to the desired dienylalcohol (Table 2, entry 1). Use of excess TBAF greatly increased the product yield. The required excess can be explained by the presence of excess (4-bromobut-2-ynyl)trimethylsilane **4** in the reaction mixture, which competitively consumes the fluoride.

After obtaining these optimized reaction conditions for ketone addition followed by diene formation, the substrate scope was evaluated. Aliphatic methyl ketone **1a** is an excellent substrate for this reaction (Table 3, entry 1). Ketone **1b,** which is more sterically hindered due to the presence of a secondary carbon α to the carbonyl group, is somewhat less reactive, but afforded the desired product in 41% yield (entry 2). Cyclohexanone gave the corresponding diene **2c**, albeit in poor yield (entry 3). Aromatic ketones including acetophenone and *p*-methylacetophenone afford the desired diene in 45% and 53% yield, respectively (entries 4 and 5). It was observed that the nature of the substituent in the aromatic group affects the rate of the reaction. Allenylation of ketone **1f** containing a slightly electron-withdrawing group in the *para* position afforded diene **2f** in 67% after the starting material was consumed (48 h). Reactions involving the electron-rich ketone **1g** did not go to completion after 48 h. Although a 50% yield of product **2g** was obtained, 40% of the starting material was also recovered (entry 7).

In an attempt at the asymmetric synthesis of 3° butadienylcarbinols **2**, ketone **1d** was submitted to the reaction conditions that

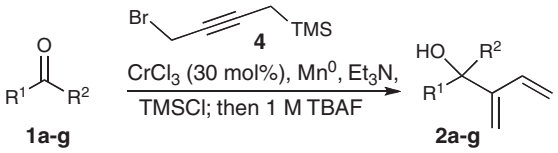
Table 2
Optimization of desilylation conditions[a]

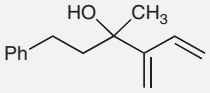
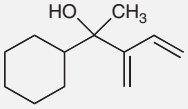
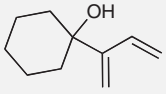
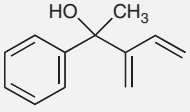
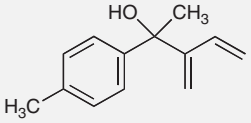
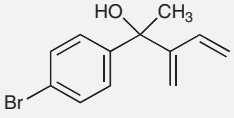
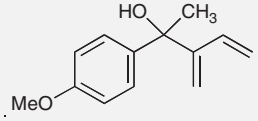


Entry	TBAF (equiv)	Conversion[b] (%)
1	2	25
2	3	45
3	5	68
4	8	88

[a] $CrCl_3$ (30 mol %), **4** (3 equiv), Mn^0 (2 equiv), Et_3N (1 equiv) TMSCl (2 equiv), rt, 24 h, then 1 M TBAF in THF, rt, 16 h.
[b] Determined by ^1H NMR.

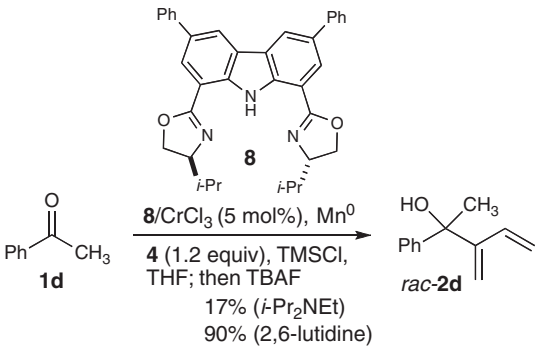
Table 3
Scope of the reaction[a]



Entry	Ketone	Product		Yield[b] (%)
1	**1a**		**2a**	69
2	**1b**		**2b**	41
3[c]	**1c**		**2c**	23
4	**1d**		**2d**	45
5	**1e**		**2e**	53
6[c]	**1f**		**2f**	67
7[c]	**1g**		**2g**	51

[a] $CrCl_3$ (30 mol %), **4** (3 equiv), Mn^0 (2 equiv), Et_3N (1 equiv) TMSCl (2 equiv), rt, 24 h; then 1 M TBAF in THF, rt, 16 h.
[b] Isolated yield.
[c] Reaction time: 48 h.

we had previously developed for the enantioselective synthesis of 2° 1,3-butadien-2-ylcarbinols from aldehydes.[9] As shown in Eq. (3), a racemic mixture of **2d** was obtained with 17% conversion under our standard conditions. Further optimization of the reaction conditions increased the conversion to 90% when 2,6-lutidine was used as the base, when only 1.2 equiv of **4** was utilized. This represents a substantial increase over the yield observed in the absence of ligand (Table 2, entry 4), but no enantioselectivity was observed in the product mixture. Although this is a disappointing result on the surface, it does demonstrate that a bulky ligand does not inhibit this already hindered C–C bond forming reaction.



(3)

In summary, we have developed a method for the synthesis of 3° 1,3-butadien-2-ylcarbinols **2** from the chromium-catalyzed addition of (4-bromobut-2-ynyl)trimethylsilane to ketones. This method overcomes some of the disadvantages of the previous approaches to this class of functionalized molecules. More importantly, this is, to the best of our knowledge, the first chromium-catalyzed nucleophilic addition to ketones to afford 3° allenylalcohol products **5**. These conditions strongly favor the formation of homoallenyl alcohols over their propargylic isomers. Aliphatic as well as aromatic ketones are suitable substrates for this reaction.

Acknowledgments

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Supplementary data

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.104.

References and notes

1. (a) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925–1928; (b) Bertolini, T. M.; Nguyen, Q. H.; Harvey, D. F. *J. Org. Chem.* **2002**, *67*, 8675–8678; (c) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1997**, *38*, 7887–7890; (d) Taylor, R. E.; Hearn, B. R.; Ciavarri, J. P. *Org. Lett.* **2002**, *4*, 2953–2955; (e) Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2451–2458.
2. (a) Luo, M.; Iwabuchi, Y.; Hatakeyama, S. *Chem. Commun.* **1998**, 267–268; (b) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100–104; (c) Lu, W.; Ma, J.; Yang, Y.; Chan, T. H. *Org. Lett.* **2000**, *2*, 3469–3471; (d) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271–2274; (e) Naodovic, M.; Xia, G.; Yamamoto, H. *Org. Lett.* **2008**, *10*, 4053–4055.
3. Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981–998.
4. Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2794.
5. (a) Nunomoto, S.; Yamashita, Y. *J. Org. Chem.* **1979**, *44*, 4788–4791; (b) Pornet, J.; Randrianoelina, B.; Miginiac, L. *J. Organomet. Chem.* **1979**, *174*, 15–26.
6. Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1942–1945.
7. Halazy, S.; Krief, A. *Tetrahedron Lett.* **1980**, *21*, 1997–2000.
8. Alcaraz, L.; Cox, K.; Cridland, A. P.; Kinchin, E.; Morris, J.; Thompson, S. P. *Org. Lett.* **2005**, *7*, 1399–1401.
9. Durán-Galván, M.; Connell, B. T. *Eur. J. Org. Chem.* **2010**, 2445–2448.
10. Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752–2753.
11. (a) Lee, P. H.; Kim, H.; Lee, K. *Adv. Synth. Cat.* **2005**, *347*, 1219–1222; (b) Lee, A. S.-Y.; Chu, S.-F.; Chang, Y.-T.; Wang, S.-H. *Tetrahedron Lett.* **2004**, *45*, 1551–1553; (c) Brown, H. C.; Khire, U. R.; Narla, G.; Racherla, U. S. *J. Org. Chem.* **1995**, *60*, 544–549.