ORGANIC LETTERS

2008
Vol. 10, No. 8
1629−1632

Nickel-Catalyzed Allylation of Allyl Carbonates with Homoallyl Alcohols via Retro-Allylation Providing 1,5-Hexadienes

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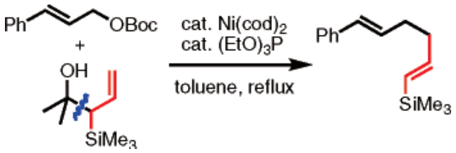
Received February 14, 2008

ABSTRACT



A highly efficient and mild method for the synthesis of 1,5-hexadienes, nickel-catalyzed reactions of Boc-protected allyl alcohols with homoallyl alcohols, has been developed. Nickel-mediated retro-allylation allows for the use of homoallyl alcohols as allylmetal equivalents in the synthesis of 1,5-hexadienes.

Palladium-catalyzed cross-coupling reactions of allyl electrophiles with allylmetals are potentially useful for the synthesis of 1,5-hexadienes.[1−5] Despite its seeming simplicity, the reactions usually suffer from low yields because of β-hydride elimination from (substituted-allyl)palladium intermediates such as crotylpalladium[6] and concomitant formation of undesired homocoupling products.[7] In most cases, allylstannanes were used as the allylmetal, which required a troublesome purification procedure.[3] Thus, efficient methods for the synthesis of 1,5-hexadienes from allylmetals and allyl electrophiles are rare and should be developed.

We have recently developed palladium-catalyzed allylation reactions of aryl halides with homoallyl alcohols as allylmetal equivalents by taking advantage of palladium-mediated retro-allylation.[8,9] Pursuing a new efficient method for the synthesis of 1,5-hexadienes, we attempted to apply the retro-allylation-based methodology to the palladium-catalyzed reaction of

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[1] Reviews: Negishi, E.; Liao, B. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 1, Chapter III.2.10.

[2] Pioneering work: (a) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595−2598. (b) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599−2602.

[3] With allylstannanes: (a) Yoshida, J.; Funahashi, H.; Iwasaki, H.; Kawabata, N. *Tetrahedron Lett.* **1986**, *27*, 4469−4472. (b) Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 5739−5742. (c) Yamamoto, Y.; Hatsuya, S.; Yamada, J. *J. Org. Chem.* **1990**, *55*, 3118−3128. Intramolecular versions: (d) Cuerva, J. M.; Gómez-Bengoa, E.; Méndez, M.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 7540−7541. (e) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620−3628.

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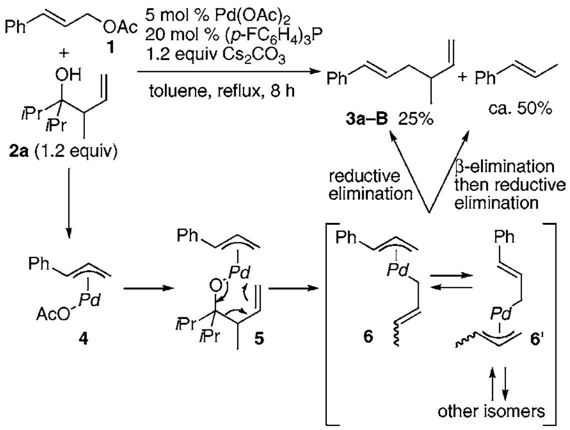
[8] (a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210−2211. (b) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463−4469. (c) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2007**, *63*, 5200−5203. (d) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 12650−12651. (e) Ohmura, T.; Awano, T.; Suginome, M.; Yorimitsu, H.; Oshima, K. *Synlett* **2008**, 423−427.

[9] Reviews for carbon−carbon bond cleavage of tertiary alcohols: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 9423−9463. (b) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201−216. (c) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462−1467. (d) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315−1321. (e) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2005**, *14*, 1−20.

10.1021/ol800335v CCC: $40.75

cinnamyl acetate (**1**) with homoallyl alcohol (**2a**) (Scheme 1). However, the reaction was unsatisfactory, highlighting the difficulty in achieving efficient synthesis of 1,5-hexadienes: branched-coupling product **3a−B** was obtained in only 25% yield, and β-methylstyrene was mainly formed. The formation of β-methylstyrene would result from predominant β-hydride elimination from intermediate **6′** or other isomers[6] over productive reductive elimination from **6**. Many attempts to find suitable reaction conditions for the palladium-catalyzed allylation reaction of **1** with **2a** failed.

Scheme 1. Palladium-Catalyzed Allylation of Cinnamyl Acetate (**1**) with Homoallyl Alcohol **2a**[a]

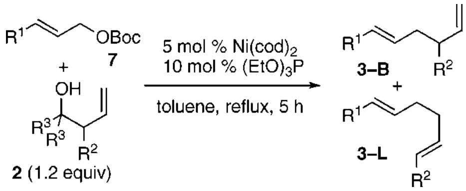


[a] The italicized Pd means that the palladium has either no, one, or two phosphine ligands.

We then turned our attention to nickel catalysis, although little is known about the nickel-catalyzed cross-coupling reaction of allylmetals with allyl electrophiles[10] and no information about nickel-mediated retro-allylation was reported. After screening reaction conditions, we found that a combination of 5 mol % of Ni(cod)$_2$ (cod = 1,5-cyclooctadiene) and 10 mol % of triethyl phosphite catalyzed the allylation reaction of Boc-protected cinnamyl alcohol **7a** (Boc = *t*-butoxycarbonyl) with **2a** in the absence of base in refluxing toluene (Table 1, entry 1).[11] The reaction afforded the corresponding coupling products **3a−B** and **3a−L** in high yield in a ratio of **3a−B**/**3a−L** = 37:63. Unfortunately, the ligand effect on the isomer ratio was almost negligible as far as we examined.

Electronic as well as steric factors of the aryl groups of **7** had little influence on this allylation reaction (Table 1, entries 2−4). Replacement of the methyl group in **2a** (R^2 = Me) with a heptyl group (R^2 = nC$_7$H$_{15}$) slightly improved the regioselectivity (entry 5). Cyclohexyl-substituted homoallyl alcohol **2c** reacted with **7a** to yield the corresponding 1,5-hexadiene in a higher branched/linear ratio of 9:91 (entry 6). The highest branched/linear ratio was observed in the reaction of **7a** with *t*-butyl-substituted homoallyl alcohol **2d** (3:97, entry 7).

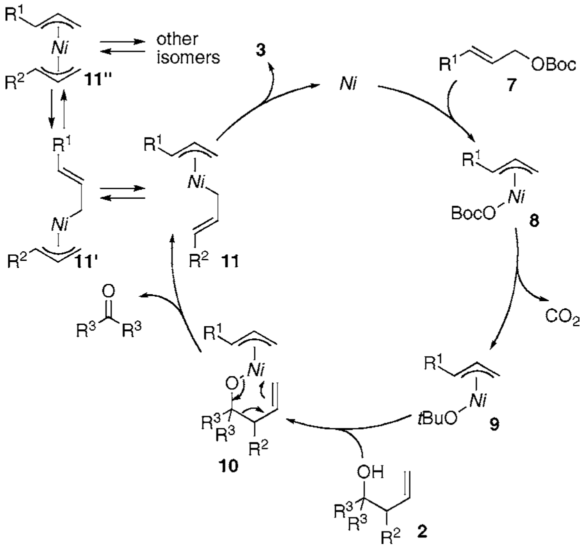
Table 1. Nickel-Catalyzed Allylation of Boc-Protected Cinnamyl Alcohols **7** with Branched Homoallyl Alcohols **2**



entry	R¹	7	R²	R³	2	3	yield %	B/L
1	Ph	**7a**	Me	*i*Pr	**2a**	**3a**	91	37:63
2	4-MeOC$_6$H$_4$	**7b**	Me	*i*Pr	**2a**	**3b**	70	40:60
3	4-CF$_3$C$_6$H$_4$	**7c**	Me	*i*Pr	**2a**	**3c**	78	33:67
4	2-MeC$_6$H$_4$	**7d**	Me	*i*Pr	**2a**	**3d**	86	37:63
5	Ph	**7a**	nC$_7$H$_{15}$	Me	**2b**	**3e**	60	26:74
6	Ph	**7a**	cC$_6$H$_{11}$	Me	**2c**	**3f**	77	9:91
7	Ph	**7a**	*t*Bu	Me	**2d**	**3g**	79	3:97

It is worth noting that the reaction of Boc-protected crotyl alcohol **7e** with phenyl-substituted alcohol **2e** (eq 1) yielded **3a** in the same branched/linear ratio as is shown in entry 1 of Table 1. The same branched/linear ratio strongly suggests that the reactions proceed via the same diallylnickel intermediate. Based on this fact, a plausible mechanism is proposed in Scheme 2. Oxidative addition of **7** to a nickel catalyst followed by decarboxylation would afford alkoxy-

Scheme 2. Plausible Reaction Mechanism[a]



[a] The italicized Ni means that the nickel has either no, one, or two phosphite ligands.

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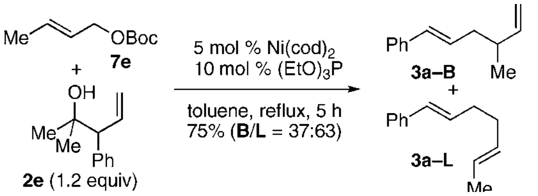
(10) Stoichiometric reactions of π-allylnickels with electrophiles including allylic ones were well documented: (a) Billington, D. C. *Chem. Soc. Rev.* **1985**, *14*, 93−120. (b) Billington, D. C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.1.

(11) **Typical Procedure:** Ni(cod)$_2$ (3.4 mg, 0.0125 mmol) was placed in a 20 mL reaction flask. Toluene (1.0 mL) and P(OEt)$_3$ (4 mL, 0.025 mmol) were added, and the resulting suspension was stirred for 10 min at room temperature. Carbonate **7a** (59 mg, 0.25 mmol) and homoallyl alcohol **2a** (51 mg, 0.30 mmol) were then added, and the mixture was heated at reflux for 5 h. The reaction was then quenched with water (2 mL). Extraction followed by purification on silica gel provided a mixture of (*E*)-1-phenyl-1,5-heptadiene (**3a−L**) and 4-methyl-1-phenyl-1,5-hexadiene (**3a−B**) in 91% combined yield (39 mg, 0.23 mmol, **B**/**L** = 37:63).

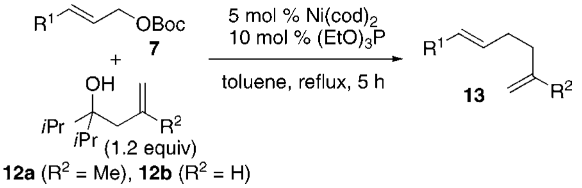
(π-allyl)nickel intermediate **9**. Ligand exchange with **2** would yield **10**. Retro-allylation[12] would then take place to afford **11** with concomitant formation of ketone R$^3{}_2$C═O. Here the configurations and modes of coordination of the allyl ligands R^{1}CHCHCH$_2$ and R^{2}CHCHCH$_2$ would be completely scrambled to yield a mixture of several diallylnickel intermediates such as **11**, **11′**, and **11″**. Reductive elimination prior to β-hydride elimination would afford product **3** and regenerate the initial zerovalent nickel catalyst.



(1)

Methallylation of various Boc-protected allyl alcohols **7** proceeded smoothly by using **12a** (Table 2, entries 1−8).

Table 2. Nickel-Catalyzed Allylation of Boc-Protected Cinnamyl Alcohols **7** with Homoallyl Alcohols **12a** and **12b**



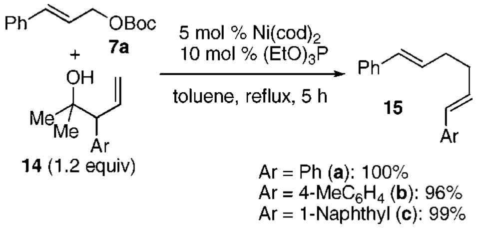
entry	R^1	7	12	13	yield %
1	Ph	**7a**	**12a**	**13a**	99
2	4-MeOC$_6$H$_4$	**7b**	**12a**	**13b**	71
3	4-CF$_3$C$_6$H$_4$	**7c**	**12a**	**13c**	94
4	2-MeC$_6$H$_4$	**7d**	**12a**	**13d**	84
5	4-MeC$_6$H$_4$	**7f**	**12a**	**13e**	100
6	2-furyl	**7g**	**12a**	**13f**	76
7	2-thienyl	**7h**	**12a**	**13g**	76
8	MePh$_2$Si	**7i**	**12a**	**13h**	82
9	Ph	**7a**	**12b**	**13i**	96
10	4-MeOC$_6$H$_4$	**7b**	**12b**	**13j**	81[a]
11	4-CF$_3$C$_6$H$_4$	**7c**	**12b**	**13k**	80[a]
12	2-MeC$_6$H$_4$	**7d**	**12b**	**13l**	84
13	4-MeC$_6$H$_4$	**7f**	**12b**	**13m**	88
14	2-thienyl	**7h**	**12b**	**13n**	62
15	MePh$_2$Si	**7i**	**12b**	**13o**	89[a]

[a] Xylene was used instead of toluene.

Furyl- and thienyl-substituted **7g** and **7h** also participated in the reaction. Interestingly, the reaction of **7i** having a methyldiphenylsilyl group with **12a** afforded 5-methyl-1,5-hexadienylsilane **13h** as the sole product in high yield. Allylation with **12b** also proceeded smoothly (entries 9−15), although a higher temperature was necessary to attain high yields in some cases (entries 10, 11, and 15).

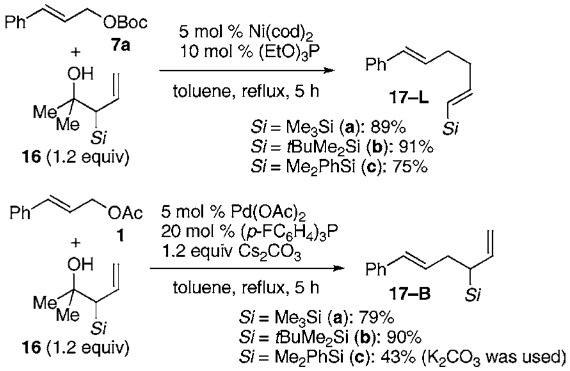
The reactions of **7a** with aryl-substituted homoallyl alcohols **14** afforded the corresponding cross-coupling products 1,6-diaryl-1,5-hexadienes **15** exclusively in excellent yields (Scheme 3). None of the homocoupling products were observed in the reactions that yielded **15b** and **15c**.

Scheme 3. Synthesis of 1,6-Diaryl-1,5-hexadienes (**14a** = **2e**)



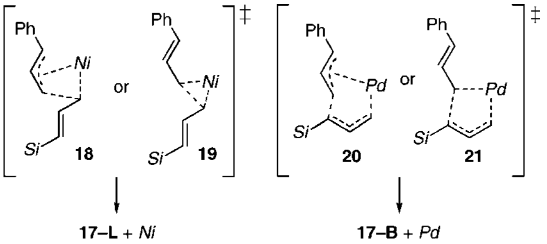
The nickel-catalyzed reactions of **7a** with silyl-substituted homoallyl alcohols **16** yielded the corresponding linear cross-coupling products **17−L** in high yields (Scheme 4). Interestingly, the sense of the regioselectivity was opposite when a palladium catalyst was used. The palladium-catalyzed reactions of **1** with **16** afforded branched allylsilanes **17−B** exclusively.

Scheme 4. Selective Preparation of Vinylsilanes and Allylsilanes under Nickel and Palladium Catalysis



The reason for the different regiochemical outcomes is not clear at this stage. The mode of reductive elimination

Scheme 5. Plausible Transition States for Reductive Elimination



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(12) Another plausible path yielding **11** or other isomers is β-carbon elimination from **10**. However, ab initio calculations revealed that retro-allylation is a far more favorable process than β-carbon elimination in the case of ruthenium: Sakaki, S.; Ohki, T.; Takayama, T.; Sugimoto, M.; Kondo, T.; Mitsudo, T. *Organometallics* **2001**, *20*, 3145−3158.

from diallylnickel species would be different from that of diallylpalladium (Scheme 5). In the case of nickel, the carbon−carbon formation would take place between the less substituted carbons of the allyl moieties on the nickel via a transition state **18** or **19**. In contrast, the carbon−carbon formation from diallylpalladium would take place with allylic rearrangement via a transition state **20** or **21**.[3e]

In summary, we have developed an efficient method for the synthesis of 1,5-hexadienes, nickel-catalyzed reactions of Boc-protected allyl alcohols with homoallyl alcohols. Nickel-mediated retro-allylation allows for the use of homoallyl alcohols as allylmetal equivalents in the synthesis of 1,5-hexadienes.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research from MEXT and JSPS. S.H. and K.H. acknowledge JSPS for financial support.

Supporting Information Available: Characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800335V