ORGANIC LETTERS

2005
Vol. 7, No. 20
4395−4398

Phosphine-Triggered Complete Chemo-Switch: From Efficient Aldehyde–Alkyne–Amine Coupling to Efficient Aldehyde–Alkyne Coupling in Water

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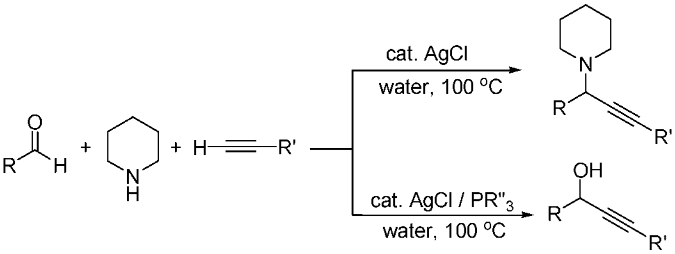
Received July 5, 2005

ABSTRACT



A phosphine ligand served as a remarkable chemo-switch for the silver-catalyzed reaction of alkynes with aldehydes in the presence of amines in water. Exclusive aldehyde–alkyne–amine coupling product was observed in the absence of phosphine, whereas in the presence of a phosphine ligand, exclusive aldehyde–alkyne coupling product was obtained.

There has been increasing interest in the development of efficient, economical, and environmentally friendly fundamental reactions for chemical synthesis.[1] Toward such a goal, we have focused on two themes: (1) the development of C−C bond-forming reactions in aqueous media that can proceed without the deployment of protecting group strategies and (2) the direct utilization of C−H bonds for C−C bond formation. One such subject is the development of Grignard-type reactions in water.[2] Catalytic addition of C−H bonds to carbonyls and imines would provide an atom-economical and greener approach to classic Grignard-type reactions which require stoichiometric amounts of metal and organic halides.[3] The addition of terminal alkynes to aldehydes is of great interest as a Grignard-type reaction because of the versatility of the corresponding propargylic alcohols.[4] Compared with the classical methods that use metal acetylides,[4,5] an alternative and more atom-economical approach involves the catalytic addition of terminal alkynes to aldehydes.[6] Recently, Carreira and co-workers developed a $Zn(OTf)_2$-catalyzed addition of alkynes to aliphatic aldehydes.[7] Shibasaki et al. reported a catalytic alkynylation of aldehydes and ketones with $InBr_3$ or $In(OTf)_3$ as catalyst.[8]

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(3) For a recent review, see: Dyker, G. *Angew. Chem.* **1999**, *38*, 1698.

(4) For a review, see: Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095.

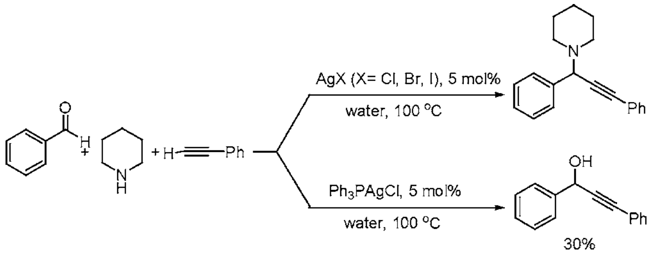
(5) For a recent example, see: (a) Kang, Y.-F.; Wang, R.; Liu, L.; Da, C.-S.; Yan, W.-J.; Xu, Z.-Q. *Tetrahedron Lett.* **2005**, *46*, 863. (b) Fang, T.; Du, D.-M.; Lu, S.-F.; Xu, J.-X. *Org. Lett.* **2005**, *7*, 2081.

10.1021/ol051575+ CCC: $30.25

Previously, we reported a $RuCl_3/InCl_3$-catalyzed alkynylation of aldehydes in water. However, the reaction gave the corresponding propargyl alcohols in only moderate yields.[9] Herein, we report a highly efficient addition of alkynes to aldehydes catalyzed by silver salts in water as solvent, which resulted from a remarkable ligand effect.[10]

While developing A^3-coupling (three-component coupling of aldehydes, alkynes, and amines) and AA^3-coupling reactions (asymmetric three-component coupling of aldehydes, alkynes, and amines),[11] we found that silver salts, such as AgCl, AgBr, and AgI, efficiently mediated A^3-coupling reactions in water and ionic liquids.[11e,f] To explore the scope of this reaction we examined various silver complexes. When triphenylphosphinesilver chloride was used as a catalyst in water, the only detected product was from the alkynylation of aldehyde instead of the imine-addition product (Scheme 1).

Scheme 1. Ligand-Controlled Alkynylation of Imine and Carbonyl



We postulated that a silver acetylide complexed with a phosphine ligand was involved as a key intermediate. We reasoned that the phosphine ligand might be weakening and activating the silver−carbon bond in the silver acetylide. Simple alkynylsilver reagents are usually too stable to participate in nucleophilic additions to carbonyls. Coordination of the electron-donating P-ligand increases the electron density on silver, resulting in a weakening of the silver−carbon bond.[12] In light of this, we examined various reaction conditions to optimize this new catalytic reaction (Table 1).

Table 1. Effect of Anion, Base, and Ligand on the Alkynylation of PhCHO[a]

entry	cat.	base (equiv)	yield[b] (%)
1[c]	AgF/PPh_3	piperidine (1)	31
2	*$AgPPh_3Cl$*	piperidine (1)	30
3	$AgPPh_3Br$	piperidine (1)	23
4	$AgPPh_3I$	piperidine (1)	6
5[c]	$PPh_3/AgOTf$	piperidine (1)	11
6	$AgPPh_3Cl$	Et_3N (1)	30
7	$AgPPh_3Cl$	DABCO (1)	6
8	$AgPPh_3Cl$	K_2CO_3 (1)	16
9	*$AgPPh_3Cl$*	i-Pr_2NEt (1)	42
10	−	*i*-Pr_2NEt (1)	−
11	$AgPPh_3Cl$	−	trace
12[c]	AgCl/BINAP	*i*-Pr_2NEt (1)	10
13[c]	AgCl/(*p*-CF_3-$C_6H_4)_3P$	*i*-Pr_2NEt (1)	trace
14[c]	AgCl/n-Bu_3P	*i*-Pr_2NEt (1)	48
15[c]	AgCl/(*p*-MeO-$C_6H_4)_3P$	*i*-Pr_2NEt (1)	46
16[c]	AgCl/Bn_3P	*i*-Pr_2NEt (1)	44
17[c]	AgCl/(*o*-Tol)$_3$P	*i*-Pr_2NEt (1)	trace
18[c]	AgCl/Cy_3P	*i*-Pr_2NEt (1)	50
19[c]	AgCl/Cy_3P	*i*-Pr_2NEt (0.2)	52
20	*Cy_3PAgCl*	*i*-Pr_2NEt (0.2)	52

[a] Conditions: a mixture of the catalyst (5 mol %), PhCHO (0.5 mmol), phenylacetylene (1 mmol), and base (0.5 mmol) in 2 mL of water was heated at 100 °C overnight. [b] NMR yield with $MeNO_2$ as internal standard. [c] Ratio of P/AgCl = 1.5:1.

The following conclusions were drawn: (1) changing the silver counterion from chloride or fluoride lowered the yield (entries 1−5) and a noncoordinating anion ($^-$OTf) disfavored the reaction (entry 5); (2) a noncoordinating amine such as *i*-Pr_2NEt was generally the base (entries 6−9); (3) electron-donating P-ligands favored the reaction, and the combination of Cy_3PAgCl with 0.2 equiv of *i*-Pr_2NEt gave the best results (entries 12−20). It is also worth mentioning that the reaction is not sensitive to air. It should be noted that both the catalyst and the substrates are not soluble in the water and that the reaction takes place “on water”.[13] Other solvents and cosolvents were also tested; the best result was observed when water alone was used as solvent. In toluene or under neat conditions, no reaction was observed at all. The introduction of an organic solvent generally resulted in a decrease in yield.

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(6) This reaction can also be carried out under strongly basic conditions; see: (a) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463. (b) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702. (c) Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416. (d) Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 185. (e) Imahori, T.; Hori, C.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090.

(7) For a review on the zinc acetylide system: (a) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. For a catalytic system: (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Fässler, R.; Tomooka, C. S.; Frantz, D. E.; Carreira, E. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5843. Also see: (d) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. For stoichiometric addition to aldehyde, see: (f) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (g) Boyall, D.; Frantz, D. Z.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.

(8) Takita, R.; Fukuta, Y.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 1363.

(9) Wei, C.; Li, C.-J. *Green Chem.* **2002**, *4*, 39.

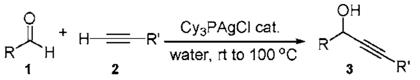
(10) It is widely accepted that metal acetylides from Group IB fail to participate in the nucleophilic C═O addition and in most cases, silver acetylide was utilized as a stoichiometric reagent only: (a) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661. (c) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 2525. (d) Pouwer, R. H.; Williams, C. M.; Raine, A. L.; Harper, J. B. *Org. Lett.* **2005**, *7*, 1323.

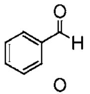
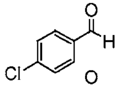
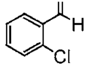
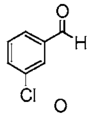
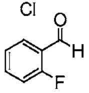
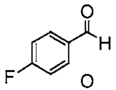
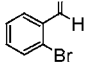
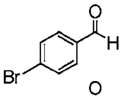
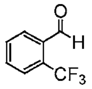
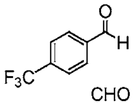
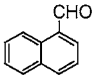
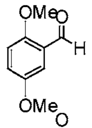
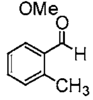
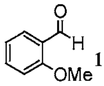
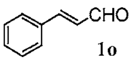
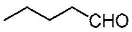
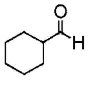
(11) For a review: (a) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. Also see: (b) Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5683. (d) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (e) Wei, C.; Li, Z.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473. (f) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2443.

(12) A similar activation was proposed in Py-box-Cu(I)-catalyzed AA^3 Coupling; see ref 11b.

(13) Quite recently, a series of reactions “on water” were reported; see: Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 2.

Table 2. Alkynylation of Aldehydes Catalyzed by Silver in Water[a]



entry	aldehyde	alkyne	condition	yield (%)[b]
1	 **1a**	Ph—≡—H **2a**	70°C, 1 d	69
2	 **1b**	**2a**	80°C, 12 h	85
3	 **1c**	**2a**	60°C, 12 h	98
4	 **1d**	**2a**	60 °C, 12 h	86
5	 **1e**	**2a**	100 °C, 12 h	87
6	 **1f**	**2a**	100 °C, 6 h	79
7	 **1g**	**2a**	60 °C, 12 h	90
8	 **1h**	**2a**	90 °C, 12 h	82
9	 **1i**	**2a**	80 °C, 6 h	93
10	**1i**	≡—Hex-n **2b**	90 °C, 1.5 d	77
11[c]	 **1j**	**2a**	rt, 2 d	64
12	 **1k**	**2a**	90 °C, 1 d	89
13	 **1l**	**2a**	90 °C, 12 h	82
14	 **1m**	**2a**	90 °C, 1 d	80
15[c]	 **1n**	**2a**	90 °C, 1 d	87
16	 **1o**	**2a**	70 °C, 1 d	35 (43%conv.)
17	 **1p**	**2a**	100 °C, 12 h	63
18	 **1q**	**2a**	70 °C, 2 d	81
19	$(CH_2O)_n$ **1r**	**2a**	60 °C, 12 h	74[d]

[a] Cy_3PAgC1 (5 mol %), *i*-Pr_2NEt (20 mol %), aldehyde (0.5 mmol), alkyne (1.5−2 equiv) in 2 mL of water. [b] Isolated yield. [c] 10 mol % of catalyst was used. [d] **1r**/**2a** = 4/1, $PhC{\equiv}CCH_2OCH_2OH$ was isolated as a byproduct in 21% of yield.

We later found that a variety of aldehydes could be effectively reacted with phenylacetylene and other terminal alkynes under the present reaction conditions (Table 2). Note that the alkynylation of paraformaldehyde was also highly effective. The presence of an electron-withdrawing group increased the reactivities of the aldehydes whereas a CF_3 group on the 4-position decreased the yield due to the ready isomerization of the product to the corresponding chalcone.[14] It should be noted that an aldehyde with a free hydroxyl group (**1s**) also reacted to give the expected addition product in 73% yield (Figure 1).

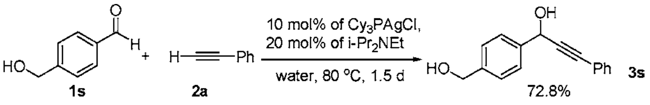
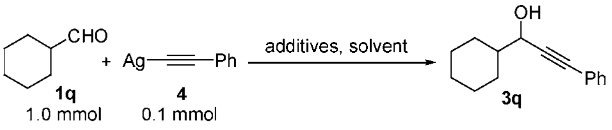


Figure 1. Alkynylation of **1s** catalyzed by silver in water.

To more fully understand the precise effect of the P-ligand in these reactions, several stoichiometric experiments were performed using silver acetylide **4** as a reagent. The results are summarized in Scheme 2. The data in entries 3 and 4 suggested that silver acetylide was dually activated by both the phosphine ligand and water.

Scheme 2. Effect of Phosphine Ligand



entry	conditions	result[a]
1	water, 95 °C, overnight	no reaction
2	toluene, 95 °C, overnight	no reaction
3	+ 0.11 mmol PCy_3 water, 35 °C, overnight	68% of **3q**
4	+ 0.11 mmol PCy_3 toluene, 35 °C, 10 h 80 °C, overnight	no reaction trace
5	+ 0.11 mmol PCy_3, 1.5 mmol phenylacetylene, 2 mL H_2O, 95 °C, overnight	86% of **3q**
6	+ 0.11 mmol PCy_3, 1.5 mmol phenylacetylene, 0.2 mmol i-Pr_2NEt, 2 mL H_2O, 95 °C, overnight	432% of **3q**

[a] The yield was calculated on the basis of **4**.

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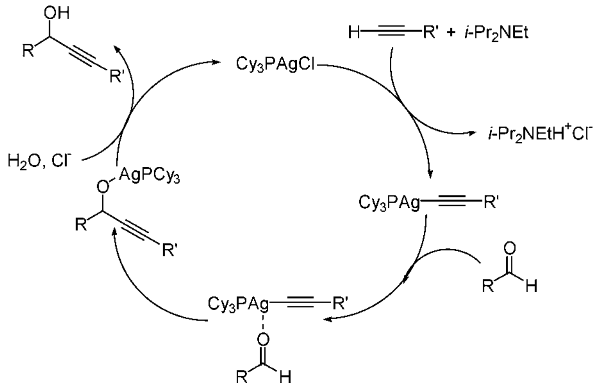
(14) The side reaction is the isomerization of the product to chalcone, which can be inhibited by decreasing either the temperature or reaction time.

Thus, a tentative mechanism for the silver-catalyzed aldehyde–alkynylation in water is described in Scheme 3.[15]

In conclusion, a highly efficient alkynylation of aldehydes was developed by using silver-phosphine complexes as catalysts in water. The reaction is dually promoted by the electron-donating phosphine ligand and water. The scope, mechanism, and the enantioselective version of this reaction are currently under investigation.

Scheme 3. Mechanism of the Alkynylation Catalyzed by Silver in Water



Acknowledgment. We are grateful to the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, Merck Frosst, and McGill University for support of this research.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Reacting **4** with 1 equiv of PCy_3 in CH_2Cl_2 gave $[Ag_4(C{\equiv}CPh)_4(PCy_3)_2]$ as a stable crystal. On the other hand, $[Ag_4(C{\equiv}CPh)_4(PPh_3)_4]$ can be obtained as stable crystal by mixing **4** with PPh_3 in CH_2Cl_2. See: (a) Lin, Y.-Y.; Lai, S.-W.; Che, C.-M.; Cheung, K.-K.; Zhou, Z.-Y. *Organometallics* **2002**, *21*, 2275. (b) Teo, B. K.; Xu, Y. H.; Zhong, B. Y.; He, Y. K.; Chen, H. Y.; Qian, W.; Deng, Y. J.; Zou, Y. H. *Inorg. Chem.* **2001**, *40*, 6794.