Silver-Catalyzed Direct Addition of Terminal Alkynes to Simple Cyclic Ketones in Water

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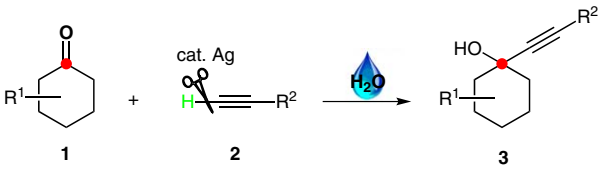
Abstract: The first catalytic addition of terminal alkynes to simple cyclic ketones in water catalyzed by silver was developed. Cyclic ketones were reacted with terminal alkynes efficiently in water to give the corresponding propargyl alcohols.

Key words: Grignard-type reactions in water, silver catalysis, ketone–alkyne addition, propargyl alcohol

The classical Grignard-type nucleophilic addition of organometallic reagents to carbonyl compounds provided an important milestone in the history of organic chemistry. However, such fundamental reactions have two broadly defined essential requirements: (1) the necessity of an aprotic environment (i.e., anhydrous conditions and protection of protic functional groups) and, (2) the pregeneration of highly reactive stoichiometric organometallic reagents.[1] As an effort to overcome the aprotic requirement, we and others have carried out extensive research on Grignard-type reactions in aqueous media.[2] On the other hand, recent efforts have been directed at catalytic direct nucleophilic addition of C–H bonds to various electrophiles, which provides atom-economical alternatives to the classical stoichiometric reactions.[3] One of the most successful achievements of such reactions is the catalytic direct addition of terminal alkynes to aldehydes.[4] However, such reactions generally still require anhydrous conditions and the absence of protic functional groups.

On the other hand, our own laboratory has pioneered a wide range of direct catalytic additions of terminal alkynes to various electrophiles in water.[5] For example, terminal alkynes were efficiently added directly to aldehydes,[6] imines,[7] iminiums,[8] acyliminiums,[9] acid halides,[10] as well as unsaturated carbonyl compounds in water.[11] To react with the much more challenging ketones, we found that the use of a silver catalyst[12] together with an electron-rich phosphine[13] or an N-heterocyclic carbene ligand[14] allows the direct addition of terminal alkynes to highly electron-deficient ketones. However, the catalytic direct addition of terminal alkynes to simple ketones in water has never been successful. We reasoned that such a challenge can potentially be met via further increasing the activity of the alkynyl–silver intermediate by using an even more electron-donating ligand or by destabilizing the intermediate through increased steric bulkiness of the ligand. Herein, we wish to report that terminal alkynes were added to simple ketones efficiently via the activation of alkyne C–H bonds catalyzed by silver to afford Grignard-type nucleophilic addition products in water (Scheme 1).



Scheme 1 Silver-catalyzed alkynylation of cyclic ketones

To begin our study, we examined the reaction between cyclohexanone (**1a**) and phenylacetylene (**2a**) by using our earlier AgCl–PCy_3 (tricyclohexylphosphine), AuCl–PMe_3 (trimethylphosphine)[15] and $Pd(OAc)_2$–PMe_3 catalytic systems. However, using AgCl–PCy_3 (tricyclohexylphosphine) as the catalyst, we could obtain only trace amounts of the desired product (Table 1, entries 1–3). Then, we reasoned that the use of a sterically bulky ligand might provide additional assistance in transferring the alkynyl moiety to the less reactive ketone by destabilizing the alkynyl–silver bond and thus lowering the activation energy of the overall reaction. Dialkylbiaryl phosphines like the Buchwald's ligands RuPhos (**4**; Figure 1) and XPhos (**5**; Figure 1) have been shown to generate highly active catalysts for a range of cross-coupling reactions.[16] We were pleased to see that the desired product was obtained in 22% yield by using AgCl–RuPhos (5%) as the catalyst and DIPEA (diisopropylethylamine) as the base after 24 hours at 100 °C in water (Table 1, entry 4); whereas XPhos was not an effective ligand (Table 1, entry 5). When we increased the catalyst loading to 10% and used an excess amount of ketone, we could obtain the target product in 62% yield (or 54% yield using a syringe pump to add excess alkyne; Table 1, entry 6). Encouraged by these preliminary results, we then tested dif-

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ferent silver salts under the same reaction conditions. AgF, AgBr and AgI also gave similar promising results (Table 1, entries 7–9). It is noteworthy that the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base gave the product in 80% yield (or 77% yield using a syringe pump to add excess alkyne; Table 1, entry 10). We also investigated the reaction temperature and the reaction time; however, either increasing or decreasing the temperature and either shortening or prolonging the reaction time were not helpful to increase the yield of the desired product (Table 1, entries 11–14).

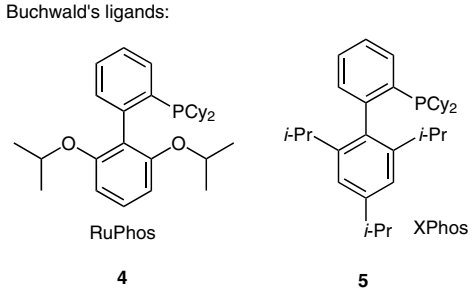


Figure 1

Subsequently, with the optimized reaction conditions in hand, various substituted cyclohexanones, were similarly coupled with phenylacetylene in water to afford the corresponding propargyl alcohol products in good to excellent yields. Selected examples are summarized in Table 2. The substituents on the cyclohexanone did not affect the reaction yield significantly. It is surprising that when cycloheptanone was used as the ketone, the product was obtained in 67% yield, but no desired product was obtained for cyclopentanone (Table 2, compare entries 2 and 3). We also tested alkynylation of cyclohexanone with different alkynes under the same conditions; to our delight, alkynes bearing hydroxyl groups can also be used directly without any protection to get the target product in good yields (Table 2, entries 14, 15).

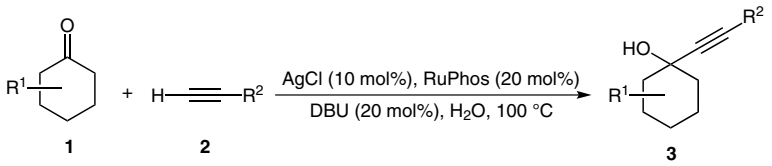
In conclusion, we have succeeded in performing the first catalytic addition of terminal alkynes to simple cyclic ketones in water catalyzed by silver.[17] Various cyclohexanones and cycloheptanone were reacted with terminal alkynes efficiently in water to give the corresponding propargylic alcohols. Further improvement in the reactivity of the catalyst and applications of this reaction in syntheses are currently ongoing in our laboratory.

Table 1 Optimization of Reaction Conditions

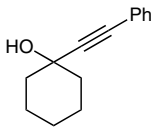
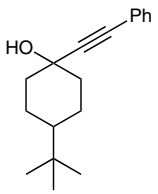
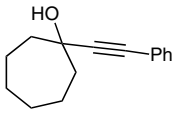
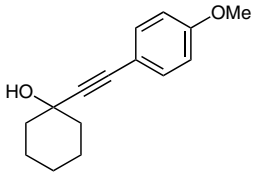
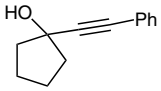
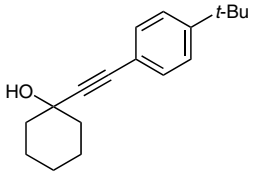
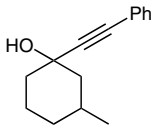
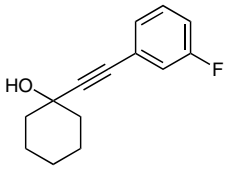
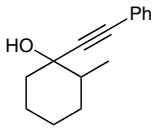
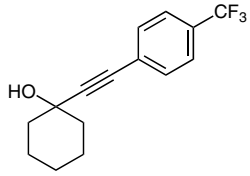
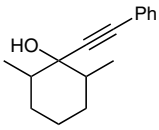
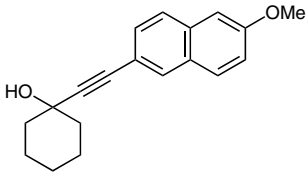
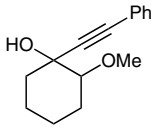
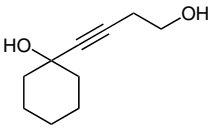
Entry	Catalyst (mol%)	Ligand (mol%)	Base (mol%)	Temp (°C)	Time (h)	Yield (%)[a]
1	AgCl (10)	PCy_3 (10)	DIPEA (20)	100	24	trace
2	AuCl (5)	PMe_3 (5)	DIPEA (20)	80	24	n.d.
3	$Pd(OAc)_2$ (5)	PMe_3 (20)	–	60	24	n.d.
4	AgCl (5)	RuPhos (10)	DIPEA (20)	100	24	22
5	AgCl (5)	XPhos (10)	DIPEA (20)	100	24	n.d.
6	AgCl (10)	RuPhos (20)	DIPEA (20)	100	24	62[b] (54)[c]
7	AgF (10)	RuPhos (20)	DIPEA (20)	100	24	21
8	AgBr (10)	RuPhos (20)	DIPEA (20)	100	24	37
9	AgI (10)	RuPhos (20)	DIPEA (20)	100	24	27
10	AgCl (10)	RuPhos (20)	DBU (20)	100	24	80[b] (77)[c]
11	AgCl (10)	RuPhos (20)	DBU (20)	48	48	75
12	AgCl (10)	RuPhos (20)	DBU (20)	100	12	57
13	AgCl (10)	RuPhos (20)	DBU (20)	r.t.	24	trace
14	AgCl (10)	RuPhos (20)	DBU (20)	80	24	43

[a] Isolated yield.
[b] Reaction conditions: **1a** (1 mmol), **2a** (0.25 mmol), sliver complex freshly prepared for use, H_2O (0.25 mL) under argon at 100 °C for 24 h.
[c] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol) addition by a syringe pump over 12 h, then react for another 12 h.

Table 2 Substrate Scope of the Alkyne–Ketone Addition in Water

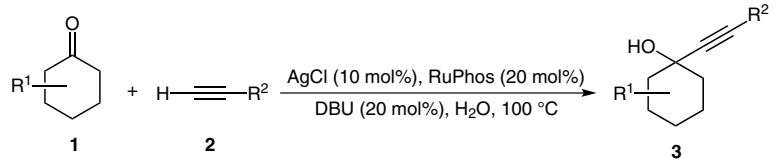


1 **2** **3**

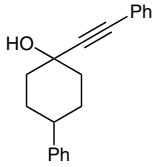
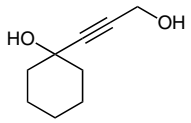
Entry	Product **3**	Yield (%)	Entry	Product **3**	Yield (%)[a]
1	 **3a**	80	9	 **3i**	75
2	 **3b**	67	10	 **3j**	43
3	 **3c**	N.R.	11	 **3k**	49
4	 **3d**	71	12	 **3l**	52
5	 **3e**	64	13	 **3m**	73
6	 **3f**	63	14	 **3n**	60
7	 **3g**	61	15	 **3o**	71

[a] Isolated yield.

Table 2 Substrate Scope of the Alkyne–Ketone Addition in Water (continued)



1 2 3

Entry	Product **3**	Yield (%)	Entry	Product **3**	Yield (%)[a]
8	 **3h**	79	16	 **3p**	56

[a] Isolated yield.

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(17) **General Reaction Procedure**: Degassed CH_2Cl_2 (0.25 mL) was added to a microwave tube containing the ligand RuPhos (23.2 mg, 0.05 mmol) and AgCl (3.6 mg, 0.025 mmol) under argon. The resulting suspension was stirred at r.t. until a clear, colorless solution was obtained; then the solvent was removed under vacuum. Cyclohexanone (**1a**; 26 μL, 0.25 mmol), DBU (7.5 μL, 0.05 mmol) and degassed H_2O (0.5 mL) were subsequently added under argon followed by the addition of phenylacetylene (**2a**; 104 μL, 1 mmol) using a syringe pump over 12 h. The reaction mixture was stirred for another 12 h at 100 °C, then cooled and

extracted with EtOAc (3 × 10 ml). The combined organic phase was concentrated and purified by flash column chromatography on silica gel (hexane–EtOAc, 10:1) to give the desired product **3a** as a white solid (40 mg, 80%). The NMR data are in full agreement with those previously reported in the literature.[18] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.43 (m, 2 H), 7.26–7.30 (m, 3 H), 1.99–2.03 (m, 3 H), 1.57–1.77 (m, 7 H), 1.28 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 131.7, 128.3, 128.1, 122.9, 93.8, 83.6, 72.2, 43.2, 28.0, 22.3.

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