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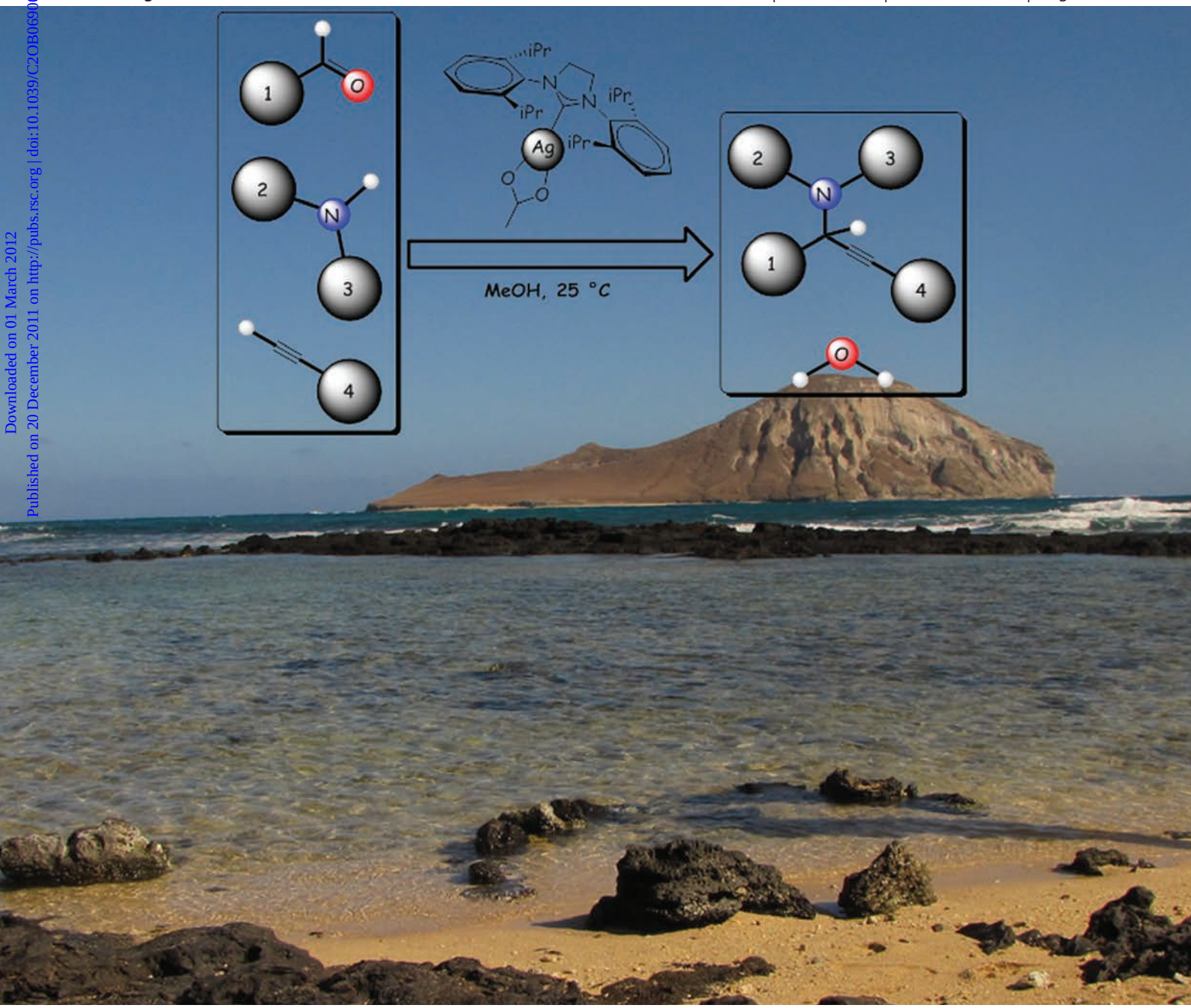

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COMMUNICATION

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COMMUNICATION

Well-defined (*N*-heterocyclic carbene)–Ag(I) complexes as catalysts for A^3 reactions†‡

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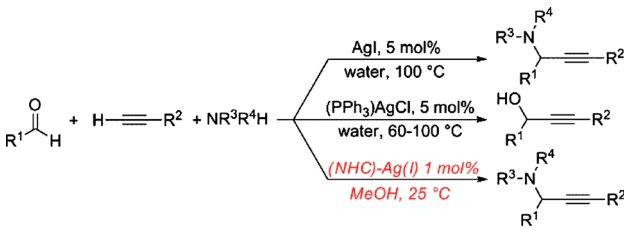
The use of well-defined (*N*-heterocyclic carbene)–Ag(I) complexes for the A^3 reaction allows for the coupling of unactivated aldehydes at room temperature and very short reaction times.

The use of the A^3 coupling reaction has gained a lot of attention since the first examples of this protocol were reported in the early 2000s by Ishii,[1] Carreira[2] and Li.[3] This highly efficient multicomponent coupling involves the combination of an aldehyde, and amine and an alkyne in the presence of a transition metal catalyst, leading to the formation of propargylamines, which are recurrent components of biologically active pharmaceuticals and natural products, as well as valuable intermediates for the synthesis of nitrogen-containing compounds.[4] A wide variety of transition metal catalysts have been used in this reaction, such as Ru, Re, Ir, Au, Cu, and more recently Fe, Co, Ni and Zn.[5]

Li and co-workers reported in 2003 the first examples of Ag-catalyzed A^3 reactions.[6] The particularity of this catalytic system was that it was especially effective towards aliphatic aldehydes, in contrast to Cu and Au systems, more effective towards aromatic aldehydes, and less undesired trimerization of the aldehyde was observed. Reactions were carried out in water at 100 °C, under N_2 and for several hours. When (PR_3)–Ag(I) complexes were used instead,[7] the authors observed a switch in activity, obtaining exclusively the aldehyde–alkyne coupling product (Scheme 1).[8] The authors postulated that a phosphine–Ag–acetylide was a key intermediate in the reaction, and suggested that the coordination of the ligand increased the electron density on Ag, activating the Ag–C bond towards the nucleophilic addition to the carbonyl. In contrast to those results, it has been shown that the use of Ag complexes bearing even more electron donating *N*-heterocyclic carbenes (NHCs)[9] instead of phosphines allows for a switch back of the reactivity towards the A^3 coupling.[10,11]

Despite this different reactivity, the use of NHCs as ligands for the A^3 reaction has barely been explored. To the best of our knowledge, only two (NHC)–Ag(I) catalytic systems have been reported: one of them using well-defined complexes in air and at high temperature,[10] and another using recyclable, polymer-supported (NHC)–Ag(I) complexes, which can operate at room temperature, under N_2 and needing long reaction times.[11] In both cases, the ligands and the corresponding complexes were specifically synthesized for this reaction. We report herein that the use of well-defined complexes derived from commercially available NHC ligands allows for A^3 coupling reactions to take place at room temperature, in air and in much shorter reaction times (Scheme 1).

The synthesis of the (NHC)–Ag(I) complexes used in this study (Fig. 1) was done according to very straightforward procedures reported in the literature and starting from commercially available NHCs or their precursors, imidazolium salts.[12] After determining that the use of methanol as solvent afforded the highest yields when 1 mol% of (IPr)AgCl (**1**) was used as catalyst (Table 1, entry 11), variations of this complex were screened for activity towards the same set of substrates, using even lower catalyst loading (Table 2). We observed that changing the carbene IPr to its saturated counterpart SIPr did not have a considerable effect in the formation of product (Table 2, entry 2). On the other hand, the activity of the catalyst was notably affected by the nature of the anion in the order OAc > Cl > Br ≫ I. This trend had been observed previously (for the halides



Scheme 1 Ligand-controlled alkynylation of carbonyls and imines.

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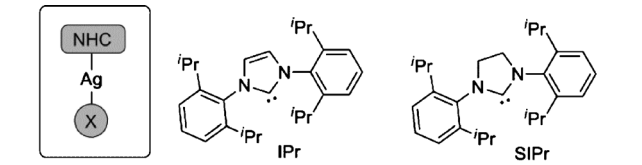
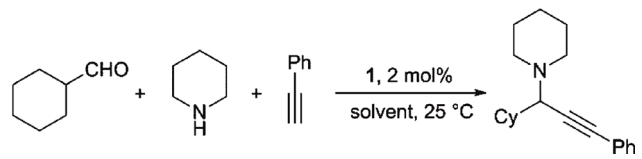
‡**General Procedure for the A^3reaction:** All reactions were set up in air. The catalyst (n mol%) was added to a vial equipped with a magnetic bar, followed by the aldehyde (1 mmol), amine (1.1 mmol), alkyne (1.1 mmol) and solvent (0.5 mL). The vial was then sealed with a screw cap fitted with a septum and the mixture allowed to stir on a stirring plate at the corresponding temperature. The reaction was monitored by gas chromatography. When it was determined that the reaction was finished, the solvent was evaporated in vacuum and the product isolated by flash chromatography. The amount of product shown is the average of two runs.



NHC = IPr, X = Cl, (IPr)AgCl (**1**)
NHC = SIPr, X = Cl, (SIPr)AgCl (**2**)
NHC = IPr, X = Br, (IPr)AgBr (**3**)
NHC = IPr, X = I, (IPr)AgI(**4**)
NHC = IPr, X = OAc, (IPr)Ag(OAc) (**5**)
NHC = SIPr, X = OAc, (SIPr)Ag(OAc) (**6**)

Fig. 1 (NHC)–Ag(I) complexes tested in this study.

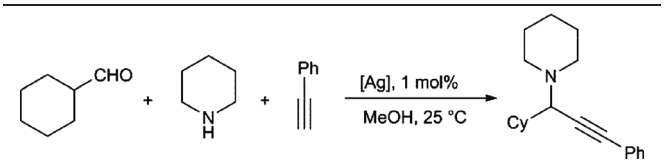
Table 1 Solvent selection



Entry	Solvent	Time (h)	Yield (%)[a,b]
1	neat	3	62
2	acetone	3	63
3	DCM	3	69
4	MeCN	3	96
5	toluene	3	9
6	DMF	3	57
7	water	3	19
8	isopropanol	1	88
9	methanol	1	98
10	isopropanol	0.25	68
11	methanol	0.25	94

[a] Reaction conditions: aldehyde, 1 mmol; amine, 1.1 mmol; alkyne, 1.1 mmol; solvent, 0.5 mL [b] GC yield (hexamethylbenzene as internal standard); average of 2 runs.

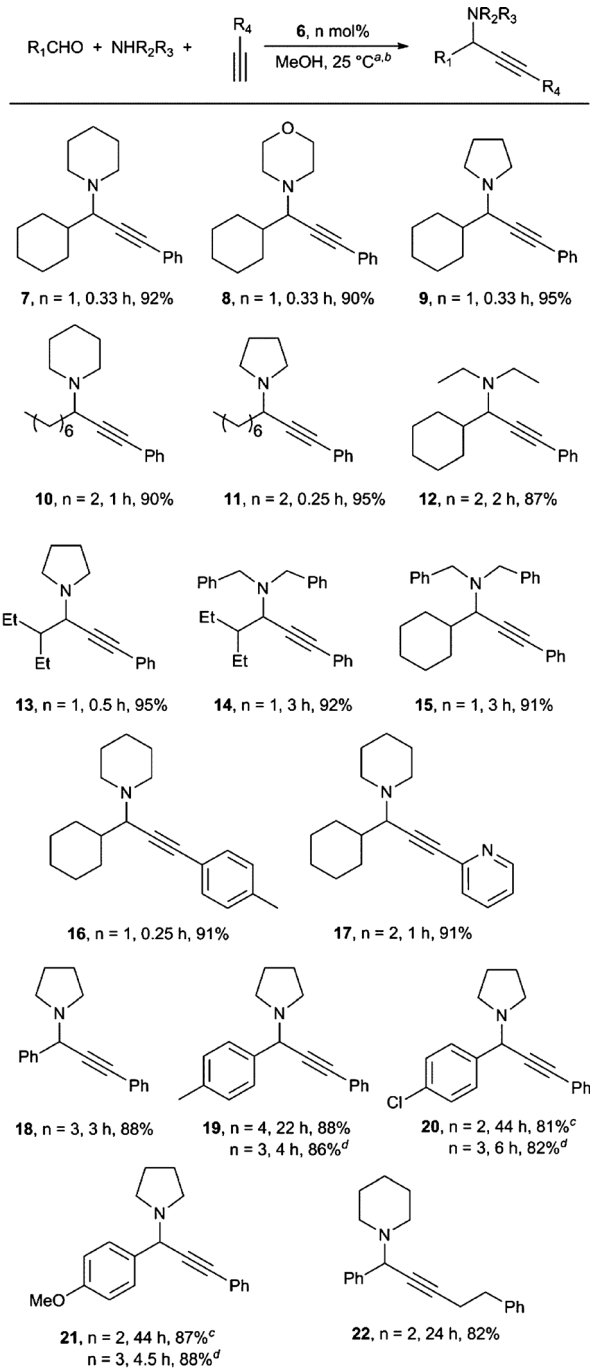
Table 2 Catalyst selection



Entry	Complex	Time (min)	Yield (%)[a,b]
1	**1**	20	86
2	**2**	20	88
3	**3**	20	70
4	**4**	20	9
5	**5**	20	91
6	**6**	20	96

[a] Reaction conditions: aldehyde, 1 mmol; amine, 1.1 mmol; alkyne, 1.1 mmol; methanol, 0.5 mL. [b] GC yield (hexamethylbenzene as internal standard); average of 2 runs.

only) by Zou and co-workers, who used it to suggest that the first step of the catalytic cycle involves the coordination of the alkyne to an (NHC)AgX complex, followed by the formation of the corresponding silver alkynide.[10] This coordination would be favoured with a less bulky anion.[13] We found that the use of



[a]Reaction conditions: aldehyde, 1 mmol; amine, 1.1 mmol; alkyne, 1.1 mmol; methanol, 0.5 mL. [b]Average of two runs. [c]GC yield showed (hexamethylbenzene as internal standard). [d]Reaction at 50 °C.

Scheme 2 Substrate scope.

1 mol% of (SIPr)Ag(OAc) (**6**) allowed for the coupling to occur in only 20 min (Table 2, entry 6). It is worth mentioning that all reactions were set up in open air, in technical grade methanol and without any purification of the coupling partners.

Following this optimized protocol, we were able to couple a variety of aldehydes, amines and alkynes to obtain the corresponding propargylamines in very good yields (Scheme 2). In agreement with Li's results using AgI,[6] the use of our (NHC)–Ag system was more effective towards the coupling of aliphatic

aldehydes (Scheme 2, compounds **7–17**). A distinctive feature of this protocol is that, in contrast to other (NHC)–Ag(I) systems,[10,11] the use of complex **6** allows for the coupling of unactivated aryl aldehydes at room temperature, albeit requiring much longer reaction times (Scheme 2, compounds **18–22**). These reaction times can be decreased considerably by increasing the temperature and/or the catalyst loading.

In summary, we have developed a general (NHC)–Ag(I) catalyzed protocol for the A^3 coupling of unactivated alkyl and aryl aldehydes, at room temperature and using low catalyst loadings. Studies on expanding the scope of the reaction and the development of an enantioselective protocol are currently ongoing in our labs.

Acknowledgements

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