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Glaser-Hay hetero-coupling in a bimetallic regime: a Ni(II)/Ag(I) assisted base, ligand and additive free route to selective unsymmetrical 1,3-diynes†

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A Ni(OAc)₂/Ag(OTf) catalysed coupling of aryl alkynes and propargylic alcohol/ether/ester gave the corresponding unsymmetrical 1,3-diynes in good to excellent yields. The reaction does not require bases, ligands or additives and shows excellent hetero-selectivity, thereby addressing the current challenges in the field of coupling of two different terminal alkynes.

The synthesis of unsymmetrical 1,3-divnes has attracted a great deal of attention due to their widespread applications in organic synthesis and materials science.¹ Due to their ubiquitous structural motifs, they exhibit a range of biological activities like antifungal, anticancer, anti-HIV and antibacterial properties, and also play an important role in the design of functional materials such as optical materials, conductive plastics, high density fibres and liquid crystals.^{2,3} Furthermore, conjugated diynes have unique behaviour towards transition metals, and these organometallic materials display various novel properties, such as luminescence, conductivity, and photovoltaic behavior.⁴ Therefore, the development of an efficient procedure for the synthesis of unsymmetrical 1,3-diynes still evokes curiosity and challenge to a synthetic chemist. Over the past few decades, Glaser⁵ and Cadiot-Chodkiewicz⁶ couplings have been the major methods for the synthesis of 1,3-divnes. In 1986, Glaser pioneered the synthesis of poly-yne core structures via the homo-coupling of terminal alkynes by utilizing the oxidative dimerization of copper(I)phenylacetylide upon exposure to air.⁵ During the last few years, various modifications of Cu-salt mediated Glaser coupling have been developed (Scheme 1).⁷⁻⁹ Among these, special mention may be made of the work by Leigh and co-workers who utilized the bimetallic combination of Ni(II) and Cu(I) in stoichiometric quantities to promote the homocoupling of alkynes in rotaxane synthesis.^{8c} In the Glaser-Hay variant, catalytic copper(1) chloride is used in the presence of stoichiometric tetramethylenediamine (TMEDA) and oxygen,



Scheme 1 Alkynes to diynes: the journey so far

leading to decreased reaction times and improved yields of the homo-coupling product.¹⁰ Unfortunately, one major drawback of this reaction is chemo-selectivity, which results in a mixture of products when different terminal alkynes are used in situ. The selectivity towards unsymmetrical 1,3-diynes is improved in the Cadiot-Chodkiewicz coupling wherein a terminal alkyne is reacted with an alkynyl halide in the presence of a Cu salt and an amine base.⁶ The use of a halide as a reactant, an amine as a solvent and hydroxylamine hydrochloride as a reductive reagent brings in complexity to the system in terms of the green demand and work-up protocol. A bimetallic variant of the above reaction has been recently reported.¹¹ A very recent report by Liu et al. describing gold catalysed coupling between an alkyne and an



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alkynyl hypervalent iodine(III) reagent is also noteworthy.¹² In spite of the success as above, the direct hetero-coupling of two terminal alkynes leading to selective formation of unsymmetrical 1,3-diynes remains a challenge. In this regard three reports are noteworthy. Shi and co-workers obtained excellent heteroselectivity by using [(dppm)(AuBr)₂]/phen as a catalyst and PhI(OAC)₂ (2 equiv.) as an oxidant.¹³ Yin et al. achieved heteroselectivity using Cu(0)/TMEDA as the catalyst and CHCl₂/O₂ as the oxidant.14 Lei and co-workers utilized the catalytic combination of Ni(II)/Cu(I)/TMEDA to achieve hetero-selectivity in which one of the alkynes is used in 5-fold excess.¹⁵ One may note that there exist rich opportunities in the area of bimetallic/dual-reagent catalysis with emphasis on green/sustainable chemistry.¹⁶ While addressing the issue of the activation of alkyne and propargyl alcohol, we were drawn in to the challenge of executing a Glaser-Hay hetero-coupling for the synthesis of unsymmetrical 1,3-diynes under base, ligand, additive free conditions. In this communication we are delighted to report the coupling between an aromatic alkyne and propargylic substrate using a catalytic combination of Ni(II)/Ag(I) under aerobic conditions to give rise to the corresponding unsymmetrical 1,3-divne. The excellent hetero-selectivity and the absence of any additives in the reaction medium are the most noteworthy feature of this reaction (Scheme 1).

In a model study, we first examined the cross coupling between phenyl acetylene 1 and propargyl alcohol 2 in the presence of catalytic nickel(II) and silver(I) salts but in the absence of bases and additives in different solvents at 110 °C under aerobic conditions (Table 1). To our gratification, we found that with the combination of Ni(OAc)₂·4H₂O and AgOTf the hetero cross coupling reaction dominated over the homo coupling and the desired product 3 was obtained in excellent yield (Table 1, entry 4). Dimethylformamide happened to be the solvent of choice (Table 1, entries 1-4). We also tested the reaction with Ag(1) salts having a bulkier and/or better leaving anionic counterpart (Table 1, entries 4-10). While in all cases 3 were obtained in varying amounts, the yield was highest with silver triflate (Table 1, entry 4). Note that individually AgOTf or Ni(OAc)₂·4H₂O could not promote the hetero-coupling reaction (Table 1, entries 11 and 15). Interestingly, individually AgOTF was efficient for homo coupling of aryl alkynes (Table 1, entry 11), while Ni(OAc)₂ $4H_2O$ was inactive suggesting the importance of the bimetallic combination. It is surprising that other nickel salts tested also failed to promote the desired coupling reaction (Table 1, entries 13-15). Note that the bimetallic combination of Cu(I)/Ni(II) was also ineffective towards heterocoupling in the present Glaser-Hay coupling (Table 1, entries 16 and 17). A reaction attempted in an acetic acid medium in the presence of other nickel salts/complexes gave only the homocoupling product from phenylacetylene (Table 1, entries 18 and 19).

With the optimized reaction conditions in hand, next we explored the substrate scope by varying the arylalkyne **1** as well as the -ynolic substrate 2 (Table 2). With stepwise substitution of the hydrogen atoms at the C-1 position (methylene group next to –OH) of propargyl alcohol with a methyl group, the reaction time increases (Table 2, products **3b**, **3c**, **3f**, **3g**, **3j**, **3k**, **3n**, **3o**, **3r** and **3s**). A similar trend has been noted with

 Table 1
 Optimization of reaction conditions^a

	Ph	Ni[cat.](10mol%) Ag[cat.](10mol%)	Ph	^	ЭН
	ОН	110 °C, solvent, 3 h	Ph +	Ph	
	2		4		
ţ	Silver catalyst	Nickel catalyst	Solvent	3^{b} (%)	4^{b} (%)
L	AgOTF	Ni(OAc) ₂ ·4H ₂ O	1,4-Dioxane	0	5
2	AgOTF	Ni(OAc) ₂ ·4H ₂ O	Toluene	0	0
;	AgOTF	Ni(OAc) ₂ ·4H ₂ O	MeCN	17	9
ŀ	AgOTF	Ni(OAc) ₂ ·4H ₂ O	DMF	87	11
5	AgClO ₄	Ni(OAc) ₂ ·4H ₂ O	DMF	56	8
5	AgNO ₃	Ni(OAc) ₂ ·4H ₂ O	DMF	79	8
7	Ag ₂ O	Ni(OAc) ₂ ·4H ₂ O	DMF	69	12
3	$AgBF_4$	Ni(OAc) ₂ ·4H ₂ O	DMF	64	6
)	AgPF ₆	Ni(OAc) ₂ ·4H ₂ O	DMF	54	8
0	AgSbF ₆	Ni(OAc) ₂ ·4H ₂ O	DMF	81	11
1	AgOTF		DMF	0	65
2	AgOTF	NiCl ₂	DMF	0	20
3	AgOTF	NiCl ₂ ·6H ₂ O	DMF	Trace	25
4	AgOTF	Ni(PPh ₃) ₂ Cl ₂	DMF	0	20
5	_	Ni(OAc) ₂ ·4H ₂ O	DMF	0	0
6	c	NiCl ₂ ·6H ₂ O	DMF	0	25
7	c	Ni(OAc) ₂ ·4H ₂ O	DMF	Trace	35
8	AgOTF	Ni(PPh ₃) ₂ Cl ₂	CH ₃ COOH	Trace	10
9	AgOTF	NiCl ₂ ·6H ₂ O	CH ₃ COOH	0	15
Reaction conditions: phenylacetylene 1 (0.25 mmol) proparayl alcohol					

^a Reaction conditions: phenylacetylene 1 (0.25 mmol), propargyl alcohol 2 (0.5 mmol), [Ag] (10 mol%), [Ni] (10 mol%), solvent (1 ml), 110 °C, air, 3 h. ^b Yields of isolated pure products. ^c CuI (10 mol%).

elongation in the carbon chain length as in but-3-yn-1-ol (Table 2, products 3d, 3h, 3l). The generality of the reaction with respect to substitution in the aromatic ring of arylalkynes has been tested. Both electron donating as well as electron withdrawing groups are well tolerated (Table 2, products 3e–3s). Notably in the case of the nitro group, the hetero coupling is more facile and the yields of the desired 1,3-diynes have been excellent (Table 2, products 3q–3s). The reaction was also tested with pyridylalkyne as a representative heteroarylalkyne and the coupling proved to be successful and the corresponding products 3t and 3p were obtained in 60% isolated yields (Table 2). The compatibility of the reaction with propargylic ether and propargylic ester was also established (Table 2, products 3u and 3v). The yield of the homocoupling products 4 from aryl terminal alkynes varied in the range of 3–20% (ESI,† Table TS1).

The following experiments provide insights into the initial bond activation steps. While silver triflate alone can mediate the homocoupling of phenylacetylene, the hetero-coupling with propargylic alcohol requires the presence of a Ni(π) catalyst, which clearly establishes the bimetallic reactivity. Preliminary investigation on the interaction of Ni(π) and Ag(1) with the alkyne was carried out using UV-vis spectroscopy, which suggested possible interaction between Ni(π) and propargyl alcohol and that of Ag(1) with phenyl acetylene (ESI†). The above result encouraged us to further investigate the interactions using ¹H NMR as a probe in CDCl₃ or DMSO-d₆ as a solvent with 2-methylbut-3-yn-2-ol **2c** and phenylacetylene **1a** as the representative reagents and 1,2,3-trimethoxybenzene (TMB) as the internal reference (ESI†). Upon incremental addition of Ni(π), the intensity of the –OH

Table 2 Substrate scope for the hetero cross coupling of different alkynes with Ni(OAc)_2·4H_2O and AgOTf^a



 a Reaction conditions: arylalkyne 1 (0.25 mmol), alkyne 2 (0.5 mmol), [Ag] (10 mol%), [Ni] (10 mol%), solvent (1 ml), 110 $^\circ C$, air.

peak of propargyl alcohol 2c slowly decreased without causing any significant change in other peaks, which suggests the binding of propargyl alcohol to Ni(π). On the other hand, marginal peak shifts were noticed when 2c and Ag(η) were mixed.¹⁷ In sharp contrast, upon mixing phenyl acetylene **1a** and AgOTf in CDCl₃, a white precipitate was instantly obtained. The precipitate was dissolved in DMSO-d₆ and ¹H NMR was recorded. In the resulting spectrum, the –CH peak of phenyl acetylene **1a** was completely absent and the aromatic region was shifted, suggesting the formation of the corresponding



Fig. 1 Proposed mechanism for the formation of 1,3-hetero coupled diynes.

silver acetylide.¹⁷ Based on the above results, a plausible mechanism is proposed (Fig. 1, L = OAc or donor ligand). The mechanism invokes prior activation of propargyl alcohol by Ni(π) to generate I, and the formation of silver(τ)acetylide II from phenyl acetylene and Ag(τ). A transmetallation reaction involving I and II would generate the nickel(π) acetylide intermediate III. As the propargylic (sp)C–H in III is activated by the nickel centre, we suggest a metallation step by the silver salt to give intermediate IV and sequential transmetallation to yield the crucial intermediate V. A reductive elimination from V would generate the desired hetero-coupled diyne product along with Ni(0). The latter is expected to oxidize by air to generate Ni(π), thereby completing the catalytic cycle.¹⁸

In conclusion, we report an inexpensive, milder, aerobic method for the synthesis of unsymmetrical conjugated diynes from functionally different alkynes by oxidative cross-coupling. This has been successfully achieved by simply mixing two different transition metals salts Ni(OAc)₂·4H₂O and AgOTf in catalytic amounts. This method is more efficient and atom economic. It shows a good functional group tolerance and substrate scope with good to excellent yields of the desired product. The formation of hetero coupled diynes instead of homocoupled analogues has brought high selectivity without any base, ligand and additives. In addition, it is the first example of a Ni(π)/Ag(i) cooperative system which promotes efficient hetero-coupling of two different alkynes. We believe that the bimetallic system could potentially open up newer C–H activation strategies involving sp(C) and sp²(C) centres. Work in this direction including mechanistic studies is in progress.

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Conflicts of interest

There are no conflicts to declare.

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