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Z-Selective Dimerization of Aromatic Terminal Alkynes Catalyzed by an Iridium(I)–N-Heterocyclic Carbene–Phosphine System

Calum D. Forsyth, William J. Kerr,* Laura C. Paterson

Department of Pure and Applied Chemistry, WestCHEM, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, Scotland, UK
Fax +44(141)5484246; E-mail: w.kerr@strath.ac.uk

Abstract: The development of an iridium-catalyzed regio- and stereoselective dimerization process has enabled the formation of (*Z*)-enyne products. More specifically, low catalyst loadings of an iridium(I) complex, featuring a bulky N-heterocyclic carbene–phosphine ligand combination, has been successfully employed in this selective head-to-head dimerization of terminal alkynes via C–H activation.

Key words: alkynes, enynes, dimerization, C–H activation, iridium

The dimerization of terminal alkynes is one of the most expedient and atom-economical routes towards conjugated enyne compounds.[1] Indeed, such products are versatile building blocks in organic synthesis,[2] as well as in materials science.[3] As such, a number of transition metals have emerged within catalyst systems for this transformation, including gold,[4] palladium,[5] iron,[6] nickel,[7] iridium,[8] and, very recently, zirconium.[9] However, the establishment of methods that deliver desirable levels of regio- and stereocontrol provides a continuing challenge within this area. Scheme 1 displays the potential enyne isomers obtainable via this dimerization process. In addition to these products, competing cyclotrimerization[10] or butatriene formation[8c,d,11] are also observed reaction outcomes. Nevertheless, the formation of branched enynes, that is, head-to-tail coupled products **A**, has been readily achieved via Au and Pd catalysis.[4,5] Additionally, the head-to-head coupled (*E*)-enynes **B** have been prepared without incident, employing a range of metal catalysts.[6,7,8b–d,12]
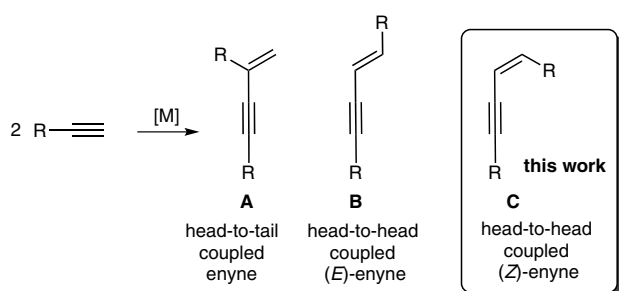
In contrast, the *Z*-selective head-to-head homodimerization of terminal alkynes **C** is much less common. Whilst synthetic methods have emerged towards a *Z*-selective pathway,[8a,c,d,9,12b,13] this arena is still relatively underdeveloped. Indeed, there remains a requirement for a robust and reliable reaction protocol for the dimerization of alkynes over a wide range of substrates to form products such as **C**. Herein we now report a catalytic process for the delivery of head-to-head dimerized alkyne products with *Z*-selectivity using low loadings of transition-metal catalyst.

Recent research within our laboratory has led to the preparation and application of a series of novel iridium(I) complexes featuring both a sterically demanding N-heterocyclic carbene (NHC) along with an appreciably encumbered phosphine ligand (Figure 1).[14] Such complexes are readily handled, and we have previously showcased the ability of these complexes to facilitate hydrogen isotope exchange by arene C–H activation,[14] with activity far in excess of the current industry standard, Crabtree's catalyst.[15] More recently, work within our laboratories has highlighted the extremely efficient performance of these novel complexes in selective hydrogenation reactions.[16]
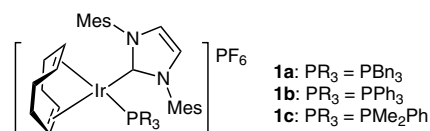

Figure 1 Iridium(I) complexes bearing a bulky NHC–phosphine ligand combination

1a: PR₃ = PBn₃
1b: PR₃ = PPh₃
1c: PR₃ = PMe₂Ph

As part of our ongoing endeavors to extend the applicability of our emerging catalyst series, we wished to investigate their ability to promote a selective alkyne dimerization process through activation of a terminal alkyne C–H bond (Scheme 2). Indeed, we anticipated that the specific electronic and steric properties imparted by the mixed NHC–phosphine ligand system would lead to efficient alkyne coupling.

Scheme 1 Homodimerization of terminal alkynes
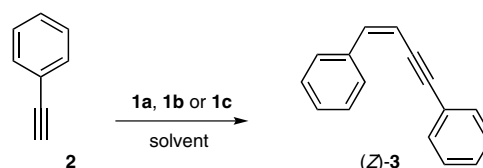
Scheme 2 Head-to-head homodimerization of terminal alkynes
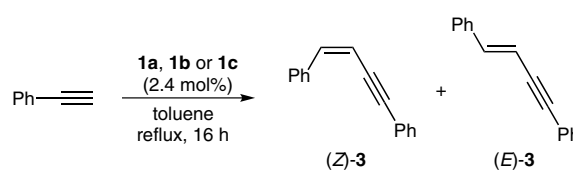
In order to evaluate this hypothesis, alkyne homodimerization, promoted by complexes **1a–c**, was investigated using phenylacetylene as our starting substrate (Table 1). Pleasingly, on our initial application, complex **1a** promoted the desired transformation at a catalyst loading of only 2.4 mol%, with 87:13 selectivity towards the Z-isomer, albeit in a modest 29% yield. Notably, none of the head-to-tail homodimerized product was observed. Complexes **1b** and **1c** were also screened; whilst, again, none of the head-to-tail isomer was identified, lower Z/E ratios and chemical yields were exhibited. In all of these initial processes, appreciable byproduct formation was also noted. From our previous studies,[14,16] complex **1a** has, to date, proved to be the most versatile of this new group of catalysts. Accordingly, we were encouraged by the initial result in this study with **1a** to further probe the synthetic utility of this novel species.

Table 1 Homodimerization Studies with Complexes **1a–c**

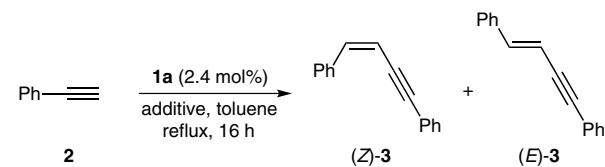| Entry	Complex	Yield of **3** (%)[a]	Z/E[b]
1	**1a**	29	87:13
2	**1b**	22	72:48
3	**1c**	26	67:33

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.

With the promising initial result in hand, we were keen to enhance the performance of our emerging iridium catalyst system as applied to this alkyne dimerization. Our goal was to increase the yield of the regioselective head-to-head coupling process whilst simultaneously improving the observed stereoselection. In this regard, through the stabilization of key reaction intermediates and the promotion of a certain reaction pathway, it is known that the addition of specific ligands within such transition-metal-mediated processes can enhance alkyne coupling efficiency and selectivity.[6,7,8c,d] As such, we probed the use of various additives within our developing system, with a range of representative results displayed in Table 2. As shown by entry 2 (Table 2), the dimerization of phenylacetylene proceeded very effectively in the presence of tribenzylphosphine (Bn$_3$P; 30 mol%), with a much improved yield of 82% being obtained, coupled with enhanced levels of Z selectivity. Performing similar processes with Bn$_3$P under more forcing reaction conditions (sealed tube or microwave) did not offer any improvement in terms of yield or selectivity. It has previously been reported that altering the nature of phosphine additives has a pronounced effect on the dimerization stereoselectivity observed.[8c] Accordingly, an alternative electron-rich phosphine (tri-

butylphosphine) was employed within this study. However, this failed to induce prominent Z-selectivity; as noted in Table 2, entry 5, a reversal of stereoselectivity in favor of the (E)-enyne was displayed. Furthermore, alternative additives either delivered the product(s) in diminished yields or failed to promote the reaction at all (Table 2, entries 6–8).

Table 2 Additive Study

Entry	Additive (mol%)	Yield of **3** (%)[a]	Z/E[b]
1	–	29	87:13
2	Bn$_3$P (30)	82	90:10
3[c]	Bn$_3$P (30)	73	72:28
4[d]	Bn$_3$P (30)	71	79:21
5	Bu$_3$P (30)	38	34:66
6	dppb (30)	–	–
7	COD (30)	–	–
8	Et$_3$N (30)	28	82:18

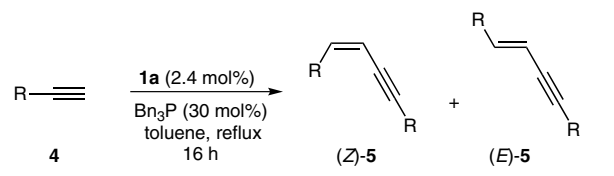[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Reaction performed in a sealed tube.
[d] Reaction performed in a microwave reactor at 120 °C for 1 h.

Following the establishment of this procedure with iridium complex **1a** at relatively low catalyst loading, coupled with Bn$_3$P additive, a number of alternative terminal alkyne substrates were examined (Table 3). Pleasingly, in every case, the head-to-head (Z)-enyne product was prepared in excess. Initially, we probed the applicability of our optimal conditions using 4-tolylacetylene (Table 3, entry 2) with an isolated yield of 72% and a Z/E ratio of 81:19 being obtained. Our attention then turned to further substituted aryl alkynes, specifically containing *para*-substituted halogens. More specifically, many transition-metal catalysts promote protodehalogenation, and we were eager to test the ability of our catalyst to facilitate the desired transformation in a completely chemoselective manner. The homodimerization of 4-fluorophenylacetylene proceeded in an excellent yield with good stereocontrol (Table 3, entry 3). Especially pleasing was the ability of complex **1a** to facilitate the homodimerization of 4-chlorophenylacetylene (Table 3, entry 4) and 4-bromophenylacetylene (Table 3, entry 5) in good yield with appreciable levels of stereoselectivity. The electronic nature of the substrates was investigated further with the electron-donating 4-methoxyphenylacetylene (Table 3, entry 6) being reacted under the optimized conditions. Disappointingly, the desired products were formed in poor yield with only

a slight bias towards the (*Z*)-enyne product; the majority of the mass balance in this instance was made up of unreacted starting alkyne. In contrast, the electron-withdrawing 4-trifluoromethylphenylacetylene underwent dimerization in good yield with the (*Z*)-enyne, again, being formed preferentially.
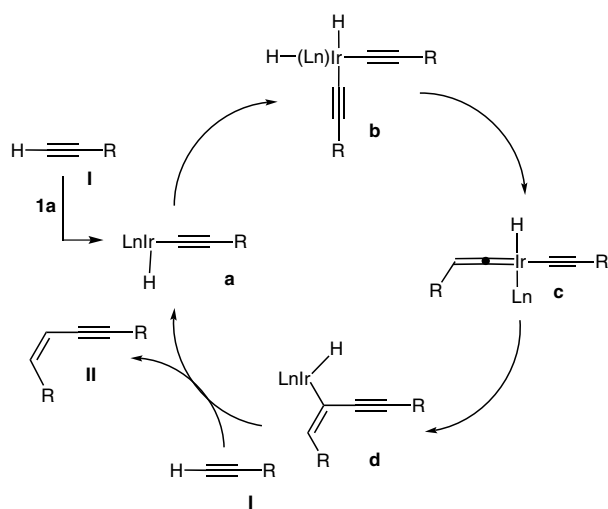
Table 3 Substrate Scope

Entry	Alkyne **4** (*R*)	Yield of **5** (%)[a]	*Z/E*[b]
1	Ph	82	90:10
2	4-MeC$_6$H$_4$	72	81:19
3	4-FC$_6$H$_4$	82	85:15
4	4-ClC$_6$H$_4$	74	77:23
5	4-BrC$_6$H$_4$	79	85:15
6	4-MeOC$_6$H$_4$	16	55:45
7	4-F$_3$CC$_6$H$_4$	75	77:23

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.

Based on our observed reaction products, as well as appreciation of previously elucidated pathways of similar transformations,[8c,11a,17] we propose that the reaction proceeds by the pathway described below (Scheme 3). The iridium complex undergoes an initial oxidative addition, with terminal alkyne **I**, to form complex **a**. It is believed that the electron-rich ligand environment then facilitates a subsequent oxidative addition of a second alkyne unit to deliver intermediate **b**; such Ir(V) species have been the subject

of increasing attention in recent years.[18] Following this, in a well-precedented process,[11a,19] complex **b** can isomerize to the vinylidene complex **c** by intraligand hydrogen transfer. Intramolecular migration of the alkyne unit onto the α-carbon of the vinylidene moiety results in formation of the *cis*-enyne iridium species **d**. As supported by the detailed observations of Wakatsuki when employing Ru complexes within related processes,[11a] the *cis* form of the enyne unit within **d** is believed to be favored to avoid any repulsive interactions between the (alkenyl) R group and the specific bulky ligand sphere around Ir, which would occur in the *trans* form. The cycle is completed by protodemetalation to provide the desired product **II** and returning intermediate **a**. Mechanistic studies relating to the use of our emerging iridium catalysts within a series of synthetic transformations are presently ongoing within our laboratories.

In summary, as part of a program of work within our laboratory to expand the applicability of novel iridium complexes **1**, we have now developed a catalytic system for effective alkyne dimerization. As promoted by the electron-rich nature and combined steric bulk of the ligand set within the catalyst system, the established method delivers specifically the head-to-head coupled products in a *Z*-selective process. Under the optimized reaction conditions, complex **1a** facilitates the homodimerization of a range of aryl alkynes with excellent levels of regiochemical control.

Scheme 3 Potential mechanistic pathway

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