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Iridium-catalyzed 1,5-(aryl)aminomethylation of 1,3-enynes by alkenyl-to-allyl 1,4-iridium(I) migration†

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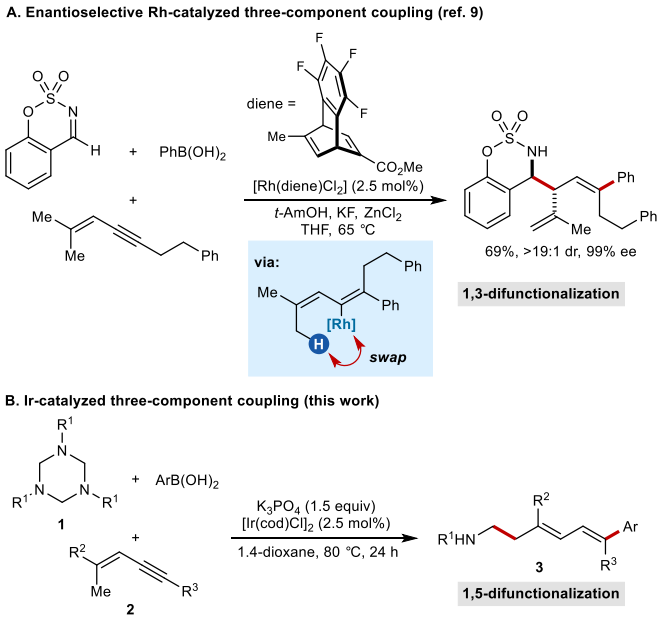
A novel multicomponent coupling reaction involving the iridium-catalyzed 1,5-difunctionalization of 1,3-enynes with arylboronic acids and triazinanes is described. A key step in this 1,5-(aryl)aminomethylation reaction is the alkenyl-to-allyl 1,4-iridium(I) migration.

Difunctionalization reactions, not including (formal) cycloadditions that result in overall annulation, are a diverse family of useful transformations. Although 1,2-difunctionalizations of alkenes are the most common,[1] other reaction types such as 1,1-difunctionalization,[2] 1,3-difunctionalization,[3] and 1,4-difunctionalizations[4] of π-unsaturated systems or cyclopropanes are also known. However, to the best of our knowledge, 1,5-difunctionalizations are rare, and are restricted to reactions of vinylcyclopropanes.[5] Addressing this methodological gap could provide new opportunities in synthesis and enable the rapid generation of molecular complexity.

Herein, we report the first example of an iridium-catalyzed multicomponent coupling between 1,3-enynes, arylboronic acids, and triazinanes that results in a novel 1,5-functionalization to give 1,3-dienes. The key step in this reaction involves an alkenyl-to-allyl 1,4-iridium(I) migration that enables the functionalization of an otherwise unreactive C-H bond. This overall 1,5-(aryl)aminomethylation[6] reaction introduces nitrogen functionality with the concomitant formation of two new carbon–carbon bonds, thus complementing more well-known hydroaminomethylation and hydroamidomethylation reactions that result in only one new carbon–carbon bond.[7,8]

Recently, we reported the enantioselective rhodium-catalyzed three-component coupling of arylboronic acids, 1,3-enynes, and cyclic imines,[9] in which an alkenyl-to-allyl 1,4-rhodium(I) migration[10,11] is a key step (Scheme 1A). In seeking to increase the utility of this chemistry in new areas, we questioned whether cyclic imines could be replaced with triazinanes, which are known to produce formaldimines upon



Scheme 1 Three-component couplings of 1,3-enynes, arylboronic acids, and imines by alkenyl-to-allyl 1,4-metal migration.

heating.[8] Our initial experiments (Table 1) focused on the reaction of 1,3-enyne **2a**, triazinane **1a** (0.5 equiv), and $PhB(OH)_2$ (1.5 equiv). Although the use of rhodium(I) catalysis under various conditions led only to complex mixtures, we were pleased to observe that heating the three reactants in dioxane at 80 °C for 24 h in the presence of $[Ir(cod)Cl]_2$ (2.5 mol%) and K_2CO_3 (1.5 equiv) successfully gave a three-component coupling product in 14% yield as determined by ^1H NMR analysis (entry 1).[12] Unexpectedly however, the product was 1,3-diene **3a**, in which the 1,3-enyne underwent 1,5-(aryl)aminomethylation, in contrast to our previous 1,3-difunctionalization using cyclic imines.[9] Variation of the base led to increased yields of **3a** (entries 2–4), which was obtained as a mixture of *E*- and *Z*-isomers at the methyl-substituted alkene.[13] K_3PO_4 gave the highest *E*:*Z* ratio of 4.3:1 (entry 4). Although changing the solvent to MeCN or THF gave inferior

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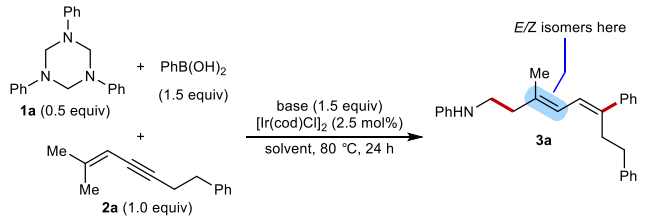
Table 1 Evaluation of reaction conditions.[a]

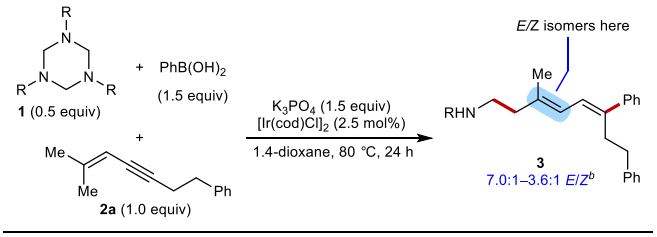


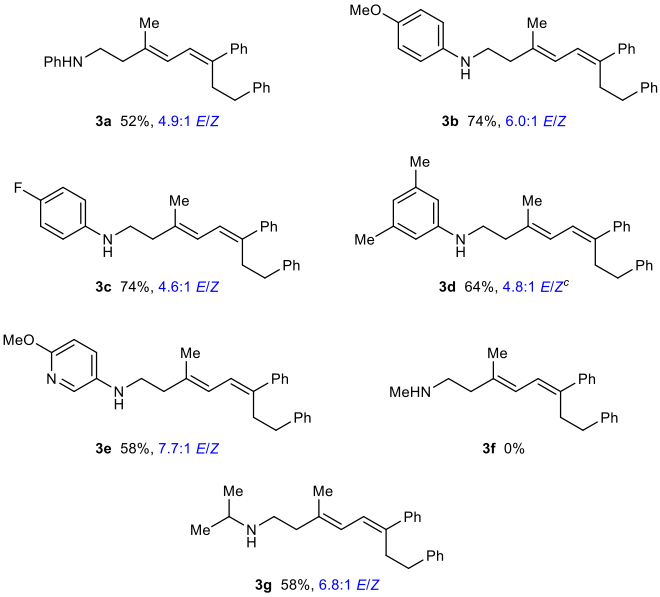
Entry	Base	Solvent	Yield (%)[b]	*E*:*Z* ratio[c]
1	K_2CO_3	1,4-dioxane	14	n.d.[d]
2	Et_3N	1,4-dioxane	26	3.3:1
3	KF	1,4-dioxane	50	4.0:1
4	K_3PO_4	1,4-dioxane	50	4.3:1
5	K_3PO_4	MeCN	15	3.5:1
6	K_3PO_4	THF	43	2.7:1
7[e]	K_3PO_4	1,4-dioxane	53	5.0:1

[a] Reactions were conducted with 0.05 mmol of **2a**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Not determined. [e] Using 30 mg of 3 Å molecular sieves.

results (entries 5 and 6), the addition of 3 Å molecular sieves was beneficial and gave **3a** in 53% NMR yield as a 5.0:1 *E*/*Z* mixture (entry 7).[14]

Table 2 Scope of the triazinane[a]



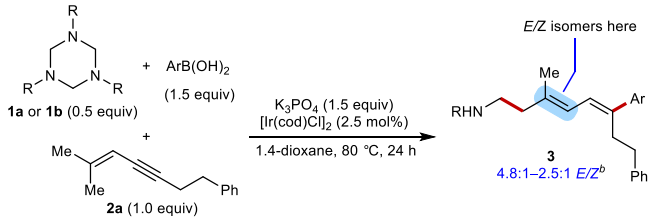


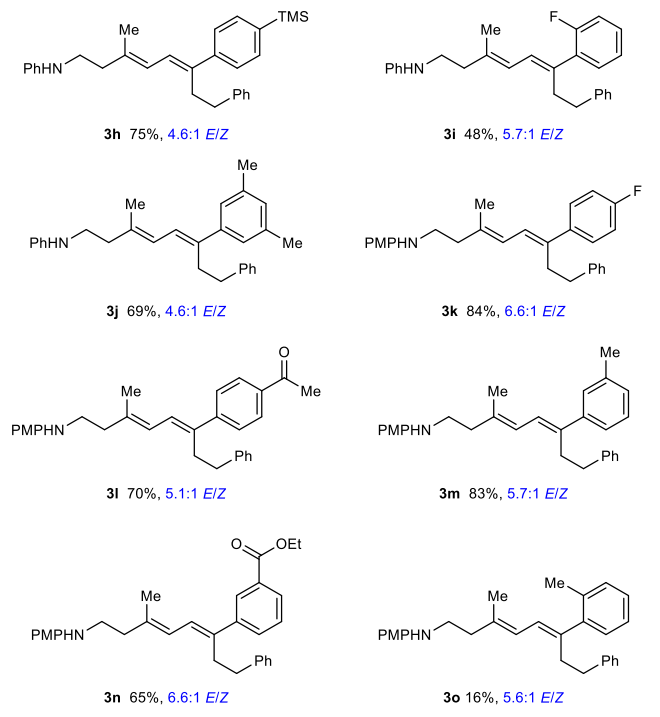
[a] Reactions were conducted with 0.30 mmol of **2a** and 100 mg of 3 Å molecular sieves. The *E*:*Z* ratios quoted after the yields are of a mixture of inseparable isomers obtained after purification. [b] Range of *E*:*Z* ratios of the crude mixtures as determined by ^{1}H NMR analysis. [c] The reaction was conducted with 0.26 mmol of **2a**.

With effective conditions in hand, the scope of the reaction with respect to the triazinane was examined in reactions with 1,3-enyne **2a** and $PhB(OH)_2$, which gave products **3a**–**3e** and **3g** in 52–74% isolated yield (Table 2). Column chromatography partially removed the minor *Z*-isomer along with unreacted **2a**. As well as triazinane **1a**, triazinanes containing *para*-methoxyphenyl or *para*-fluorophenyl groups reacted successfully to give 1,3-dienes **3b** and **3c**, respectively. A disubstituted aryl group on the triazinane was tolerated (**3d**), as was a methoxypyridyl group (**3e**). Finally, *N*-alkyltriazinanes were examined. Although 1,3,5-trimethyl-1,3,5-triazinane was ineffective (none of **3f** was obtained and unreacted **2a** was returned), the corresponding *N*-isopropyl analogue performed well to give 1,3-diene **3g** in 58% yield as a 6.8:1 mixture of *E*/*Z* isomers.

A range of different arylboronic acids with varying steric and electronic properties are tolerated in this process, as shown by their reactions with 1,3-enyne **2a** and either triazinane **1a** or **1b** (Table 3). For example, 1,5-(aryl)aminomethylation

Table 3 Scope of the boronic acid[a]



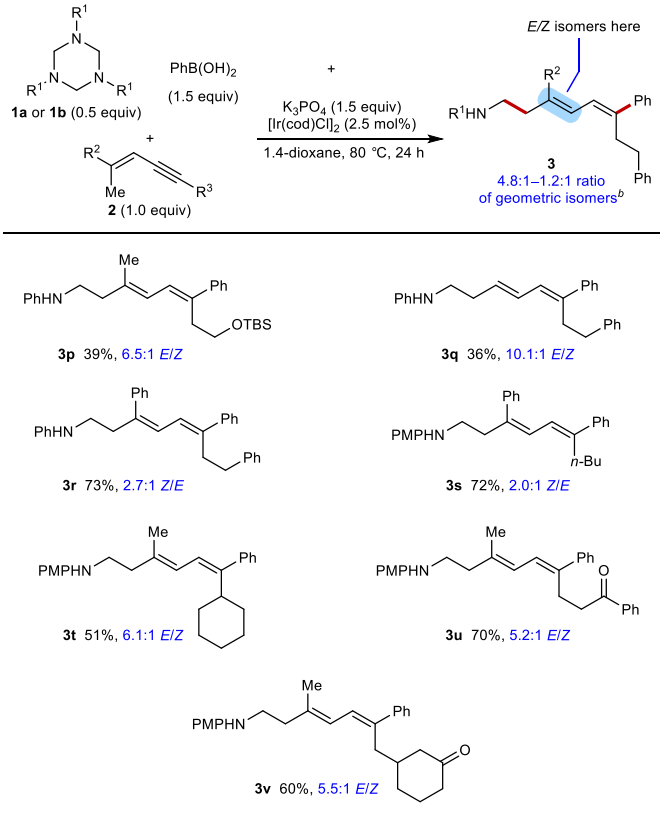


[a] Reactions were conducted with 0.30 mmol of **2a** and 100 mg of 3 Å molecular sieves. The *E*:*Z* ratios quoted after the yields are of a mixture of inseparable isomers obtained after purification. PMP = *para*-methoxyphenyl. [b] Range of *E*:*Z* ratios of the crude mixtures as determined by ^{1}H NMR analysis.

products were successfully obtained from reactions of arylboronic acids containing *para*- (**3h**, **3k**, and **3l**), *meta*- (**3m** and **3n**), or *ortho*-substituents (**3i** and **3o**). However, the yield of **3o** was only 16%, presumably because of steric hindrance. Attempted reactions using 1-phenylvinylboronic acid in place of arylboronic acids were unsuccessful, and only starting 1,3-enyne **2a** was recovered.

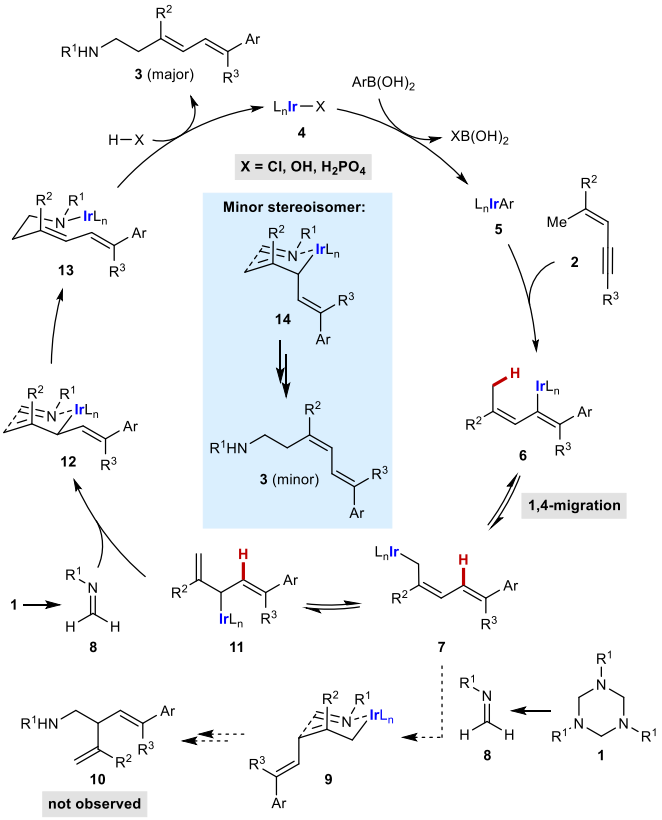
Finally, we investigated a range of 1,3-enynes in reactions with $PhB(OH)_2$ and either triazinane **1a** or **1b** (Table 4). As well as a phenethyl group (**3q** and **3r**; see also Tables 2 and 3), various other aliphatic substitutents at the alkynyl position R^3 are tolerated, including primary (**3p**, **3s**, **3u**, and **3v**) and secondary (**3t**) alkyl groups with functional groups such as a silyl ether (**3p**) or a ketone (**3u** and **3v**). When the substituent R^2 (*trans*- to the alkyne) was modified from a methyl group to a hydrogen atom (**3q**), the yield decreased but the stereoisomeric ratio increased. However, replacing this group with a phenyl group resulted in a higher yield at the expense of a lower stereoisomeric ratio (**3r** and **3s**). The presence of a methyl group *cis*- to the alkyne in the 1,3-enyne is essential for the reaction to proceed, as shown by the failure to provide any three-component coupling product from a 1,3-enyne without this structure feature.[15]

Table 4 Scope of the 1,3-enyne[a]



[a] Reactions were conducted with 0.30 mmol of **2** and 100 mg of 3 Å molecular sieves. The *E*:*Z* ratios quoted after the yields are of a mixture of inseparable isomers obtained after purification. PMP = *para*-methoxyphenyl [b] Range of ratios of geometric isomers of the crude mixtures as determined by ^{1}H NMR analysis.

A possible catalytic cycle for these reactions is shown in Scheme 2. After the formation of iridium complex **4**, which could have chloride, hydroxide, or phosphate counterions from the species present in the reaction,[16] transmetalation of **4** with the arylboronic acid gives aryliridium species **5**. Coordination of **5** with the 1,3-enyne **2**, followed by migratory insertion with the alkyne leads to alkenyliridium species **6**, which can undergo an alkenyl-to-allyl 1,4-iridium(I) migration[9] to give allyliridium species **7**. Although allylation of formaldimine **8** (derived from cracking of triazinane **1**) could occur with **7** through a chairlike conformation **9** to give 1,3-difunctionalized product **10**,[9] this mode of addition was not observed. Instead, **7** can undergo interconversion with allyliridium species **11** through a σ-π-σ isomerization. Now, allylation of **8** with **11** through a chairlike conformation **12**, in which the trisubstituted alkene occupies a pseudoequatorial position, gives the iridium amide **13**. Protonolysis of **13** releases the product **3** (major stereoisomer) and regenerates the active iridium complex **4**. The formation of the minor stereoisomer of **3** can be explained by allylation through an alternative conformation **14**, in which the trisubstituted alkene occupies a pseudoaxial position. This stereochemical model is consistent with the decreasing ratios of geometric isomers observed when R^2 changes from hydrogen to methyl to phenyl (see Table 4), as increasing the steric effect of this substituent will disfavor allylation through **12** because of increasing unfavorable non-bonding interactions of R^2 with the pseudoequatorial trisubstituted alkene. The formation of 1,5-difunctionalized products **3** rather than 1,3-difunctionalized



Scheme 2 Possible catalytic cycle

products **10** results from the imine employed, as cyclic imines give 1,3-difunctionalized products under similar conditions.[9] However, the reasons for this selectivity, which likely arises from energy differences between **9** and **12/14**, are currently not clear.

In conclusion, we have developed a novel iridium-catalyzed three-component coupling reaction of 1,3-enynes with arylboronic acids and formaldimines derived from triazinanes, to give multisubstituted 1,3-dienes. Key to the success of this reaction is an alkenyl-to-allyl 1,4-iridium(I) migration. This 1,5-(aryl)aminomethylation reaction complements more well-known hydroaminomethylation and hydroamidomethylation reactions[7,8] by forming two, rather one new carbon–carbon bond. Further work is ongoing in our laboratory to increase the scope of catalytic 1,4-metal migrations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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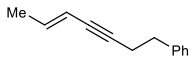
12 During our study of enantioselective rhodium-catalyzed three-component coupling of arylboronic acids, 1,3-enynes, and cyclic imines, $[Ir(cod)Cl]_2$ was found to be effective in providing racemic products. See ref. 9.

13 Assignment of the stereochemistry of the *E*/*Z* isomers was made on the basis of NOESY spectra. See the ESI for details.

14 The reason for the beneficial effect of 3 Å molecular sieves is not currently known.

15 The following 1,3-enyne did not provide any three-component coupling products under these conditions. For similar observations in Rh(III)-catalyzed oxidative annulations of 1,3-enynes, see refs. 10a and 10b.



16 The hydroxide counterions could arise from H_2O produced in the trimerization of the arylboronic acid to the boroxine.

