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$AgSbF_6$-controlled diastereodivergence in alkyne hydroarylation: facile access to *Z*- and *E*-alkenyl arenes†

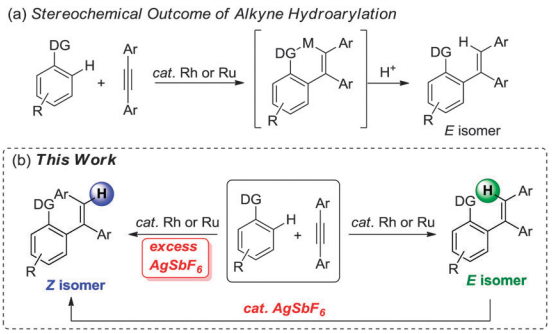
Minsik Min, Donghee Kim and Sungwoo Hong*

$AgSbF_6$-controlled diastereodivergent hydroarylation reactions were developed. Unprecedented and remarkable switching of the *E*/*Z*-stereoselectivity could be obtained by adjusting the $AgSbF_6$ loading.

The transition metal-catalyzed C–H bond functionalization is a rapidly evolving research field as atom and step-economical tools that are useful in organic synthesis and total synthesis. Among these processes, alkyne hydroarylation has been shown to be a highly efficient route for the synthesis of alkenyl arenes because it allows for the direct synthesis of functionalized alkenes directly from simple arenes and alkynes.[1,2]

Directing groups, such as amides, esters, ketones, carbamates, phosphine oxides, or sulfoxide-substituted aromatics, were shown to undergo hydroarylation with alkynes in the presence of ruthenium(II)[3] or rhodium(III)[4] complexes as catalysts, yielding trisubstituted alkenes. Recently, significant progress was made toward *E*-stereoselective (*syn* addition) coupling in hydroarylation reactions *via* a chelation-assisted concerted metalation–deprotonation pathway.[3,4] Subsequent coordinative insertion of the alkyne into the metal–carbon bond provides a metallacycle intermediate, which was then protonated by an organic acid to give the corresponding *E*-alkene derivative in a stereoselective manner (Scheme 1a).

Despite the successes reported thus far, this type of directing group-assisted hydroarylation approach has been limited to yielding the *E*-alkene products, and universal access to the *Z*-alkenyl arenes remains a distinct challenge. In this regard, new catalytic systems to override the directing group-controlled *E*-stereoselective coupling would be highly valuable for the efficient synthesis of *Z*-alkene products. During studies of transition metal-catalyzed hydroarylations of alkynes, we observed unprecedented switching in the *E*/Z-stereoselectivity through the action of $AgSbF_6$ under the reaction conditions (Scheme 1b). Herein, we describe a method



Scheme 1 Overall reaction scheme for the alkyne hydroarylation.

for $AgSbF_6$-controlled stereodivergence in a class of hydroarylation reactions between arenes and alkynes.

We began our investigation of the alkyne hydroarylation using chromones **1**, which are prevalent in a plethora of natural and bioactive compounds.[5] After surveying some potential catalytic systems,[6] we found that a catalytic system consisting of $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), and $AgSbF_6$ (16 mol%) in combination with $Cu(OAc)_2$ (10 mol%) and AcOH (2.0 equiv.) in 1,2-dichloroethane (DCE) at 100 °C provided **2a** in a 94% combined yield (Table 1, entry 1). The newly generated alkene was *E* configured, thus suggesting that the addition step proceeded in a *syn* manner. The catalyst system was found to be applicable to the reactions of chromones bearing useful substrate functional groups, and Table 1 outlines the scope of the hydroarylation reaction under the optimized reaction conditions. The use of chromones bearing substituents at the 6-position as substrates yielded a mixture of the *E* and Z configurations probably due to steric effects (entries 11, 12, 13). To our surprise, if the same reaction was carried out in the presence of additional 20 mol% of $AgSbF_6$, a completely different stereoisomeric pattern was observed, and the *Z*-selective products were obtained. The structure of the *Z*-isomer **3b** was unambiguously confirmed by X-ray crystallographic analysis.[6] This approach provides an attractive solution to the current limitations on the *E*-stereoselective coupling in the hydroarylation reactions. However, this method was not suitable for the hydroarylation of

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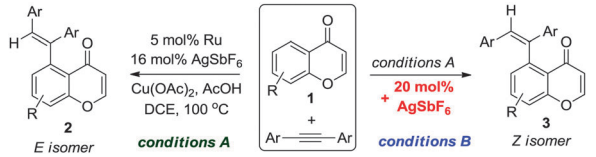
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc03602f

Table 1 Ruthenium-catalyzed hydroarylation of chromones[a]



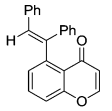
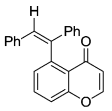
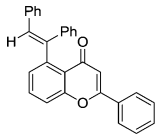
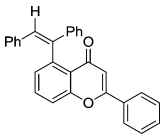
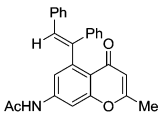
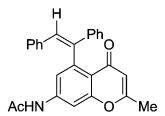
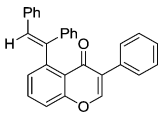
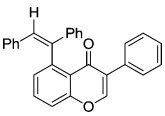
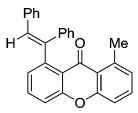
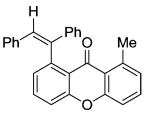
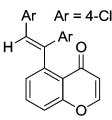
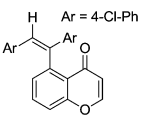
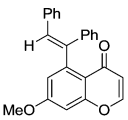
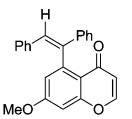
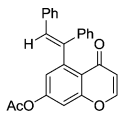
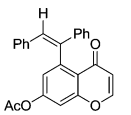
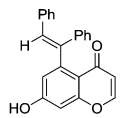
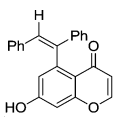
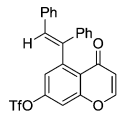
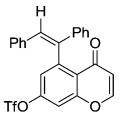
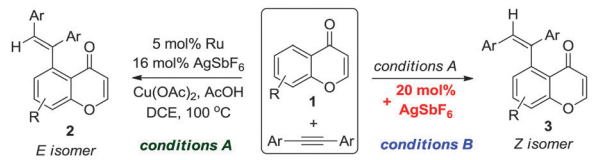
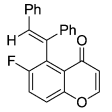
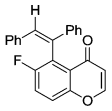
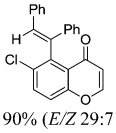
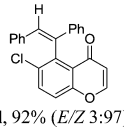
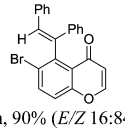
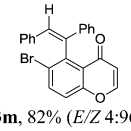
Entry	Condition A	Condition B
1	 **2a**, 94% (*E*/*Z* 91:9)	 **3a**, 87% (*E*/*Z* 8:92)
2	 **2b**, 87% (*E*/*Z* 91:9)	 **3b**, 82% (*E*/*Z* 7:93)
3	 **2c**, 83% (*E*/*Z* 92:8)	 **3c**, 63% (*E*/*Z* 19:81)
4	 **2d**, 82% (*E*/*Z* 91:9)	 **3d**, 78% (*E*/*Z* 10:90)
5	 **2e**, 80% (*E*/*Z* 90:10)	 **3e**, 66% (*E*/*Z* 7:93)
6[b]	 **2f**, 85% (*E*/*Z* 93:7)	 **3f**, 71% (*E*/*Z* 8:92)
7	 **2g**, 90% (*E*/*Z* 92:8)	 **3g**, 86% (*E*/*Z* 8:92)
8	 **2h**, 80% (*E*/*Z* 93:7)	 **3h**, 77% (*E*/*Z* 8:92)
9	 **2i**, 66% (*E*/*Z* 95:5)	 **3i**[6], 73% (*E*/*Z* 8:92)
10	 **2j**, 79% (*E*/*Z* 81:19)	 **3j**, 87% (*E*/*Z* 5:95)

Table 1 (*continued*)

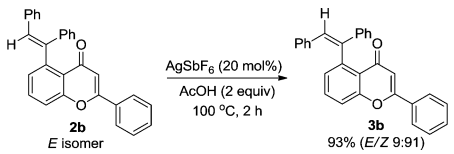


Entry	Condition A	Condition B
11	 **2k**, 92% (*E*/*Z* 60:40)	 **3k**, 91% (*E*/*Z* 5:95)
12	 **2l**, 90% (*E*/*Z* 29:71)	 **3l**, 92% (*E*/*Z* 3:97)
13	 **2m**, 90% (*E*/*Z* 16:84)	 **3m**, 82% (*E*/*Z* 4:96)

[a] Reactions were carried out under the following reaction conditions: chromone (1.0 equiv.), alkyne (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (16 mol% for condition A, 16 + 20 mol% for condition B), $Cu(OAc)_2$ (10 mol%), and AcOH (2 equiv.) in DCE at 100 °C for 2–6 h. [b] $[Ru(p\text{-cymene})Cl_2]_2$ (8 mol%), $AgSbF_6$ (28 mol% for conditions A, 28 + 20 mol% for conditions B). Isolated yields. DCE = 1,2-dichloroethane.

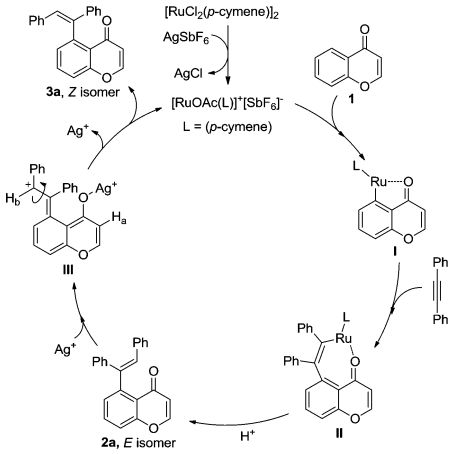
aliphatic alkynes, affording a mixture of the *E*- and *Z*-products (Scheme S1, ESI†).[6]

It is conceivable that the *Z*-alkene products arose from the isomerization of the *syn* addition products, and $AgSbF_6$ played a pivotal role in facilitating the isomerization process under the catalytic conditions employed here. To test this hypothesis, we investigated the isomerization reaction using the isomerically pure *E*-isomer **2b** as a substrate (eqn (1)). Among the Ag species screened, $AgSbF_6$ was the most effective catalyst for promoting isomerization.[6] The use of DCE as a solvent was necessary to achieve a high selectivity and reaction efficiency. No obvious effects on the isomerization were observed upon the addition of 2,6-di-*tert*-butyl-4-methyl-phenol (BHT), suggesting that a radical mechanism was unlikely to be operative.



(1)

We proposed a plausible catalytic mechanism for the hydroarylation of chromones (Scheme 2). Cationic Ru(II) species was prepared *in situ* upon treatment of the $[Ru(p\text{-cymene})Cl_2]_2$ precursor with the $AgSbF_6$ additive, and AgCl precipitated as a byproduct. A seven-membered ruthenacycle intermediate **II** was formed through coordinative insertion of the alkyne into the resulting aryl–Ru bond of the intermediate **I**. Protonolysis of the Ru–C bond of intermediate **II** afforded the *E*-alkene **2a**

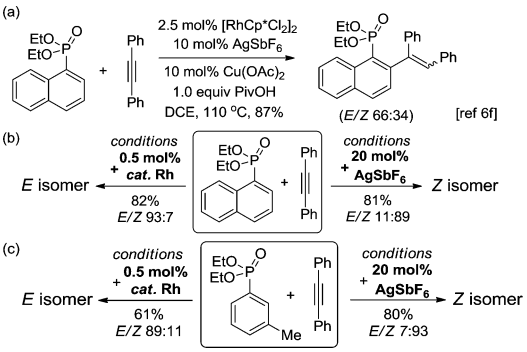


Scheme 2 Plausible reaction pathway.

and regenerated Ru(II). In the presence of an active $AgSbF_6$ species, the isomerization process would be expected to initiate through the formation of the alkyl cation **III** and bond rotation to drive the transformation of *E*-alkenyl chromone **2a** into the thermodynamically more stable *Z*-isomer **3a**. Both proton shifts (H_a and H_b) and ^{13}C NMR shift (C=O) revealed a good correlation with the π-electron densities of intermediate **III**.[6,7]

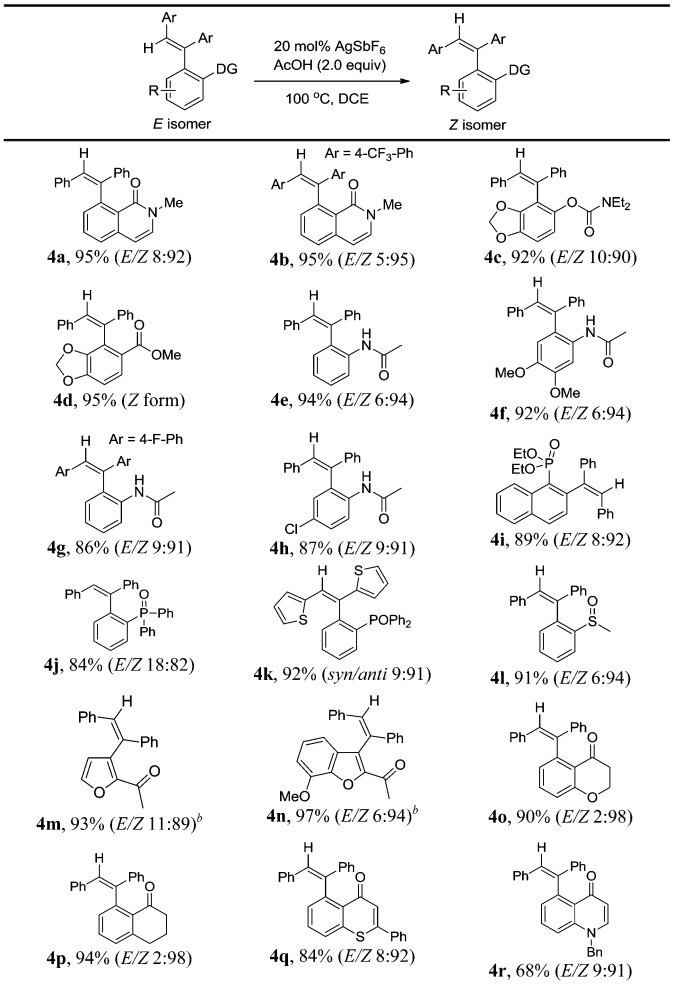
Recently, Glorius's group accomplished a phosphoryl-related directing rhodium catalyzed hydroarylation.[4f] It was reported that the use of phosphonate esters as the substrates yielded a mixture of olefinic *E*–*Z* isomers (Scheme 3a). Because the $AgSbF_6$-catalyzed alkene isomerization in DCE was observed in our study, it was reasoned that the *E*- and *Z*-mixture might have arisen from isomerization of the *E*-alkene by the action of the catalytically active $AgSbF_6$ species. This prediction was tested by conducting the hydroarylation reaction in the presence of additional 0.5 mol% $[RhCp^*Cl_2]_2$ under otherwise previously reported conditions. Indeed, the hydroarylation of the phosphonate ester substrates delivered the *E*-selective products. Furthermore, we were delighted to observe that the Rh-catalyzed hydroarylation of the phosphonate esters with alkynes allowed for the straightforward synthesis of the *Z*-selective products in the presence of additional 20 mol% $AgSbF_6$.

Next, the unusual effects of $AgSbF_6$ prompted us to investigate the generality of the phenomenon. As shown in Table 2, we explored the substrate scope of the transformation of the isomerically pure *E*-alkenyl arenes into the *Z* products. To our delight, this catalytic



Scheme 3 Rhodium-catalyzed hydroarylation.[6]

Table 2 Scope of the Ag-catalyzed isomerization reaction[a]



[a] Reactions were conducted with substrate (1.0 equiv.), $AgSbF_6$ (20 mol%), and AcOH (2 equiv.) in DCE at 100 °C. [b] $AgSbF_6$ (10 mol%) was used.

system was amenable to a variety of directing groups and permitted the construction of a series of *Z*-alkene-substituted arenes. In the majority of cases, high selectivity (>90%) was observed.

In summary, we developed a new protocol to effect alkyne hydroarylation in a stereodivergent manner. The remarkable switching of the product *E*–Z-stereochemistry was facilitated by an active $AgSbF_6$ species, which catalyzed the isomerization of the generated *E*-alkene.

This research was supported by National Research Foundation of Korea (NRF-2011-0016436) and the Institute for Basic Science (IBS) in Korea. M. Min is the recipient of a Global PhD Fellowship (NRF-2011-0007511).

Notes and references

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