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Abstract: An Ir(I)-system modified with a ferrocene derived bisphosphine ligand promotes α-selective arylation of styrenes by dual C-H functionalization. These studies offer a regioisomeric alternative to the Pd-catalyzed Fujiwara-Moritani reaction.

The intermolecular Heck reaction is the foremost method available for the C-H arylation of alkenes.[1] For processes involving styrenes, arylation occurs predominantly at the β-position.[1,2,3] In electronically predisposed cases, significant levels of α-arylation are observed,[4,5] but complete selectivity for C-C bond formation at this position can be achieved only under specialized conditions.[6,7] The related intermolecular Fujiwara-Moritani reaction, which is most effective in the presence of directing groups, operates under oxidative conditions and is attractive because it achieves C-H arylation of alkenes by dual C-H functionalization, thereby circumventing the preparation of an aryl (pseudo)halide (Scheme 1A).[8,9] The regioselectivity trends of this process mirror the Heck reaction, such that the method also does not provide a general approach to the α-selective arylation of styrenes. This type of selectivity has been observed in rare cases involving heteroarenes, but substrate scope is severely limited.[8,9] The paucity of general methods for direct styrene α-arylation often mandates multistep synthetic workarounds, thereby increasing cost, effort and waste.[10]

We have previously described Ir-catalyzed branch selective hydroarylations of styrenes with acetanilides 1 (DG = NHAc, Scheme 1B).[8,9] These processes were posited to occur via a sequence of carbonyl directed C-H activation (to I), alkene hydrometallation (to II) and C-C reductive elimination (to 3). In this report, we show that modification of the Ir-center with specific bisphosphate ligands alters the reaction outcome to provide a method for the α-selective arylation of styrenes (1 to 4). This new dual C-H functionalization method is regioisomeric with respect to the Fujiwara-Moritani and Heck reactions,[11,12] and previous Ir-catalyzed C-H alkenylation processes,[9,10] thereby providing proof-of-concept for a unique approach to the α-arylation of styrenes. Note that products mechanistically related to 4 have been observed as minor components in enamide C-H alkylation reactions.[11]

(A) Oxidative α-arylation of styrenes is challenging:

(B) α-Arylation of styrenes by Ir-catalyzed dual C-H functionalization:

Scheme 1. Introduction.

Natural abundance 13C kinetic isotope effect (KIE) experiments on our previously developed alkene hydroarylation reaction (1 to 3; DG = NHAc) are suggestive of a C-C reductive elimination pathway for the formation of 3 (see the SI).[8a,b,12,13] Accordingly, we reasoned that the proposed C-H alkenylation process outlined in Scheme 1B (1 to 4) requires a catalyst system that can enforce access to an alkene carbometallation manifold at the expense of the prevailing C-C reductive elimination pathway. It has previously been shown by Shibata and co-workers that styrene carbometallation occurs with complete branch selectivity using bisphosphine-ligated iridacycles derived from C-C bond activation of biphenylene.[14] Accordingly, if a carbometallative manifold could be accessed, then we expected high regioselectivity for the formation of III, which, in turn, would provide α-arylated styrene 4, rather than the corresponding β-arylated isomer (not depicted).

An assay of potential ligand systems was undertaken on the coupling of acetanilide 1a and styrene 2a using [Ir(cod)2OTf] as precatalyst and dioxane as solvent. From these studies, we observed that the use of dpf (L-1) afforded a 3.7 mixture of alkene 4aa and hydroarylation product 3aa, with the former generated in 23% yield. This prompted the evaluation of a variety of related ligand systems L2-L6, which were prepared in three steps from ferrocene (see the SI).[15] In general, the selectivity for alkénylation vs hydroarylation, and the yield of 4aa increased as the aromatic unit of the ligand became more electron poor, with...
L-4 providing 4aa in 24% yield and 8:2 selectivity over 3aa. However, L-5, which possesses highly electron withdrawing pentafluorophenyl units, did not provide 4aa, and instead a mixture of branched and linear hydroarylation products 3aa and iso-3aa formed. Ligand systems with more electron rich aromatic units, such as L-6, were not effective, and resulted in hydroarylation only. As L-4 provided the highest selectivity for 4aa, further optimization studies were undertaken using this ligand. Pleasingly, by increasing the reaction time to 72 hours we found that 4aa could be formed in 62% yield. The conversion of III to 4 releases an Ir(III)-dihydride, and, as indicated by GCMS analysis of crude reaction mixtures, turnover is achieved by reduction of a sacrificial equivalent of styrene to ethyl benzene. As such, we reasoned that oxidants other than styrene might offer additional improvements. In the event, by using 200 mol% t-butylethylene as an exogenous oxidant[9] and increasing the catalyst loading to 7.5 mol%, 4aa was formed with 10:2 selectivity over 3aa and could be isolated in pure form in 74% yield (further optimization studies with respect to the oxidant are detailed in the SI). For clarity, the product numbering system used in Table 1 is retained throughout subsequent discussion:

With optimized conditions in hand, we sought initially to explore scope with respect to the directing group (R², Table 2A). These studies revealed that a wide range of sterically distinct anilide-based systems can be employed (1b-i), such that 4aa-ia were all formed in good to excellent yield, with high selectivity over the corresponding hydroarylation product (3). Note that systems where R¹ = aryl are not suitable because competing ortho-selective hydroarylation of this unit predominates. The process tolerates diverse substitution on the anilide partner (Table 2B). Indeed, para-substituted systems engage efficiently (4oa-rb), and arenes possessing meta-substitution undergo highly regioselective C-H alkenylation at the less hindered ortho-position; for example, C-H arylation of styrene 2a with acetanilide 1m provided 4ma (65% yield) as a single regioisomer and with good selectivity over the corresponding hydroarylation product (5:1). The functional group compatibility of the process is good, with, for example, the potentially labile C-Br bond of 4oa remaining intact for further diversification. Ortho-substitution can impact selectivity; 4ra was formed with only 2:1 selectivity over 3ra, but generation of 4vb was highly selective. In all cases, the target products were easily separated from the minor hydroarylation products by column chromatography.

Using anilide 1f, we have assessed the scope of the alkenylation process with respect to the styrene partner (Table 3). Electronically diverse systems all participate with acceptable levels of efficiency; for example, para-fluoro system 4fd and para-methyl system 4fb were generated in 75% and 77% yield, respectively. An electronic trend is evident for alkenylation vs.

**Table 2.** Scope of the anilide component.*

| Entry | Ligand | Time (h) | X | Additive | Yield of 4aa* |
|-------|--------|----------|---|----------|---------------|
| 1     | L-1    | 24       | none | 37.0 | 23 |
| 2     | L-2    | 24       | none | 55.0 | 36 |
| 3     | L-3    | 24       | none | 64.0 | 44 |
| 4     | L-4    | 24       | none | 82.0 | 24 |
| 5     | L-5    | 24       | none | 0.55 | 0 |
| 6     | L-6    | 24       | none | 0.100 | 0 |
| 7     | L-7    | 72       | none | 8.29 | 62 |
| 8     | L-4    | 72       | t-butylethylene (200) | 10:2:0 | 74* |

* Yields and selectivities were determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as a standard. # Reaction run at 0.5 M. † Isolated yield.
hydroarylation selectivity (cf. 4fb vs 4fe), however, steric effects are more pronounced. Indeed, ortho-substitution on the styrene lowers product selectivity, such that fluoro system 4fj was formed with 2:1 selectivity over the corresponding hydroarylation product. Despite this modest selectivity, analytically pure 4fj could still be isolated in 50% yield. At the present stage, the process is applicable to styrenes only; alkyl substituted alkenes participate with low levels of efficiency with respect to both yield and product selectivity.

**Table 3. Scope of the styrene.**

| R | Yield | Notes |
|---|---|---|
| Me | 70% | 14:1 |
| Cl | 56% | 5:1 |

The anilide-based C–H alkenylation products are useful intermediates for synthesis, especially in heterocyclization processes. Treatment of the alkenylation products with POCI₃ effects smooth cycloaromatization to provide quinolines, as exemplified by the synthesis of 5a-d (Scheme 2A). Note that this de novo heteroaromatization strategy offers high levels of modularity, and its suitability for the construction of challenging polycyclic systems, such as 5c and 5d, is significant. The protocol even extended to the two-step conversion of estrone derived acetanilide 1w to the unusual quinoidal steroid 5e. Other classes of heterocyclization can also be achieved; treatment of 4aa with SelectFluor[19] or iodine[20] provided adducts 6 and 7, respectively (Scheme 2B). Free aniline 8 was accessed by acid hydrolysis of 4ha and could be converted in high yield to cinnoline 9 or dihydroquinoline 10, which possesses a tetrasubstituted stereocenter.

The C–H alkenylation processes outlined here represent proof-of-concept for a broader family of styrene α-arylation protocols. In preliminary efforts to extend the scope of our approach, we have assayed a selection of other aromatic partners leading to the observation that α-selective arylation using pyrrole 11a is feasible (Scheme 3A). Here, L-4 was not a suitable ligand, but, instead,
future challenge in the development of new processes. For pyrrole 11b, which is alylated at C3, C-H alkenylation to provide 12d was highly regioselective. Using L-4 we have also found that dehydrogenative C-C bond formation can be combined with a further dehydrogenation event. When enamide 13 was exposed to optimized conditions dehydrogenative aromatization (to 1n) was followed by C-H alkenylation, which provided 4na in 60% yield (Scheme 3B).[22]

It is pertinent to comment on mechanistic details of the processes described here. A control experiment involving reconstitution of dehydration product 3aa to optimized C-H arylation conditions did not provide alkene 4aa. This result supports the idea that 4aa is generated via a carbometallative pathway (I to III to 4 in Scheme 1B) rather than via dehydrogenation of 3aa. C-H arylation of deuterio-2c with acenitride 1q resulted in scrambling of the deuterium labels in product deuterio-4qc and in recovered deuterio-2c and 1q. This suggests that reversible styrene hydrometallation (I to II) is also operative under optimized conditions (Scheme 4). Accordingly, the minor alkene hydration products (e.g. 3aa) might arise via either C-C reductive elimination from II or C-H reductive elimination from III. At the present stage we have been unable to discriminate these pathways, such that meaningful rationalizations for product selectivity in each case cannot be made.

Scheme 4. A deuterium labelling study.

In summary, we outline a unique Ir-catalyzed method for the a-selective C-H arylation of styrenes. This dual C-H functionalization protocol offers a regioisomeric alternative to the well-established Pd-catalyzed Fujiwara-Moritani reaction. Efforts to broaden the utility of the method are ongoing and the results of these studies will be reported in due course.

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