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Enantioselective Synthesis of Substituted Indanones from Silyloxyallenes

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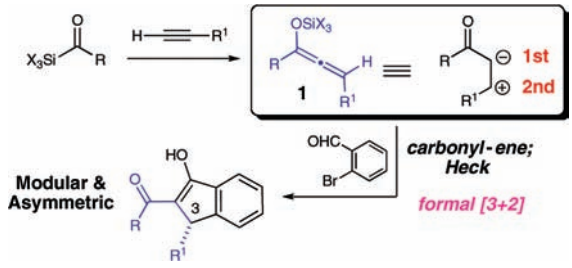
Chiral indane and indanone structures constitute the core of many pharmaceutical agents and natural products.[1] Consequently, new strategies for the stereoselective preparation of these privileged compounds from easily accessible precursors remains an important goal. The current arsenal of asymmetric approaches to access these compounds includes base-catalyzed 1,3-hydrogen rearrangements,[2a] enzymatic reductions,[2b] Negishi cross-couplings,[2d] intramolecular hydroacylations,[2e] Rh-catalyzed isomerizations[2f] and conjugate additions,[2g] and reductive Heck cyclizations.[2c] While these methods can be highly stereoselective, many tend to rely on a linear synthetic approach in which the asymmetry is introduced following installation of all the key atoms and/or construction of the basic indane core.[3] We envisioned a new modular strategy for the construction of chiral indanones by the union of appropriately substituted aryl aldehydes and silyloxyallenes in a two-step process based on a new formal [3 + 2] approach that involves an unusual transfer of stereochemical information (Scheme 1).

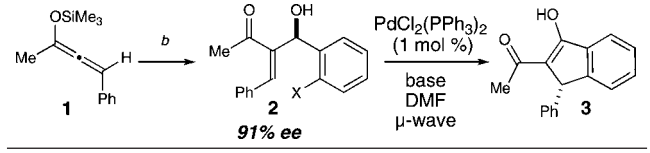
Scheme 1. Formal [3 + 2] Construction of Indanones



The asymmetric carbonyl−ene reaction of racemic silyloxyallenes provides functional-group-rich allylic carbinols with high levels of enantioselectivity.[4] These silyloxyallenes, which are easily prepared from acylsilanes and terminal alkynes,[4a] possess an initial nucleophilic component (enolsilane) that after addition to an electrophile generates a product possessing a versatile α,β-unsaturated ketone. Through the use of 2-substituted aromatic aldehydes in this process, a carbonyl−ene reaction[4b] coupled to an intramolecular Pd-catalyzed bond-forming process constructs substituted indanones with potential transfer of stereochemistry from the initial carbinol to the C3 position.[5] This controlled formal [3 + 2] approach leverages the inherent reactivity of silyloxyallenes and orchestrates their initial nucleophilicity and the subsequent electrophilic nature of the resulting intermediate to significant effect.

Our initial experiments began with the preparation of enantioenriched carbinol **2a** (91% ee) by the asymmetric carbonyl−ene reaction of racemic silyloxyallene **1a** and 2-bromobenzaldehyde.[4b,d] With this precursor in hand, the desired Heck cyclization was achieved in 15 min with 1 mol % Pd(II) in *N*,*N*-dimethylformamide (DMF) at 160 °C (microwave). Significant chirality transfer was observed (70% ee; Table 1, entry 1) despite the high reaction temperature. Lowering the reaction temperature to 120 °C in order to decrease the loss of optical activity adversely affected the yield while only mildly increasing the observed enantioselectivity (entry 2). From this temperature profile, it became evident that reaction temperatures of 140 °C or higher were necessary to achieve full conversion to the desired product. Additional 2-haloarylcarbinols for the Heck cyclization were explored (entries 4 and 5). Aryl chloride **2b** was unreactive under the reaction conditions (entry 4). Aryl iodide **2c** provided clean conversion to the product but lower levels of chirality transfer (53% ee; entry 5).

Table 1. Optimization of the Heck Cyclization[a]



entry	X	temp (°C)	base[c]	yield of **3** (%)[d]	ee (%)[e]
1	Br (**2a**)	160	Cy_2NMe	56	70
2	Br (**2a**)	120	Cy_2NMe	30	73
3	Br (**2a**)	140	Cy_2NMe	61	72
4	Cl (**2b**) (94%ee)	160	Cy_2NMe	0	0
5	I (**2c**) (90% ee)	160	Cy_2NMe	65	53
6	Br (**2a**)	140	Et_3N	53	52
7	Br (**2a**)	140	$^iPr_2NEt$	42	84
8	Br (**2a**)	**150**	**PMP**	**85**[f]	**91**

[a] Performed in a 2−5 mL microwave vial at 0.1 M for 15 min. [b] (*R*,*R*)-Cr(salen)SbF_6 (10 mol %), **1** (1.4 equiv), aldehyde (1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (20 mol %), CH_2Cl_2, −20 °C. [c] Two equivalents. [d] Isolated yield. [e] Determined by HPLC. [f] Reaction time 25 min.

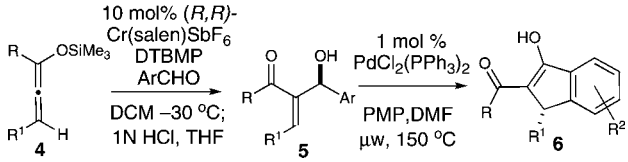
A survey of organic bases was then performed (Table 1, entries 6−8).[6] Ultimately, the hindered base 1,2,2,6,6-pentamethylpiperidine (PMP) provided the product with complete chirality transfer but slowed the reaction relative to other trialkylamines. Increasing the temperature to 150 °C and the reaction time to 25 min (entry 8) provided complete conversion with full transposition of asymmetry. Interestingly, the isolated starting material from incomplete reactions (entries 2 and 4) was recovered with no loss of optical activity during the reaction.

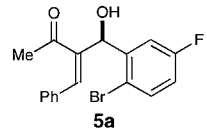
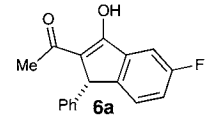
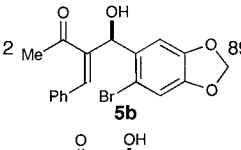
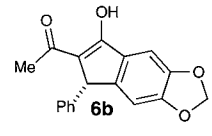
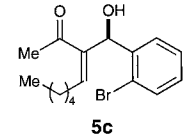
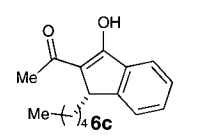
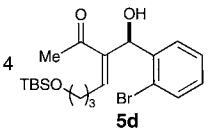
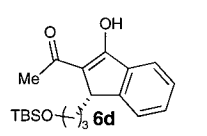
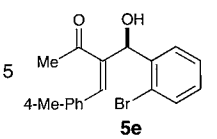
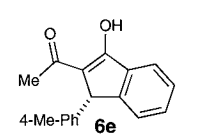
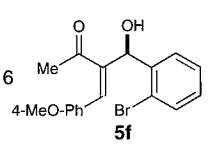
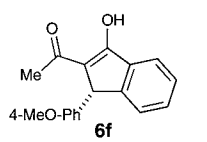
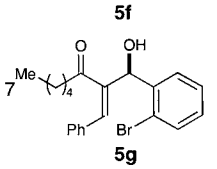
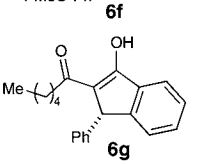
The substrate scope for the reaction is summarized in Table 2. A series of optically active carbinols (**5a**−**g**) were synthesized following the carbonyl−ene protocol. Variations of the aromatic portion as well as the alkene substituent were generated in high yields and enantioselectivities (79−91% ee). Electron-rich as well as electron-deficient aromatics performed equally well under the optimized Heck conditions, providing products with minimal erosion in optical activity. Aliphatic substitution on the alkene proceeded smoothly to the desired indanone, with only a mild decrease in enantioselectivity (entries 3 and 4). Varying the length of the ketone functionality (entry 7) furnished the carbonyl−ene product with slightly reduced enantioselectivity (86% ee) relative to that for the methyl ketone (91% ee), but excellent chirality transfer was observed during the unusual Heck cyclization.

Our current mechanistic model for this process involves intermediate **A** (Scheme 2). A reactive conformation that minimizes

10.1021/ja909669e

Table 2. Substrate Scope of the Formal [3 + 2] Cyclization



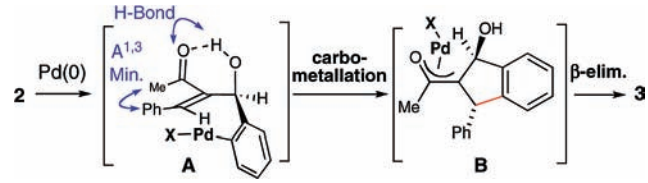
entry	ene product	yield[a] of 5 (ee)[b]	Heck product	yield[a] of 6 (ee)[b]
1	 **5a**	98 (91)	 **6a**	78 (90)[c]
2	 **5b**	89 (82)	 **6b**	75 (81)
3	 **5c**	91 (79)	 **6c**	70 (75)[c]
4	 **5d**	87 (82)	 **6d**	83 (76)[c]
5	 **5e**	71 (91)	 **6e**	92 (90)
6	 **5f**	85 (94)	 **6f**	77 (90)
7	 **5g**	70 (86)	 **6g**	84 (86)

[a] Isolated yield. [b] Determined by HPLC. [c] ee determined from a brominated analogue (see the Supporting Information).

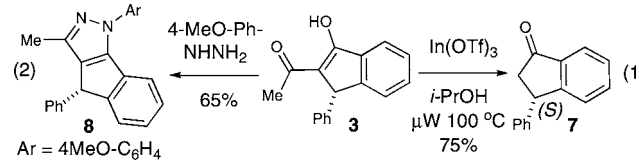
$A^{1,3}$ interactions[7] and induces a six-membered-ring hydrogen-bonded arrangement should direct carbometalation from the bottom face, as depicted. While this conformation twists the carbonyl group out of conjugation with the alkene, this orientation minimizes possible destabilizing interactions between the methyl group/carbonyl and the β-phenyl ring. The key carbometalation produces palladium enolate **B**, and β-hydride elimination installs the observed enol.[8] To probe the importance of hydrogen bonding for chirality transfer, the methyl ether of carbinol **2a** was employed as a substrate. The resulting Heck cyclization provided the methyl ether of indene **3** in 65% yield but only 14% ee.[9]

This new approach for the synthesis of indanones facilitates rapid access to related compounds in high enantioselectivity. The parent indanone **7** can be generated in 88% ee from **3** by an indium triflate-promoted retro-Claisen reaction (eq 1).[10] The presence of the 1,3-dicarbonyl system that is available directly from this new process

Scheme 2. Model for Stereochemical Transfer



provides rapid access to polycyclic heterocycles. For example, silyloxyallene **1a** can be converted to pyrazole **8** in only three steps from a silyloxyallene via chiral indene **3** (eq 2).



In conclusion, a new synthesis of enantioenriched indanones from racemic silyloxyallenes employing an asymmetric carbonyl−ene/intramolecular Heck cyclization strategy has been developed. This modular two-step procedure employs readily available coupling partners and succinctly delivers substituted carbocycles with excellent chirality transfer from optically active carbinol intermediates. The present work enhances the utility and versatility of silyloxyallenes as multifunctional reagents in organic synthesis, and the application of this indanone annulation strategy toward the synthesis of bioactive molecules is ongoing.

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Supporting Information Available: Experimental procedures, spectral data for new compounds, and crystallographic data for **8** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) (a) Reynolds, T. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15382. (b) Reynolds, T. E.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7806. (c) Reynolds, T. E.; Stern, C. A.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 2581. (d) The carbonyl−ene products (i.e., **5**) were purified by flash column chromatography and used as-is for subsequent Heck reactions. The *Z*/*E* ratio of these compounds was uniformly ≥20:1 as determined NMR spectroscopy (500 MHz).
(5) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.
(6) The use of inorganic bases or silver salts failed to provide any product.
(7) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(8) For proposed reaction pathways that invoke related Pd intermediates, see refs 2c and 2h.
(9) Presumably, PMP is less capable of disrupting H bonding. For the absolute stereochemical assignment, see the Supporting Information.
(10) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 7793. Accessing the parent indanone **7** by reductive cyclization affords only 78% ee (see ref 2c).

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