Total Synthesis

Deutsche Ausgabe: DOI: 10.1002/ange.201602024
Internationale Ausgabe: DOI: 10.1002/anie.201602024

Rapid Construction of a Benzo-Fused Indoxamycin Core Enabled by Site-Selective C–H Functionalizations

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Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday

Abstract: *Methods for functionalizing carbon–hydrogen bonds are featured in a new synthesis of the tricyclic core architecture that characterizes the indoxamycin family of secondary metabolites. A unique collaboration between three laboratories has engendered a design for synthesis featuring two sequential C–H functionalization reactions, namely a diastereoselective dirhodium carbene insertion followed by an ester-directed oxidative Heck cyclization, to rapidly assemble the congested tricyclic core of the indoxamycins. This project exemplifies how multi-laboratory collaborations can foster conceptually novel approaches to challenging problems in chemical synthesis.*

The functionalization of strong, unactivated carbon–hydrogen (C–H) bonds has loomed as a compelling challenge for organic chemistry in the last century and the present one, a "holy grail" of chemical reactivity[1] with the potential to broadly impact the chemical sciences. The collective effort to reduce organic chemistry's historic overreliance on the activating effects of preexisting functional groups by directly functionalizing unactivated C–H bonds has made impressive strides.[2] However, this rapidly growing field remains far from mature and continues to be challenged by the intrinsic difficulty of achieving site-selective C–H functionalizations in organic compounds replete with C–H bonds, as well as the need for an expanded set of new, reliable methods.[3]

The diverse and intricate structures of natural products have provided challenging molecular contexts for probing the capabilities of C–H functionalization reactions.[4] Prior syntheses of dihydroconessine (Corey, 1958),[5] aldosterone acetate (Barton, 1960),[6] cephalosporin C (Woodward, 1966),[7] and pantalenolactone E methyl ester (Taber, 1985)[8] are among the forerunners of a growing family of achievements[9] in natural product synthesis (Figure 1)[10] that were also highly reliant on pattern recognition[11] enabled by C–H functionalization logic.[9a,12]

Sato and co-workers isolated[13] the indoxamycins (Figure 2) from a marine actinomycete and elucidated their highly substituted, *cis-peri*-fused[14] 6,5,5-tricyclic frameworks. The pioneering synthesis of (±)-indoxamycin B (**2** and *ent*-**2**) by the Carreira laboratory[15] corrected the original assign-

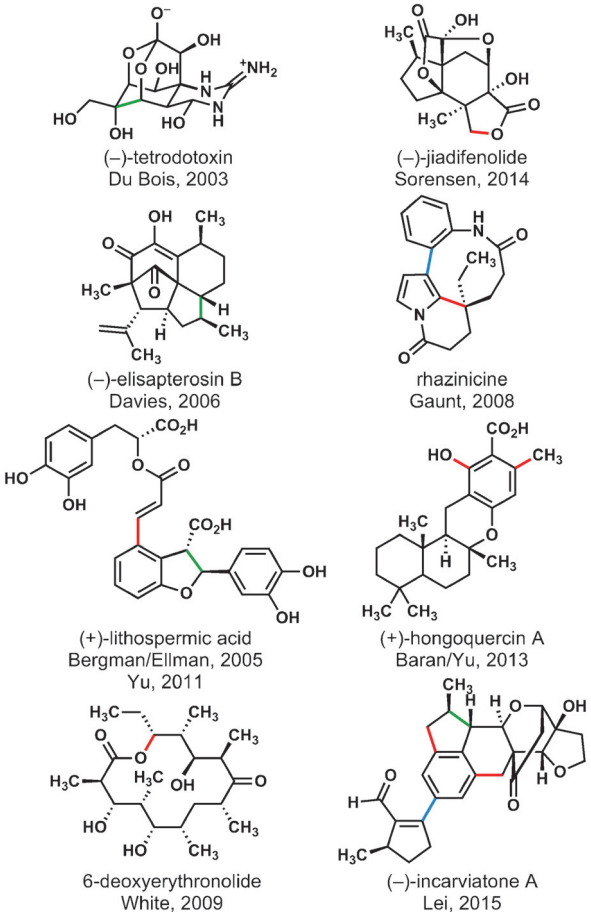

Figure 1. Selected targets in total synthesis featuring C–H functionalizations as key steps. Green: Dirhodium-catalyzed carbene insertion. Blue: Rhodium-catalyzed amination. Red: Palladium-catalyzed functionalization. Pink: Rhodium-catalyzed alkylation. Light blue: Iridium-catalyzed borylation.

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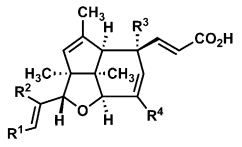
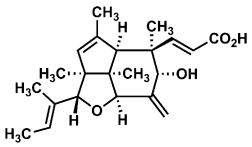
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201602024.



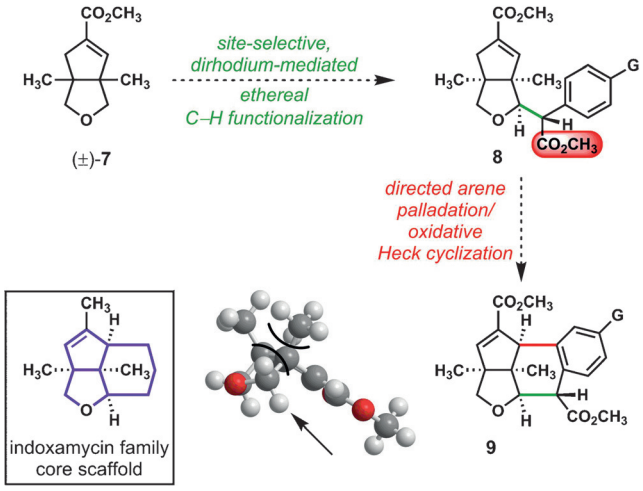
(–)-indoxamycins A-E

A (**1**): $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = CH_3$, $R^4 = CH_3$
B (**2**): $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = CH_2OH$, $R^4 = CH_3$
C (**3**): $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = CH_3$, $R^4 = CH_2OH$
D (**4**): $R^1 = CH_3$, $R^2 = CH_2OH$, $R^3 = CH_3$, $R^4 = CH_3$
E (**5**): $R^1 = CH_2OH$, $R^2 = CH_3$, $R^3 = CH_3$, $R^4 = CH_3$



(–)-indoxamycin F
(**6**)

Figure 2. The indoxamycin family of secondary metabolites.



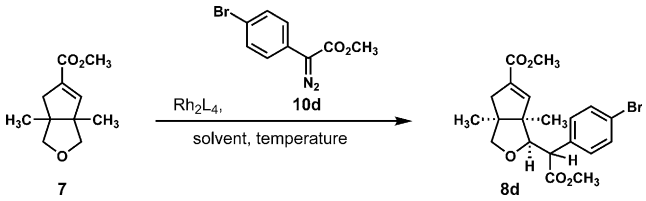
Scheme 1. An approach to the indoxamycins enabled by site-selective C–H functionalizations.

ment of the relative stereochemistry and was followed by the syntheses of Ding and co-workers, culminating in family-wide stereochemical revisions.[16] In contrast to these prior efforts, which constructed the indoxamycin *cis-peri*-fused 6,5,5-tricyclic skeleton from monocyclic building blocks, our retrosynthetic analysis (Scheme 1) was founded on the idea that the six-membered ring and the left-most alkene side chain of the indoxamycins could arise from a reaction sequence featuring site- and diastereoselective C–H functionalizations on the rigid bicyclo[3.3.0]octane **7**. An intermolecular donor/acceptor carbene C–H insertion, mediated by a dirhodium catalyst as developed by the Davies group,[17] would directly establish the first key stereocenter from a pseudo-symmetric intermediate (**7**→**8**, Scheme 1). An appealing, yet unprecedented carboxyl-directed arene palladation/Heck cyclization sequence (**8**→**9**), inspired by previous reports,[18] might then complete a rapid construction of the 6,5,5-tricyclic skeleton. Finally, we envisioned that a second site-selective intermolecular metal carbene C–H insertion[19] would occur on the convex face of the tricyclic core in **9** and permit the late-stage elaboration of the trisubstituted alkene.

Toward realizing this bold plan for synthesis, enoate **7** was found to be readily accessible from known compounds in three steps (see the Supporting Information).[20] Preliminary studies with simple, achiral dirhodium tetracarboxylates (Table 1, entries 1 and 2) demonstrated little to no C–H insertion reactivity, resulting only in the decomposition of **10** and recovery of the unreacted bicyclic ester **7**. Previously established conditions known to favor ethereal C–H insertions of donor/acceptor carbenes[17,21] suggested Rh_2(DOSP)$_4$[22] and Rh_2(PTAD)$_4$[23] as most likely to effect the desired transformation. Indeed, when (±)-**7** was treated with two equivalents of donor/acceptor diazo compound **10d** in the presence of Rh_2[(*S*)-DOSP]$_4$, the C–H insertion product **8d** was formed in 39% yield with a 20:1 diastereomeric ratio (d.r.) of the benzylic epimers (entry 3). Nuclear Overhauser effect (NOE) measurements confirmed that the C–H insertion of the rhodium-bound carbene had taken place adjacent to the tetrahydrofuranyl oxygen atom on the concave face of the bicyclo[3.3.0]octane scaffold (proximal to the α,β-unsaturated ester and away from the ring-junction methyl groups), but were insufficient to determine the configuration of the benzylic stereocenter.

In light of prior observations,[17,24] this result invited the interesting possibility of a kinetic resolution of (±)-**7** in the course of a carbene C–H insertion. To test this idea, enantioenriched (>97% *ee*) (+)-**7** and (–)-**7** (see the Supporting information) were independently subjected to the previously established reaction conditions in the presence

Table 1: Preliminary C–H insertion results with **7** and catalyst matching studies.[a]



Entry	**7**	L	Solvent (v/v, *T*)	Conv. of **7** [%] (into **8**)	d.r. (**8**)
1	(±)-**7**	OAc	DMB[b] (55 °C)	not observed	–
2	(±)-**7**	TFA	DMB[b] (55 °C)	not observed	–
3	(±)-**7**	(*S*)-DOSP	DMB/TFT (1:1, 55 °C)	49 (79)	20:1
4	(–)-**7**	(*S*)-DOSP	DMB/TFT (2:1, 55 °C)	56 (32)	1:2.1
5	(–)-**7**	(*R*)-DOSP	DMB/TFT (2:1, 55 °C)	79 (86)	6.4:1
6	(+)-**7**	(*S*)-PTAD	DMB/TFT (2:1, 55 °C)	95 (100)	>20:1
7	(–)-**7**	(*S*)-PTAD	DMB/TFT (2:1, 55 °C)	50 (100)	5:1
8	(±)-**7**	(*S*)-DOSP	TFT (80 °C)	25 (100)	20:1
9	(+)-**7**	(*S*)-PTAD	TFT (55 °C)	79 (92)	13:1
10	(±)-**7**	(*S*)-DOSP	isooctane/TFT (2:1, 55 °C)	22 (95)	>20:1
11	(+)-**7**	(*S*)-PTAD	isooctane/TFT (2:1, 55 °C)	72 (97)	>20:1
12	(+)-**7**	(*S*)-PTAD	isooctane/TFT (2:1, 75 °C)	51 (94)	15:1

[a] Concentration: 0.05 M; conversion and d.r. values determined by ^{1}H NMR spectroscopy. [b] A trace of α,α,α-trifluorotoluene was added for solubility. DOSP = 1-[(4-dodecylphenyl)sulfonyl]-(2*S*/*R*)-prolinate, PTAD = *N*-phthaloyl-(*S*/*R*)-adamantylglycine, TFA = trifluoroacetic acid.

of a single enantiomer of the dirhodium catalyst, and the conversion into the insertion product was analyzed by ^{1}H NMR spectroscopy. The outcomes (Table 1, entries 4–7) display a significant matching effect for both $Rh_2(DOSP)_4$ and $Rh_2(PTAD)_4$, particularly with the latter catalyst; the pairing of (+)-**7** with Rh_2[(*S*)-PTAD]$_4$ provided 95% conversion into C–H insertion adduct **8d** with >20:1 d.r. (entry 6).

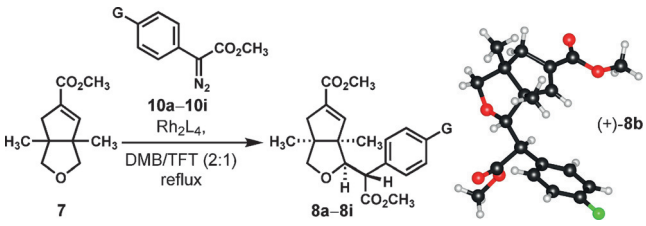
The inert, non-polar reaction medium offered by 2,2-dimethylbutane (DMB) was favored for reliably high diastereomer ratios; however, the reactions using this solvent also required the addition of small amounts of α,α,α-trifluorotoluene (TFT) to increase the solubilities of **10** and the dirhodium catalyst. The limited temperature range and currently unresolved shortage in the commercial supply of DMB led us to increase the fraction of TFT. However, in these reactions, lower conversions and diastereomer ratios were observed (Table 1, entries 8 and 9). Replacing DMB with readily available 2,2,4-trimethylpentane (isooctane) permitted increased reaction temperatures with a concomitant decrease in conversion (entries 10–12). Increased equivalents of reagent **10** were also ineffective in producing higher yields. Ultimately, two equivalents of diazo reagent **10** and a solution of DMB and TFT in a ratio of 2:1 were chosen as the optimal trade-off between DMB volume, conversion, and diastereoselectivity.

To survey the scope of this transformation, a number of substituted phenylacetic acid derivatives were prepared[21,25] and subjected to the aforementioned conditions. Only the parent methyl phenyldiazoacetate and select derivatives were found to be competent reaction partners (Table 2); diazo compounds bearing strongly electron-donating or most electron-withdrawing groups, substituents at the 2- or 3-positions, or multiple substituents (not shown) failed to produce the desired C–H functionalization adducts, giving instead a mixture of unreacted **7** and products consistent with dimerization of the diazo compound. Methyl phenyldiazoacetate (**10a**) and the derivatives **10b**–**10e** proved to be efficient coupling partners, providing **8a**–**8e** in good to excellent yields and diastereomeric ratios (Table 2, entries 1–5). X-ray crystallographic analysis of (+)-**8b** confirmed the relative and absolute stereochemical assignment shown in Table 2. Aryl triflate **10f** and pinacol boronate **10g** (entries 6 and 7) are complementary to **10d** and **10e** as they provide versatile handles for post-C–H functionalization bond formations. Importantly, this provided access to insertion adduct **8j** (see the Supporting Information) as the corresponding methyl (4-methoxyphenyl)diazoacetate proved to be an unsuccessful coupling partner. Although many of the most common electron-withdrawing groups are not compatible with the dirhodium-catalyzed functionalization conditions, **10h** and **10i** were found to be sufficiently reactive in this context (entries 8 and 9).

Work in the area of directed arene functionalization by Yu and co-workers[18,26] suggested that it should be possible to exploit the phenylacetic acid moiety in **8a**–**8j** to direct an *ortho* functionalization of the arene. Surprisingly, to the best of our knowledge, no reports existed describing the application of palladium-catalyzed, directed C–H functionalization as a trigger for Heck cyclizations. Efforts to apply potassium carboxylate directed olefination conditions[10h,18e,27] proved unsuccessful, as the corresponding substrates (not shown) did not undergo the desired Heck cyclization.

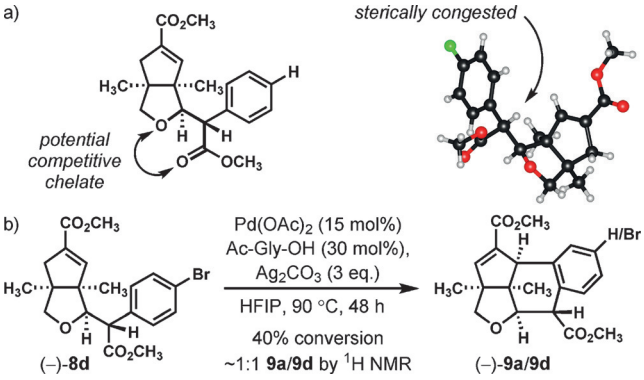
Several general challenges to the successful cyclization of **8a**–**8j** stood out as potential malefactors. Most prominent was the potential for catalyst inhibition through the formation of a bidentate chelate comprising the phenylacetic ester carbonyl group and the β-oxygen atom of the tetrahydrofuran ring (Scheme 2a). Also of concern was the congested steric environment adjacent to the phenylacetic ester moiety, which would need to accommodate a large, ligated palladium species over the course of the transformation. Additional concerns regarding the accessibility of reactive geometries were ameliorated by low-level conformation analysis suggesting that should palladation occur, achieving productive trajectories for cyclization would be possible. Indeed, ring

Table 2: Catalyst selectivity and substrate scope of the rhodium carbenoid insertion with **7**.[a]



Entry	7	10	G	L	Yield [%]	d.r.[b]
1	(−)-**7**	**10a**	H	(*R*)-PTAD	55	>20:1
2	(−)-**7**	**10b**	F	(*R*)-PTAD	56	>20:1
3	(+)-**7**	**10c**	Cl	(*S*)-PTAD	76	>20:1
4	(+)-**7**	**10d**	Br	(*S*)-PTAD	86	>20:1
5	(+)-**7**	**10e**	I	(*S*)-PTAD	52	19:1
6	(+)-**7**	**10f**	OTf	(*S*)-PTAD	74[c]	>20:1
7[d]	(−)-**7**	**10g**	Bpin	(*R*)-PTAD	64	9:1
8	(+)-**7**	**10h**	CF_3	(*S*)-PTAD	51	>20:1
9[e]	(+)-**7**	**10i**	CO_2CH_3	(*S*)-PTAD	55	17:1

[a] Concentration: 0.05 M; yields refer to isolated products after column chromatography on silica gel. [b] Ratio of the benzylic epimers. [c] Determined ^{1}H NMR spectroscopy, product inseparable from the dimerization products derived from **10**. [d] At 0.025 M owing to the solubility of **10g**. [e] DMB/TFT/CH_2Cl_2 (2:3:1), 0.025 M owing to the solubility of **10i**. pin = pinacolato, Tf = trifluoromethanesulfonyl.



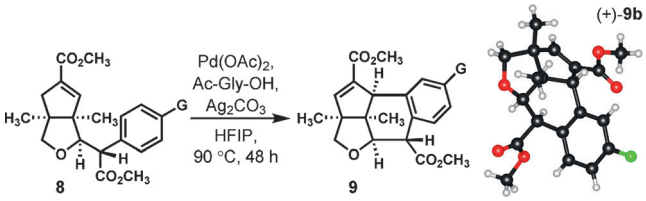
Scheme 2. a) Postulated obstacles to the successful cyclization of compounds **8a**–**8j**. b) Preliminary result for the successful cyclization of **8d**.

formation was anticipated to be diastereoselective, as approach of the arene from the convex face of the bicyclo-[3.3.0]octane system should be geometrically impossible.

Ongoing work to develop and exploit weakly coordinating directing groups[18d] resulted in the recent disclosure of conditions for an ester-directed intermolecular olefination of arenes.[28] Bearing the aforementioned concerns in mind, **8d** was subjected to these conditions, which led to the formation of the tetracyclic cyclization products **9a** and **9d** as an approximately 1:1 mixture (Scheme 2b). To the best of our knowledge, the successful execution of this directed C–H palladation/Heck cyclization sequence represents the first of its kind and is particularly noteworthy given the rigorous structural and steric demands imposed by the substrate.

Inspired by this success, we subjected **8a** to similar reaction conditions and found that it reacted with much greater efficiency (Table 3, entry 1). Compounds **8b–8e** were

Table 3: Substrate scope of the intramolecular oxidative C–H palladation/Heck cyclization.[a]



Entry[a]	8	G	Yield (BRSM) [%]	d.r.
1	**8a**	H	50 (79)	>20:1
2	**8b**	F	11 (23)	>20:1
3	**8c**	Cl	22 (55)	>20:1
4	**8d**	Br	37[b]	>20:1
5	**8e**	I	not observed	–
6	**8f**	OTf	<5	–
7	**8g**	Bpin	–	–
8	**8h**	CF_3	7 (35)	>20:1
9	**8i**	CO_2CH_3	16 (55)	>20:1
10	**8j**	OCH_3	40 (68)	>20:1

[a] $Pd(OAc)_2$ (20 mol%), Ac-Gly-OH (40 mol%), Ag_2CO_3 (3 equiv), 0.1 M. Yields refer to the isolated products; values based on the recovered starting materials are given in parentheses. [b] 1.6:1 ratio of **9a**/**9d**. HFIP = hexafluoroisopropanol.

subjected to analogous cyclizations with mixed results (entries 2–5), consistent with prior observations of reactivity.[28] The carbon–halogen bonds of **8b** and **8c** proved to be inert under the Pd^{II}/Pd^0 cycle, but the substrates failed to exhibit significant cyclization reactivity. X-ray crystallographic analysis of (+)-**9b** confirmed the stereochemical assignment shown in Table 3. Under the same conditions, **8d** reluctantly underwent cyclization with concomitant (incomplete) protodebromination to provide an inseparable mixture of **9a** and **9d**. The carbon–iodine bond of **8e** was fully reduced, leading to the sole isolation of **8a**. Attempts to effect the C–H palladation/Heck cyclization of **8f** and **8g** were also unsuccessful (entries 6 and 7), but did allow for the recovery of unreacted starting material. The electron-deficient insertion products **8h** and **8i** (entries 8 and 9) provided low to moderate yields of their corresponding tetracycles. Conversely, electron-rich, 4-methoxy-substituted **8j**, could be cyclized with better efficiency (entry 10).

Herein, we have reported a conceptually novel approach toward the core of the indoxamycin family of natural products. This design centered on the application of logic enabled by chemical methods for C–H functionalization. We have described a highly regio- and diastereoselective dirhodium tetracarboxylate catalyzed C–H insertion, which forges the first key carbon–carbon bond of the indoxamycin core, ensuing studies exploring a significant matched/mismatched catalyst effect, and the scope of competent donor/acceptor diazo compounds. The successful *ortho* functionalization of substituted benzenes with a weakly coordinating ester directing group[28] in the context of a ring-forming Heck cyclization represents, to the best of our knowledge, the first reported observation of this reactivity in a complex setting. Efforts to achieve the third, and final, planned C–H functionalization are currently underway and will be reported in due course.

Acknowledgements

This work was supported by the CCI Center for Selective C–H Functionalization (CCHF; CHE-1205646) and Princeton University. We gratefully thank the members of the NSF-CCHF for their insight and helpful discussions, Dr. Neal Byrne and Dr. Christina Kraml of Lotus Separations for the separation of the enantiomers of **7**, and Dr. Phillip Jeffrey for assistance with the X-ray crystallographic analysis of **8b** and **9b**.

Keywords: C–H bond activation · natural products · palladation · rhodium carbenes · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8270–8274
Angew. Chem. **2016**, *128*, 8410–8414

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Received: February 26, 2016
Published online: May 20, 2016

