OL Organic Letters

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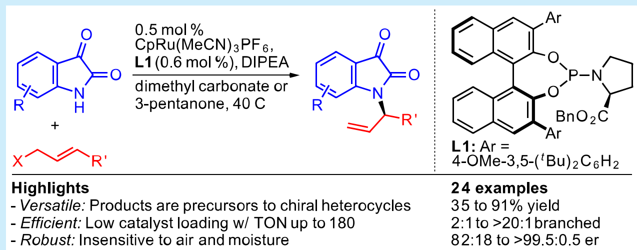
Ruthenium-Catalyzed Asymmetric Allylic Alkylation of Isatins

Barry M. Trost,* Christopher A. Kalnmals,[§] Divya Ramakrishnan,[§] Michael C. Ryan, Rebecca W. Smaha, and Sean Parkin

Cite This: *Org. Lett.* 2020, 22, 2584–2589 Read Online

ABSTRACT: A new ruthenium-based catalytic system for branched-selective asymmetric allylic alkylation is disclosed and applied to the synthesis of chiral isatin derivatives. The catalyst, which is generated *in situ* from commercially available CpRu(MeCN)$_3$PF$_6$ and a BINOL-derived phosphoramidite, is both highly active (TON up to 180) and insensitive to air and moisture. Additionally, the *N*-alkylated isatins accessible using this methodology are versatile building blocks that are readily transformed into chiral analogs of achiral drug molecules.



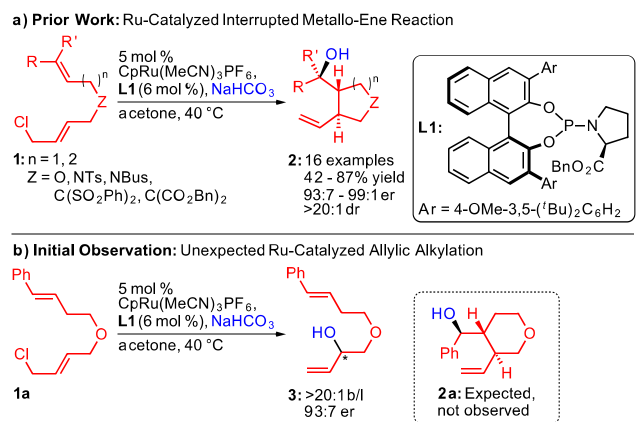
Asymmetric allylic alkylation (AAA) is a powerful technique for the enantioselective formation of carbon—carbon and carbon—heteroatom bonds. With unsymmetrically substituted electrophiles, linear and branched products can form and while the regioselectivity can be tuned using ligands, it is typically dictated by the metal. Although many metals can catalyze allylic alkylations, palladium and iridium are the most widely used. While both metals tolerate a broad range of nucleophiles, they exhibit complementary regioselectivity; Pd-catalyzed allylic alkylations are typically linear-selective, whereas branched products are favored with iridium.[1]

Although iridium is the most frequently used metal for branched-selective allylic alkylation,[2] ruthenium is an attractive alternative; while both metals can catalyze branched-selective allylic alkylations with carbon and heteroatom nucleophiles, ruthenium is roughly six times cheaper than iridium.[3] Curiously, while the use of ruthenium in branched-selective allylic alkylation[4] predates the use of iridium,[5] the former has received considerably less attention.[6]

As part of our ongoing interest in transition-metal-catalyzed cycloisomerization reactions,[7] we recently developed a novel ligand **L1** that, in conjunction with CpRu(MeCN)$_3$PF$_6$, catalyzed a stereoselective interrupted metallo-ene reaction that transformed 1,6- and 1,7-chlorodienes **1** into five- and six-membered rings **2** (Scheme 1a).[8] During these studies, we discovered that our Ru/**L1** system could also function as an allylic alkylation catalyst. When **1a** was subjected to the standard cycloisomerization conditions, none of the expected product **2a** was observed, but allylic alcohol **3** formed as a single regioisomer in a promising 93:7 er (Scheme 1b).

Intrigued by this result, we set out to investigate this unexpected reactivity more closely. We were particularly interested in evaluating nitrogen nucleophiles, which in contrast to carbon[9] and especially oxygen nucleophiles[10,11] have only been used a handful of times in intermolecular Ru-

Scheme 1. Summary of Prior Work and Initial Results

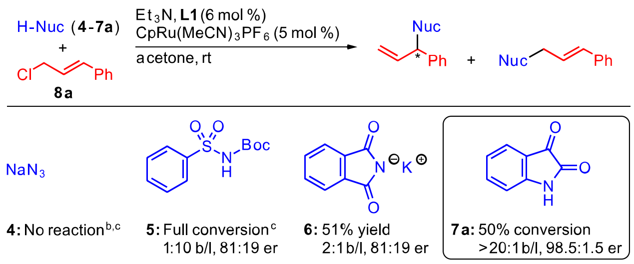


AAA reactions.[12,13] Using cinnamyl chloride (**8a**) as a model electrophile, we initiated our screening with sodium azide (**4**) but observed no reaction, even at 40 °C (Scheme 2). Switching to *N*-Boc sulfonamide **5** gave full conversion, and while the linear regioisomer was favored, the branched product was isolated in 81:19 er. With potassium phthalimide (**6**), regioselectivity improved to 2:1 in favor of the branched product, while enantioselectivity remained the same. Gratifyingly, with isatin (**7a**), near-perfect regioselectivity was observed, and while the conversion based on the nucleophile

Received: February 7, 2020
Published: March 23, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00504
Org. Lett. 2020, 22, 2584–2589

Scheme 2. Evaluation Nitrogen Nucleophiles[a]



[a]All reactions at 0.05 mmol scale at 0.5 M. Yields are isolated yields of pure branched isomer. Conversion and branched–linear (b/l) ratios determined by crude ^{1}H NMR; er determined by chiral HPLC. [b]Room temperature to 40 °C. [c]Without Et_3N.

was only 50%, the branched product was obtained in 98.5:1.5 er.

While the excellent regio- and enantioselectivity were certainly encouraging, we were excited by this result for a variety of other reasons. In addition to being versatile synthetic intermediates,[14] isatins and isatin derivatives are common motifs in biologically active molecules.[15] Furthermore, while isatins are common substrates for asymmetric catalysis, most transformations target the highly electrophilic C3 carbonyl;[16] general asymmetric methods that utilize isatins as nucleophiles are rare.[17,18]

Having identified isatin as a promising nucleophile for further study, we set out to optimize the reaction conditions (Table 1). Changing the solvent from acetone (entry 1) to either DCE (entry 2) or THF (entry 3) did not improve conversion of **7a**, and while excellent regioselectivity was maintained, enantioselectivity dropped slightly. Curiously, while incomplete conversion of **7a** was observed regardless of the solvent, the electrophile (**8a**) was always fully consumed. Examination of the crude reaction mixtures revealed significant amounts of triethylammonium salt **10**, suggesting that a side reaction between the base and the allylating agent was responsible for the low yields of **9aa**.

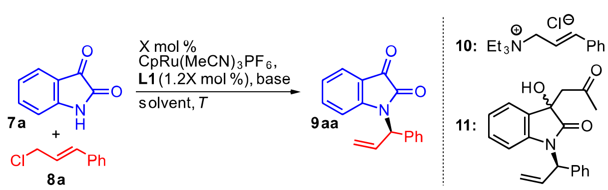
Fortunately, this undesired pathway, which occurred without the catalyst,[19] could be mitigated by using a different base. Whereas Cs_2CO_3 afforded a complicated mixture of products, simply replacing triethylamine with DIPEA enabled complete conversion of both reaction partners and led to substantially increased yields of **9aa**, even at reduced catalyst loadings (entries 4 and 5). Fortunately, these changes had no impact on either regio- or enantioselectivity.

While acetone was optimal for selectivity, we found that reactions in this solvent were often accompanied by the formation of aldol product **11**, resulting in diminished yields of **9aa**. We hypothesized that by using a less enolizable carbonyl-containing solvent, we could both avoid the formation of aldol side products and retain the selectivity observed with acetone. While ethyl acetate (entry 6) offered no improvement, both 3-pentanone (entry 7) and dimethyl carbonate (entry 8) gave increased yields and high enantioselectivities of 96.5:3.5 er and 99:1 er, respectively. Although dimethyl carbonate gave better results than 3-pentanone in this particular case, we found that this was not general and evaluated both solvents in most subsequent examples.

In evaluating the scope of nucleophiles (Scheme 3), we were pleased to find that halogens were generally well-tolerated. With 4-bromoisatin, near-perfect regioselectivity was observed and **9ba** was isolated in 82% yield and 93:7 er. While the branched–linear ratio decreased to 11:1 with 5-fluoroisatin (**7c**), excellent regio- and enantioselectivities were obtained with the analogous 5-chloro- (**7d**) and 5-iodo- (**7e**) substrates. This trend continued for 6-chloroisatin (**7f**) and 6-bromoisatin (**7g**), which afforded **9fa** and **9ga**, respectively, in comparable yields and selectivities. Although halogenation at the 7-position resulted in reduced selectivity—perhaps due to increased steric hindrance adjacent to the nucleophilic site—good reactivity was retained and **9ha** was isolated in 55% yield. With 4,6-difluoroisatin, **9ia** formed with 13:1 branched–linear selectivity and 99:1 er. While the regioselectivity dropped with a 5,6-dihalogenated substrate, **9ja** was still isolated in 59% yield.

Electron-rich isatins were also suitable nucleophiles. Methoxy substituents at the 5- and 6-positions were equally well tolerated, affording **9ka** and **9la**, respectively, with nearly identical levels of regio- and enantioselectivity. With 5-methylisatin, **9ma** was isolated in 70% yield in 91:9 er, and with 4,6-dimethylisatin, **9na** was isolated in 62% yield with near-perfect enantioselectivity. Finally, fusing an additional ring

Table 1. Reaction Optimization[a]

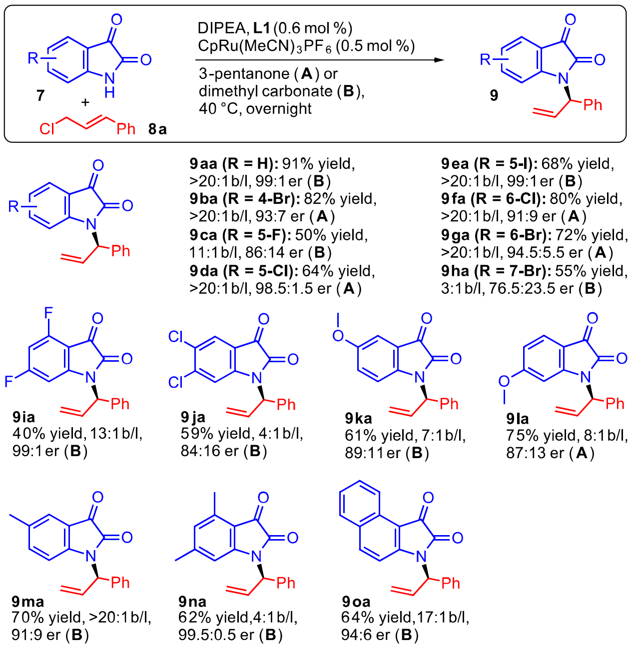


entry	solvent	base	T	X	yield	er
1[b]	acetone	Et_3N	rt	5.0	50%[c]	98.5:1.5
2[b]	DCE	Et_3N	rt	5.0	31%	92:8
3[b]	THF	Et_3N	rt	5.0	30%	90:10
4[d]	acetone	DIPEA	40 °C	1.25	75%	99.5:0.5
5[e]	acetone	DIPEA	40 °C	0.50	76%	>99.5:0.5
6[e]	EtOAc	DIPEA	40 °C	0.50	66%	96:4
7[e]	**3-pentanone**	**DIPEA**	**40 °C**	**0.50**	**83%**	**96.5:3.5**
8[e]	**$(MeO)_2CO$**	**DIPEA**	**40 °C**	**0.50**	**91%**	**99:1**

[a]Yields are isolated yields. Conversion and branched–linear (b/l) selectivity determined by crude ^{1}H NMR; er determined by chiral HPLC. [b]0.050 mmol scale at 0.5 M. [c]Conversion of isatin. [d]0.20 mmol scale at 2.0 M. [e]0.50 mmol scale at 5.0 M.

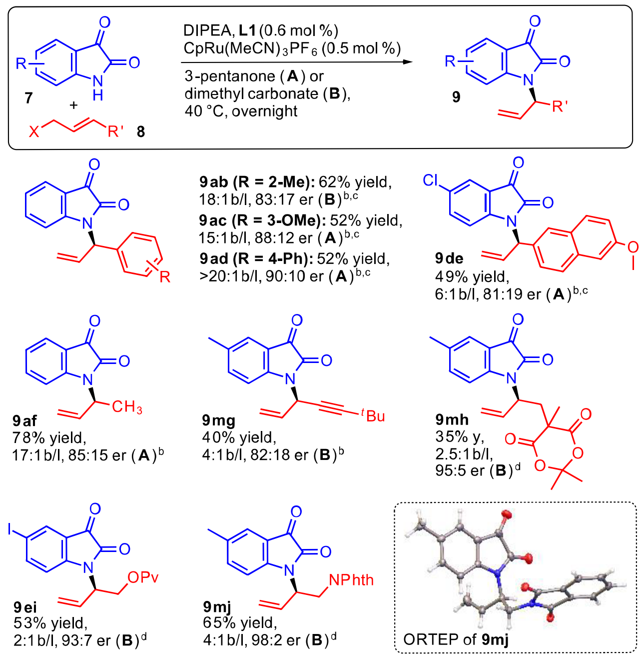
https://dx.doi.org/10.1021/acs.orglett.0c00504
Org. Lett. 2020, 22, 2584–2589

Scheme 3. Scope of Nucleophiles[a]



[a]All reactions performed on 0.5 mmol scale at 5.0 M. Yields are isolated yields of pure branched isomer. Branched–linear (b/l) ratios determined by crude ^{1}H NMR; er determined by chiral HPLC.

Scheme 4. Scope of Electrophiles[a]



[a]All reactions performed on 0.5 mmol scale at 5.0 M. Yields are isolated yields of pure branched isomer. Branched–linear (b/l) ratios determined by crude ^{1}H NMR; er determined by chiral HPLC. [b]X = Cl. [c]Initial reaction stirred overnight at 40 °C, then 0.5 mol % $CpRu(MeCN)_3PF_6$ and 0.6 mol % **L1** were added, and reaction stirred overnight at 40 °C. [d]X = Br.

to the isatin core had no adverse effects, and **9oa** was isolated in 64% yield and 94:6 er.

Substituted cinnamyl chlorides were also suitable electrophiles, but they did not fully react under the standard reaction conditions. Fortunately, full conversion could be achieved by adding a second charge of catalyst (Scheme 4). Similar yields and selectivities were obtained with *ortho*- (**9ab**), *meta*- (**9ac**), and *para*-substituted (**9ad**) aromatic rings. While extending the π-system did not impact the yield of **9de**, regio- and enantioselectivity decreased slightly. Alkyl-substituted allylic halides were also viable substrates. Switching from cinnamyl chloride to crotyl chloride (**8f**) had a negligible impact on the branched–linear ratio of **9af**, which was isolated in 78% yield and 85:15 er. Replacing the methyl group on the allyl fragment with an alkyne afforded **9mg** in 40% yield due to incomplete conversion and a reduced 4:1 branched–linear ratio.

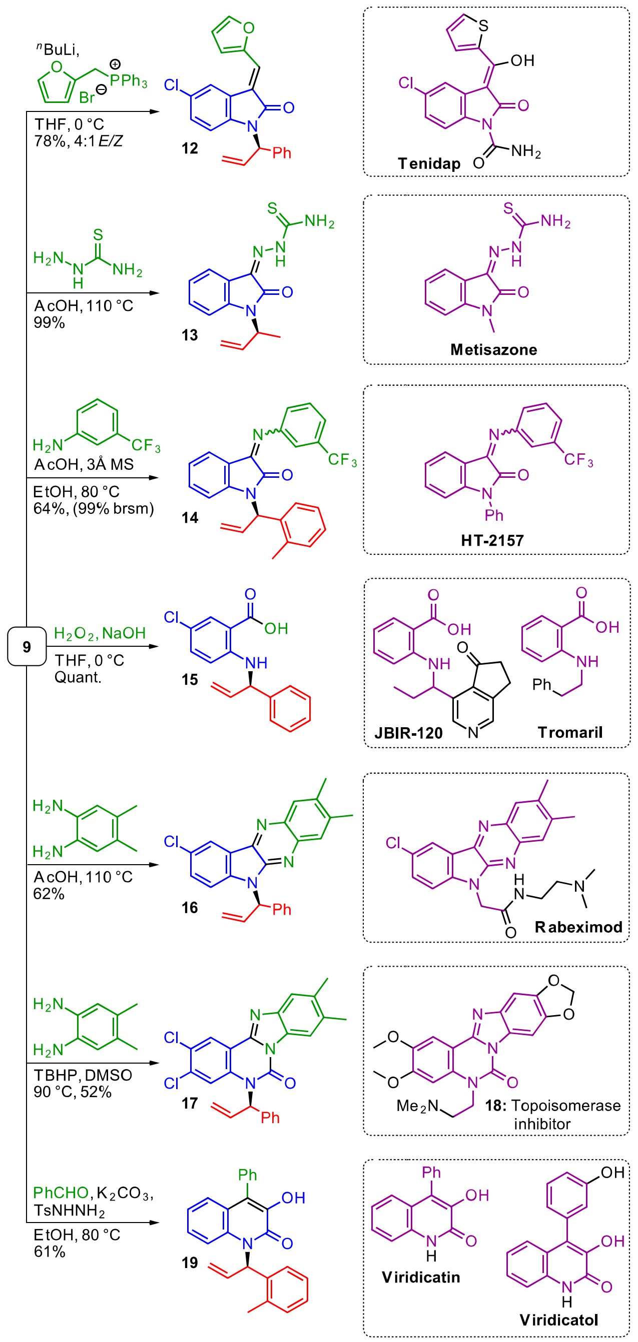
We were pleased to find that allylic bromides (**8h**–**8j**) were also suitable electrophiles, and while the regioselectivities with these substrates were lower—perhaps due to higher background reactivity—enantioselectivities were excellent. Partial conversion of Meldrum's acid derived electrophile **8h** contributed to the moderate yield of **9mh**, which was nonetheless isolated in 95:5 er. Allylic bromides with protected hydroxymethyl (**8i**) and aminomethyl (**8j**) side chains reacted uneventfully, giving rise to **9ei** and **9mj** in 93:7 er and 98:2 er, respectively. The absolute configuration of **9mj** was unequivocally determined to be (*R*) by X-ray crystallography (CCDC 1981346),[20] and the stereochemistry of all adducts **9** was assigned by analogy. While monosubstituted electrophiles are well-suited for our reaction, di- and trisubstituted electrophiles are unreactive. Allylic alkylations catalyzed by other branched-selective metals—including iridium,[2d] tungsten, and molybdenum[21]—exhibit similar limitations.

In addition to exhibiting broad scope and good selectivities, our method is quite practical. In spite of the low catalyst loading, all reactions were performed in bulk solvents under ambient atmosphere. Moreover, all reactions were carried out at high concentration in environmentally benign solvents.[22] Finally, our process is scalable; on 2.0 mmol scale, **9da** was isolated in 73% yield, albeit with diminished branched–linear selectivity (11:1) and enatioselectivity (90:10 er).

To demonstrate the utility of our products, we used them to synthesize analogs of several biologically active molecules. Unlike the predominantly achiral literature compounds we targeted, our derivatives always contain enantioenriched *N*-allyl moieties which provide versatile chiral handles for structure–activity relationship studies (Scheme 5). Olefination of **9da** with a (2-furyl)methyl Wittig reagent furnished **12**,[23] which resembles the anti-inflammatory drug candidate tenidap. Semithiocarbazide condensed with **9af** to afford metisazone analog **13** in near-quantitative yield, while condensation of **9ab** with 3-(trifluoromethyl)aniline provided access to a relative of GAL-3 antagonist HT-2157 (**14**).[24] In the presence of basic peroxide, **9da** was quantitatively converted to **15**, a notable result given that structurally similar anthranilic acids appear in both natural products (e.g., JBIR-120) and drugs (e.g., tromaril). In acetic acid, 4,5-dimethyl-1,2-phenylenediamine condensed with **9da** to afford quinoxaline **16**, which maps perfectly onto the aromatic core of the antiarthritic drug candidate rabeximod. In the presence of TBHP,[25] the same diamine reacted with **9ja** to generate **17**, which contains a tetracyclic benzimidazole scaffold similar to the one found in toposiomerase inhibitor **18**.[26] Finally, treating **9ab** with a combination of benzaldehyde and tosyl hydrazone promoted a ring expansion to generate quinolinone **19**,[27,28] providing convenient access to chiral, *N*-substituted derivatives of the viridicatin family of alkaloids.

https://dx.doi.org/10.1021/acs.orglett.0c00504
Org. Lett. 2020, 22, 2584–2589

Scheme 5. Derivatization Reactions



In conclusion, we discovered a new branched-selective allylic alkylation catalyst and used it to achieve a regio- and enantioselective synthesis of *N*-alkylated isatins. In addition to being a rare example of Ru-catalyzed asymmetric allylic alkylation using nitrogen nucleophiles, this process is also just the third general asymmetric method to use isatins as nucleophiles. Our catalyst is both active and robust and exhibits good levels of regio- and enantioselectivity across a broad range of nucleophiles and electrophiles. Finally, our products are excellent building blocks that can be rapidly transformed into a variety of structurally diverse natural product and drug analogs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00504.

Experimental procedures, characterization data, and ^{1}H/^{13}C NMR spectra for **8**, **9**, **12−17**, and **19** (PDF)

Accession Codes

CCDC 1981346 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Barry M. Trost − *Department of Chemistry, Stanford University, Stanford, California 94305, United States;* orcid.org/0000-0001-7369-9121; Email: bmtrost@stanford.edu

Authors

Christopher A. Kalnmals − *Department of Chemistry, Stanford University, Stanford, California 94305, United States;* orcid.org/0000-0003-3233-290X

Divya Ramakrishnan − *Department of Chemistry, Stanford University, Stanford, California 94305, United States*

Michael C. Ryan − *Department of Chemistry, Stanford University, Stanford, California 94305, United States*

Rebecca W. Smaha − *Department of Chemistry, Stanford University, Stanford, California 94305, United States;* orcid.org/0000-0002-8349-2615

Sean Parkin − *Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506, United States;* orcid.org/0000-0001-5777-3918

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00504

Author Contributions

[§]C.A.K. and D.R. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Tamaki Foundation and Chugai Pharmaceuticals for their generous partial financial support of our program. Part of this work was performed at the Stanford Nano Shared Facilities (SNSF), supported by the National Science Foundation under Award ECCS-1542152. D.R. thanks Stanford Chemistry for two Undergraduate Summer Research Fellowships. We also thank Dr. Elumalai Gnanamani (Stanford University) and Dr. Jana Maclaren (Stanford University) for assistance in obtaining a crystal structure of **9mj**.

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