ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Asymmetric Synthesis of Indole Homo-Michael Adducts via Dynamic Kinetic Friedel–Crafts Alkylation with Cyclopropanes

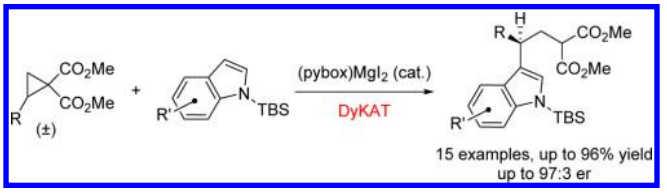
Steven M. Wales, Morgan M. Walker, and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

jsj@unc.edu

Received April 17, 2013

ABSTRACT



An enantioconvergent Friedel–Crafts alkylation of indoles with donor–acceptor cyclopropanes is described. The reaction is catalyzed by pybox•MgI_2 and proceeds via a type I dynamic kinetic asymmetric transformation (DyKAT).

Donor–acceptor (D–A) cyclopropanes are versatile reagents for atom economical synthetic transformations.[1] A particularly useful subset are those derived from 1,1-dicarboxylate esters (or congeners) with vicinal carbon or heteroatom donors. Under Lewis acid catalysis, these materials function as homo-Michael acceptors in ring-opening reactions[2] and as zwitterion equivalents in $(3+n)$-annulations.[3] Productive oligomerization pathways[4] and umpolung reactivity modes have also emerged.[5] Mechanistically, D–A cyclopropanes typically undergo stereospecific reaction through configurationally stable activated 'ion pair' intermediates, resulting in inversion at the donor site.[6] As such, chirality transfer has been demonstrated in a number of settings through deployment of optically active cyclopropanes.[2a,b,7] By contrast, more desirable strategies to access enantioenriched products without preinstallation of donor configuration are relatively rare. To this end, kinetic resolutions of racemic cyclopropanes have been achieved with nitrones,[8] amines,[9] and azomethine imines[10] under

(1) Reviews: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060. (d) Lebold, T. P.; Kerr, M. A. *Pure Appl. Chem.* **2010**, *82*, 1797–1812. (e) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293–301.

(2) Selected examples: (a) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809–2812. (b) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838–6840. (c) Sapeta, K.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 2081–2084.

(3) Recent examples: (a) Smith, A. G.; Slade, M. C.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 1996–1999. (b) Sathishkannan, G.; Srinivasan, K. *Org. Lett.* **2011**, *13*, 6002–6005. (c) Qu, J. -P.; Liang, Y.; Xu, H.; Sun, X. -L.; Yu, Z. -X.; Tang, Y. *Chem.—Eur. J.* **2012**, *18*, 2196–2201. (d) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A., II; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314–5317. (e) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088–11091.

(4) (a) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Trushkov, I. V.; Melnikov, M. Y. *J. Org. Chem.* **2011**, *76*, 8852–8868. (b) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Rakhmankulov, E. R.; Trushkov, I. V.; Semeykin, A. V.; Shimanovskii, N. L.; Melnikov, M. Y. *Chem.—Eur. J.* **2011**, *17*, 11738–11742. (c) Novikov, R. A.; Timofeev, V. P.; Tomilov, Y. V. *J. Org. Chem.* **2012**, *77*, 5993–6006.

(5) (a) Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618–18621. (b) Chagarovskiy, A. O.; Ivanova, O. A.; Budynina, E. M.; Trushkov, I. V.; Melnikov, M. Y. *Tetrahedron Lett.* **2011**, *52*, 4421–4425.

(6) (a) Cram, D. J.; Yankee, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6329–6331. (b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251–10253. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650.

(7) Selected examples: (a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015. (b) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 8597–8599. (c) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201. (d) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770–3772. (e) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075–12079. (f) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem.—Eur. J.* **2012**, *18*, 4844–4849.

10.1021/ol4010646

chiral Lewis acid catalysis, while the Trost group have reported ligand controlled enantioconvergent cycloadditions of vinyl-cyclopropanes and olefins via allyl-palladium intermediates.[11] In a different realm, our laboratory has demonstrated that cyclopropanes bearing donors with electron-releasing substituents are suitable substrates for type I dynamic kinetic asymmetric transformations (DyKAT's)[12] by virtue of their increased rate of configurational inversion upon Lewis acid association.[13,14] Herein, we now report the extension of our catalytic system developed previously for DyKAT annulations of racemic cyclopropanes **1** and dipolarophiles **2** to Friedel–Crafts alkylation reactions (Figure 1).

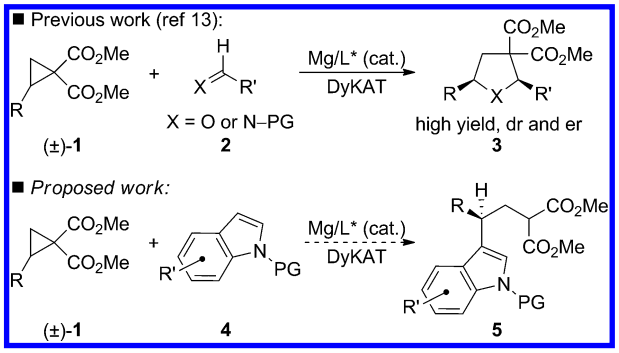
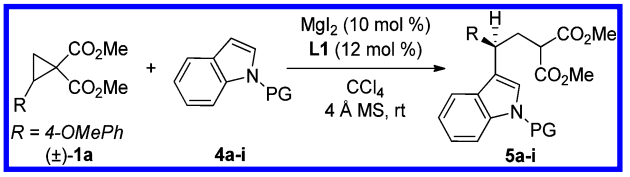


Figure 1. Proposed asymmetric Friedel–Crafts alkylation.

The ubiquitous indole nucleophile[15] was an ideal starting point for these investigations. We were interested in developing a homologue of the extensively studied asymmetric conjugate addition of indoles to arylidine malonates and related carbonyl Michael acceptors,[16] as a potential entry to underexplored chiral space. Additional inspiration came from Kerr's findings that indoles readily cleave D–A cyclopropanes under Lewis acid[17] or H-bond activation[18] in the racemic mode.

Table 1. Protecting Group Screening[a,b]



entry	PG (**4**)	product	yield (%)[c]	er[d]
1	Me (**4a**)	**5a**	85[e,f]	62.5:37.5
2	CH_2Ph (**4b**)	**5b**	77[e,g]	76:24
3	$CHPh_2$ (**4c**)	**5c**	22	nd
4	Boc (**4d**)	**5d**	0	–
5	$SiMe_2Ph$ (**4e**)	**5e**	67[e]	91.5:8.5
6	$SiMe_2(t\text{-Bu})$ (**4f**)	**5f**	76[e]	91:9
7	$SiMe_2(c\text{-Hex})$ (**4g**)	**5g**	51	nd
8	$SiEt_3$ (**4h**)	**5h**	61	nd
9	$Si(i\text{-Pr})_3$ (**4i**)	**5i**	35	nd

[a] Reactions performed with 1.0 equiv of **1a** ($[\mathbf{1a}]_0$ = 0.05 M) and 1.5–1.7 equiv of **4**. [b] 100% consumption of **1a** in <24 h in all cases. [c] Determined by ^1H NMR spectroscopy with mesitylene as the internal standard. [d] Determined by chiral HPLC analysis. [e] Isolated yield. [f] The (3 + 2)-annulation product was also isolated in 10% yield. [g] The (3 + 2)-annulation product was also isolated in 16% yield.

Our opening experiment was performed with *N*-Me-indole and cyclopropane **1a** under our previously optimized conditions for asymmetric cycloadditions (**L1** = (*S*,*S*)-4-Cl-(*t*-Bu)-pybox),[13a,b] providing the desired alkylation product **5a** in a modest but encouraging 62.5:37.5 er (Table 1, entry 1). Subsequent attempts to improve the enantioselectivity using pybox and DBFOX ligands derived from other amino alcohols were unsuccessful;[19] thus we proceeded to explore modulations of the N-protecting group (PG).[20] We reasoned that more sterically encumbered and/or electronically deactivating *N*-substituents would be required for the obligatory background 'racemization' of **1a** to become competitive with the rate of alkylation and began testing this hypothesis with the moderately sized benzyl group (Table 1, entry 2). After observing an increase in the er, we introduced a second Ph group by way of the benzhydryl moiety, but this change dramatically lowered the yield (entry 3). Not surprisingly,[18] the Boc group diminished the indole reactivity even further to the point that decomposition/oligomerization of **1a** was the sole reaction pathway (entry 4). Useful levels of both yield and enantioselectivity were eventually

(8) (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765. (b) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918–3921.

(9) Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066–9069.

(10) Zhou, Y.-Y.; Li, J.; Ling, L.; Liao, S.-H.; Sun, X.-L.; Li, Y.-X.; Wang, L.-J.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1452–1456.

(11) (a) Trost, B. M.; Morris, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6167–6170. (b) Trost, B. M.; Morris, P. J.; Sprague, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 17823–17831.

(12) Steinreiber, J.; Faber, K.; Griengl, H. *Chem.—Eur. J.* **2008**, *14*, 8060–8072.

(13) (a) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122–3123. (b) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688–9692. (c) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhaus, P. D.; Sanders, S. D. *J. Org. Chem.* **2010**, *75*, 6317–6325.

(14) Tang has recently reported a DyKAT annulation of electron-rich D–A cyclopropanes and cyclic enol silyl ethers; see: Xu, H.; Qu, J. -P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4004–4007.

(15) For a review on the electrophilic functionalization of indoles, see: Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644.

(16) Selected examples: (a) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030–9031. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041. (c) Liu, L.; Ma, H.; Xiao, Y.; Du, F.; Qin, Z.; Li, N.; Fu, B. *Chem. Commun.* **2012**, *48*, 9281–9283.

(17) (a) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949–5952. (b) Grover, H. K.; Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 220–223.

(18) Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180–4183.

(19) Ad-pybox, Ph-pybox, Bn-pybox, Inda-pybox, Ph-DBFOX, and (*t*-Bu)-DBFOX all provided **5a** in er's of < 53:47.

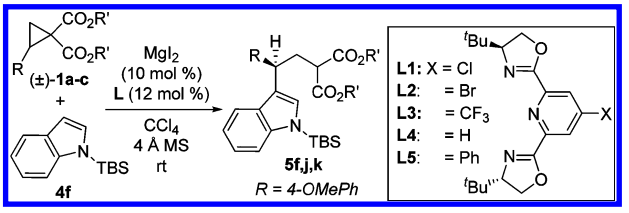
(20) The absence of a PG resulted in side products of *N*-alkylation.

(21) For examples of *N*-TBS-indoles in asymmetric catalysis, see: (a) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal.* **2007**, *349*, 1863–1867. (b) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561–5564. (c) Cai, Y.; Zhu, S. -F.; Wang, G. -P.; Zhou, Q. -L. *Adv. Synth. Catal.* **2011**, *353*, 2939–2944.

obtained upon experimentation with silyl PGs (entries 5−9), with TBS providing optimal results (entry 6).[21]

Having established TBS as a suitable PG, we proceeded to examine a set of 4-X-(*t*-Bu)-pybox ligands (Table 2, entries 1−5). Consistent with our previous studies,[13] optimum results were obtained with halo substitution, although the notably higher yield with **L2** (X = Br, entry 2) made this the particular ligand of choice for further experimentation.[22,23] We continued by reducing the indole equivalents from 1.7 to 1.1 (entry 6) or using the indole as the limiting reagent (entry 7); however, these alterations provided no advantage. In our previous experience,[13b] deviations from dimethyl ester activation have produced comparable but inferior results; thus we were not surprised to re-encounter this trend with the dibenzyl analogue **1b** (Table 2, entry 8). In this alkylation manifold, however, a notable increase in er occurred with the diisopropyl ester **1c** (entry 9), although ultimately we chose to continue with dimethyl malonate-derived cyclopropanes due to yield considerations.

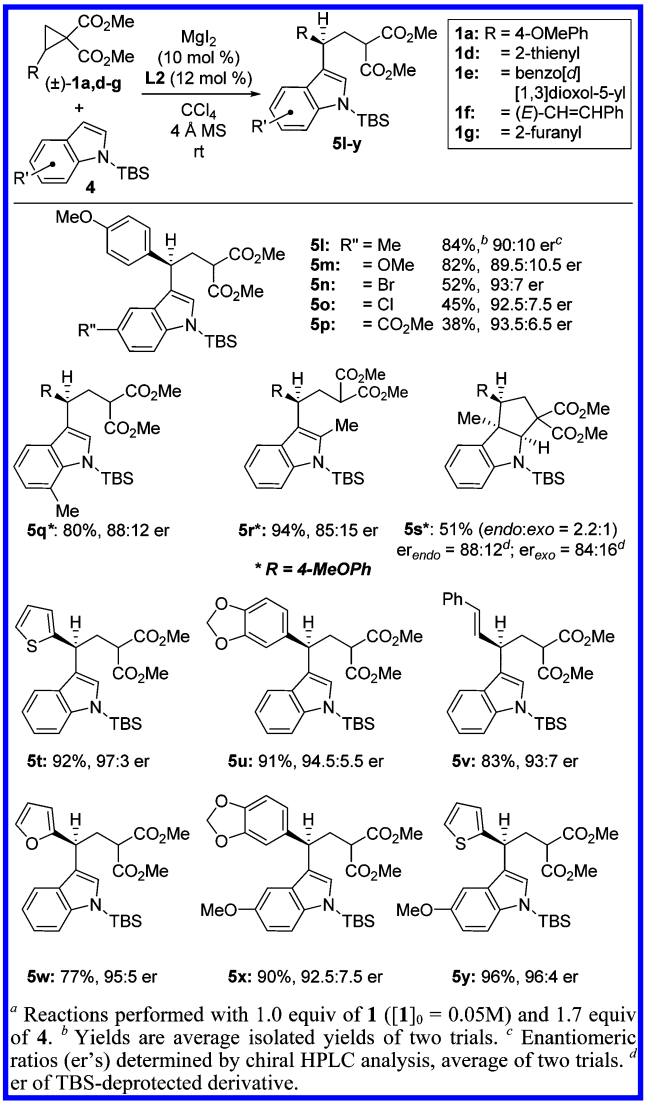
Table 2. Additional Optimization Studies[a,b]



entry	R′ (**1**)	product	**L**	yield (%)[c]	er[d]
1	Me (**1a**)	**5f**	**L1**	76[e]	91:9
2	Me (**1a**)	**5f**	**L2**	81[f]	90.5:9.5
3	Me (**1a**)	**5f**	**L3**	53	83:17
4	Me (**1a**)	**5f**	**L4**	81	86:14
5	Me (**1a**)	**5f**	**L5**	72	85:15
6[g]	Me (**1a**)	**5f**	**L2**	73	89.5:10.5
7[h]	Me (**1a**)	**5f**	**L2**	69[i]	90.5:9.5
8	Bn (**1b**)	**5j**	**L2**	80[e]	90:10
9	*i*-Pr (**1c**)	**5k**	**L2**	75[e]	94.5:5.5[j]

[a] Reactions performed with 1.0 equiv of **1** ([**1**]$_0$ = 0.05 M) and 1.7 equiv of **4f**. [b] 100% consumption of **1** in < 24 h in all cases except entry 7. [c] Determined by ^{1}H NMR spectroscopy with mesitylene as the internal standard. [d] Determined by chiral HPLC analysis. [e] Isolated yield from a single trial. [f] Average isolated yield of two trials. [g] With 1.1 equiv of *N*-TBS-indole. [h] With 2.0 equiv of **1a** and 1.0 equiv of **4f**. [i] Isolated yield based on indole. [j] Er of TBS-deprotected derivative.

With optimized conditions established, the scope of the asymmetric Friedel−Crafts alkylation was examined (Figure 2). A range of indoles with electronically diverse substituents provided the desired enantioenriched alkylation products.[24] Yields were generally high with the exception of electron-deficient indoles bearing halo or ester



[a] Reactions performed with 1.0 equiv of **1** ([**1**]$_0$ = 0.05M) and 1.7 equiv of **4**. [b] Yields are average isolated yields of two trials. [c] Enantiomeric ratios (er's) determined by chiral HPLC analysis, average of two trials. [d] er of TBS-deprotected derivative.

Figure 2. Substrate scope.[a]

substituents.[25] In these instances, the slower rates of alkylation led to a greater extent of unproductive decomposition of **1a**. More sterically demanding 2- and 7-methylindoles were well tolerated. In the former case a marginal decrease in enantioselectivity occurred, presumably as a consequence of the increased indole nucleophilicity.[18] As observed by Kerr[26] and Ila,[27] the presence of a 3-methyl substituent induced cyclization of the putative intermediate giving pentannulation product **5s** in a useful er, albiet in modest yield and with *endo* diastereoselectivity.[28]

Dynamic cyclopropane reactivity was extended to substrates bearing thienyl (**1d**), benzo[*d*][1,3]dioxol-5-yl (**1e**),

(22) See the Supporting Information for solvent screening results.

(23) In the absence of molecular sieves, slightly lower yields were observed and **1** partially isomerized (< 5%) to alkenes.

(24) Only traces of (3 + 2)-annulation products were observed. These impurities were easily removed by flash chromatography (higher R_f).

(25) Under the standard conditions, an experiment with 1-benzyl-5-bromoindole provided the alkylation product in 64% yield and 86:14 er.

(26) (a) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671–5675. (b) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704–4709. (c) England, D. B.; Woo, T. K.; Kerr, M. A. *Can. J. Chem.* **2002**, *80*, 992–998.

(27) Venkatesh, C.; Singh, P. P.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2006**, 5378–5386.

(28) Higher levels of *endo* diastereoselectivity (up to 100:1) were obtained with aryl donors by Kerr and Ila in racemic preparations with Yb(OTf)$_3$ and BF$_3$ respectively; see refs 26 and 27.

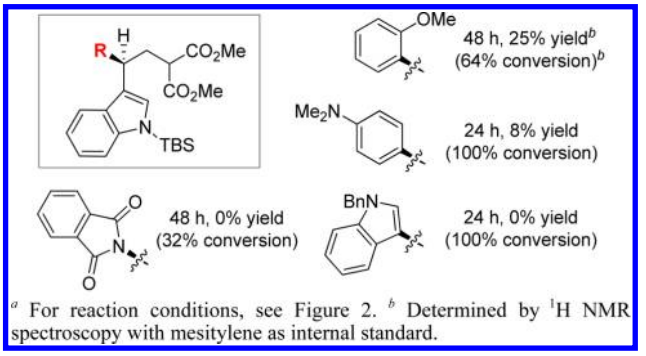


Figure 3. Unsuccessful cyclopropane donors.[a]

styrenyl (**1f**), and furanyl (**1g**) donors, all of which in fact provided alkylation products with higher enantiopurity than obtained with test substrate **1a**. Among these, **1d** provided the best results (up to 96% yield and 97:3 er). Of note, all reactions proceeded with complete cyclopropane consumption within 24 h, with the exception of those giving **5s** and **5v**, which required *ca*. 3 d. All products were stable to silica gel chromatography, and subsequent TBS-deprotection was routine with aqueous acid.[29] Exemplary secondary transformations have been documented for racemic analogues.[17a,18,26a]

Under the optimized conditions, we have thus far been unable to effectively alkylate *N*-TBS-indole with electron-rich cyclopropanes bearing 2-OMePh and phthalimido[30] substituents (Figure 3). In both cases cyclopropane reactivity is sluggish, presumably due to steric shielding of the electrophilic site. In contrast, with nitrogen-bearing carbon-based donors including 4-NMe_2Ph[4a] and *N*-Bn-indol-3-yl,[4b] cyclopropane decomposition has been problematic (Figure 3). Other aryl nucleophiles in combination with **1a** as an alkyating agent have also been explored, albeit with limited success. Furan and thiophene are unreactive, while *N*-Bn- and *N*-TBS-pyrroles have provided low yields (30−40%) of alkylation products as regioisomeric mixtures arising from substitution at both the 2- and 3-positions of the pyrrole ring.

Our previous mechanistic studies[13] of **L1**/**L2**•MgI_2 catalyzed formal cycloadditions have elucidated a type I DyKAT whereby nucleophilic attack occurs on the transient cyclopropane (*S*)-**1** to furnish products of donor site

(29) See the Supporting Information for selected examples.

(30) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386–389. See also refs 7e and 7f.

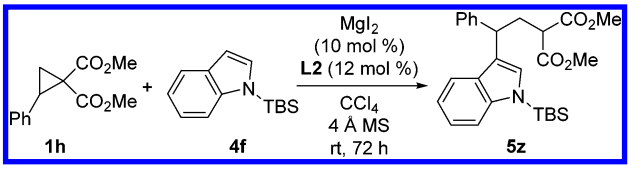
(31) For cyclopropanes **1d** and **1g**, the Cahn−Ingold−Prelog priorities change because of the thienyl and furanyl group; thus it is the (*R*) enantiomers that are reactive.

(32) CCDC 932134 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

(33) The absolute configurations of other reaction products were assigned by analogy.

(34) The indole-ring opening of enantiopure vinyl- and phenyl-cyclopropane diesters was also found to be stereospecific under $Zn(NTf_2)_2$ catalysis; see ref 17b.

Table 3. Stereochemical Experiments[a]



cyclopropane	conversion (%)[b]	yield (%)[b]	er recovered **1h** (*R*:*S*)[c]	er **5z** (*R*:*S*)[c,d]
rac-**1h**	61	49	94:6	86.5:13.5
S-**1h**	87	75	7.5:92.5	>99.5:0.5
R-**1h**	16	10	>99.5:0.5	3:97

[a] Reactions performed with 1.0 equiv of **1h** ($[\mathbf{1h}]_0$ = 0.05 M) and 1.7 equiv of **4f**. [b] Determined by ^{1}H NMR spectroscopy with mesitylene as the internal standard. [c] Determined by chiral HPLC analysis. [d] Er of TBS-deprotected derivative.

inversion.[31] In accord with this precedent, a crystal of alkylation product **5f** (generated from an enriched sample of 98:2 er) was determined to have the (*R*)-configuration by X-ray crystallography.[32,33] To gain further insight, phenylcyclopropane **1h** was utilized as a mechanistic probe owing to its configurational stability to Lewis acids (Table 3).[13] Not surprisingly, deployment of racemic-**1h** under the standard conditions resulted in a kinetic resolution whereby enriched (*R*)-**1h** was returned, while stereospecific alkylations were observed with the (*S*) and (*R*) enantiomers. A significant rate preference was conferred for (*S*)-**1h**.

Taken collectively with our previous data[13] and Kerr's findings,[34] these results point conclusively toward an enantioconvergent Friedel−Crafts alkylation proceeding by a type I DyKAT, whereby stereospecific nucleophilic trapping of the Lewis acid activated (*S*)-cyclopropane occurs through a transient diastereomic intermediate.

In summary, we have reported a dynamic kinetic asymmetric Friedel−Crafts alkylation of indoles with D−A cyclopropanes, providing homo-Michael adducts in moderate to high enantiopurity. The identification of TBS as a suitable PG ensured the smooth transition of our previously established DyKAT conditions to this alkylation setting. Efforts to uncover new stereoselective transformations of D−A cyclopropanes are ongoing in our laboratory.

Acknowledgment. We thank the NSF (CHE-0749691) for financial support. S.M.W. acknowledges the American Australian Association for an Amgen Fellowship. X-ray crystallography was performed by Dr. Peter White (UNC−CH).

Supporting Information Available. Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.