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Research Article

Stereoretentive Catalytic [3+2]-Cycloaddition/Rearrangement/Decarboxylation Reactions of Indoles with Non-Racemic Donor−Acceptor Cyclopropanes

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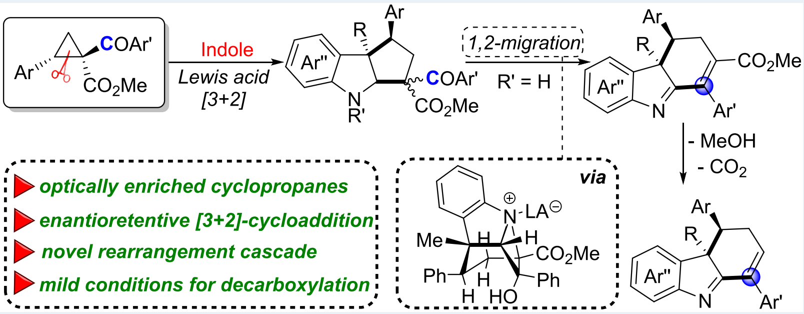

ABSTRACT: A highly enantioselective synthesis of chiral dihydro-3*H*-carbazole-2-carboxylate derivatives is reported *via* a "one-pot" cyclopentannulation-rearrangement cascade reaction that is sequentially catalyzed by nickel(II) perchlorate hexahydrate and scandium(III) trifluoromethanesulfonate with 3-methylindole and non-racemic donor−acceptor cyclopropanes in high yields and enantioretention under mild reaction conditions. Highly diastereoselective [3+2]-cycloaddition is dependent on 3-methylindole substituents. In addition, a further transformation of these dihydro-3*H*-carbazole-2-carboxylates *via* hydrolysis and decarboxylation under unexpectedly mild reaction conditions provides straightforward access to the decarboxylated compounds in moderate yields with high retention of enantiomeric purity.

KEYWORDS: *cycloaddition, donor−acceptor cyclopropanes, enantioretention, rearrangement, decarboxylation*

■ INTRODUCTION

[3+n]-Cycloaddition reactions have become useful transformations for the construction of carbocyclic and heterocyclic compounds.[1] Major contributions have come from catalytic reactions of vinyldiazo compounds[2] and methods that employ donor−acceptor cyclopropanes,[3] with both processes offering mechanistic and structural advantages in ring formation. For the asymmetric synthesis of chiral compounds, the use of vinyldiazo compounds requires a metal catalyst with chiral ligands (Scheme 1a), and although the vast majority of asymmetric cycloaddition reactions of donor−acceptor cyclopropanes are performed with racemic cyclopropane compounds catalyzed by Lewis acids with chiral ligands, optically active cyclopropane compounds can serve the same role using Lewis acids without chiral ligands.[4] Cycloaddition with catalyst-activated donor−acceptor cyclopropanes can occur by an S_N1 pathway, in which the chirality of the reactant is lost, or by an S_N2 pathway, which occurs by inversion of configuration (Scheme 1b). In most studies, the S_N1 pathway is considered to be a major contributor,[3] but a few reports have described the outcome of cycloaddition using enantiomerically enriched donor−acceptor cyclopropanes.[4]

Indole and substituted indoles are one of the very few substrate classes for which both vinylcarbene and donor−acceptor cyclopropane methodologies have been demonstrated.[5] Electrophilic addition to the 3-position is preferred for cycloaddition, and methyl substitution at the 3-position facilitates this transformation,[6] whereas methyl substitution at the 2-position often results in formal C−H insertion at the 3-position.[7] Tang and co-workers have described a highly enantioselective cyclopentannulation of 3-alkyl-substituted indoles with donor−acceptor cyclopropanes using copper(II) triflate with a chiral Box ligand (Scheme 2a).[8] To complement this investigation, we have investigated the cyclopentannulation of 3-methylindole with a comparable chiral donor−acceptor cyclopropane using achiral Lewis acid catalysts (Scheme 2b). The outcome reveals a stepwise

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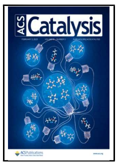

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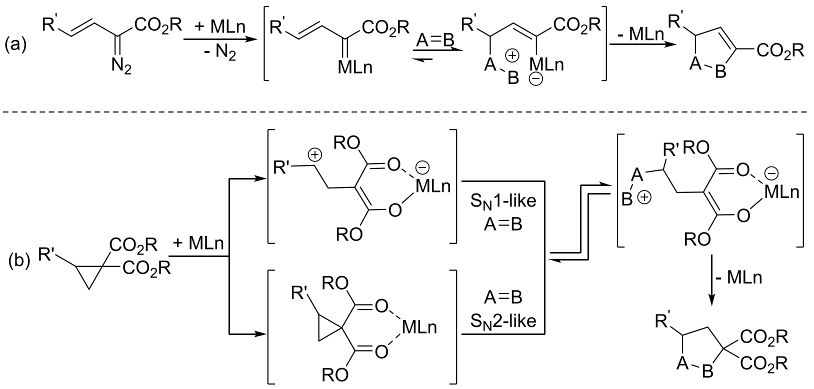
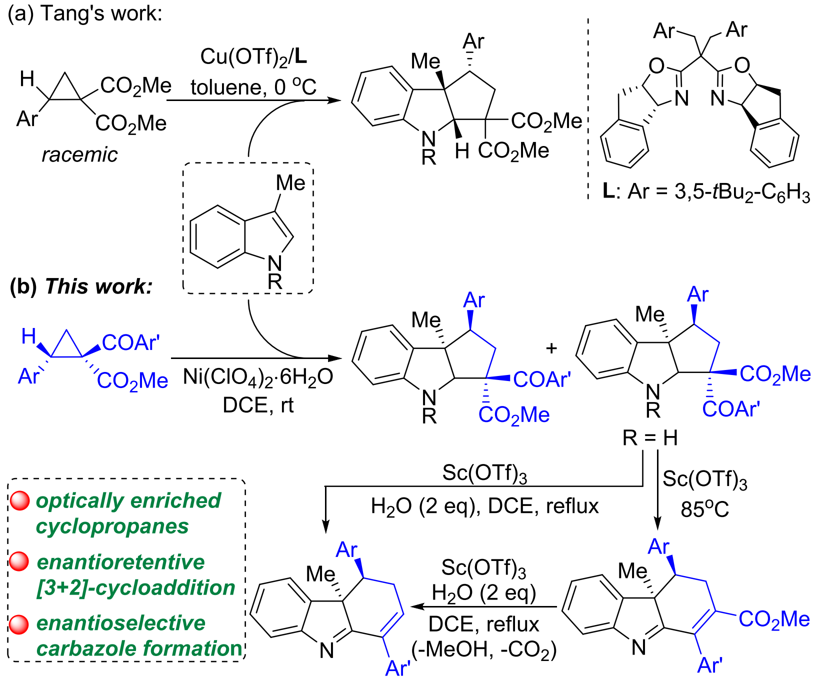
Scheme 1. Catalytic Cycloaddition Reactions with (a) Vinyldiazo Compounds and (b) Donor−Acceptor Cyclopropanes



Scheme 2. Enantioselective Cycloaddition of 3-Methylindole with (a) Racemic Donor−Acceptor Cyclopropanes Using a Chiral Catalyst and (b) Non-Racemic Donor−Acceptor Cyclopropanes Using an Achiral Catalyst



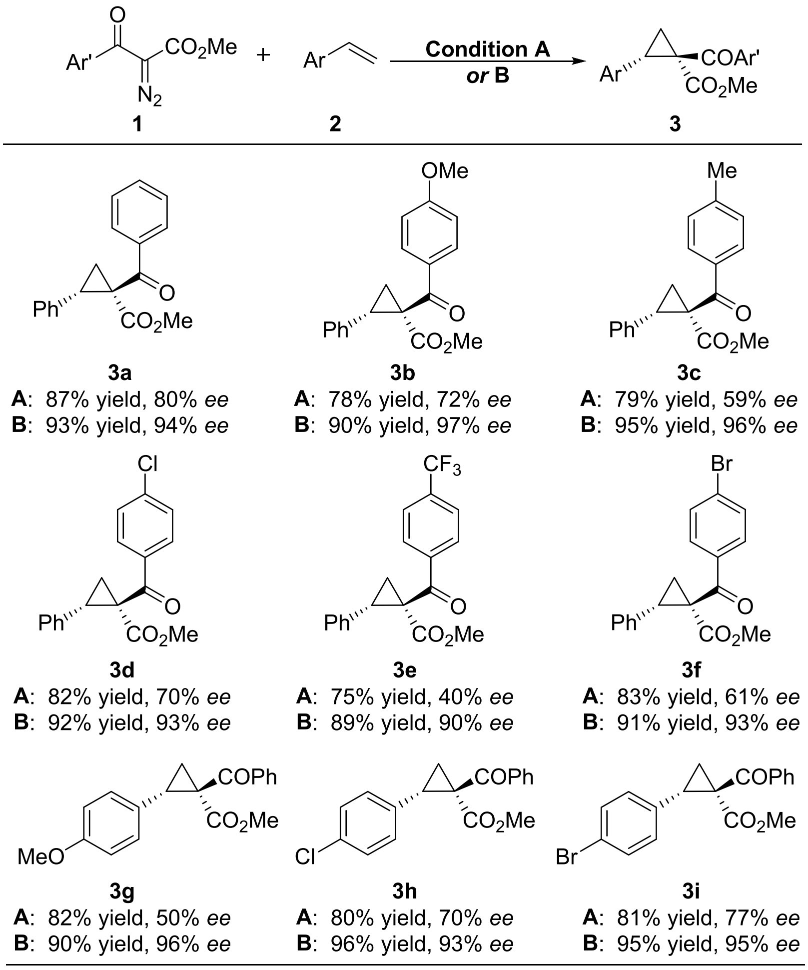
cycloaddition process with dominant retention of optical purity, which is more complex than previously reported. Catalyst-controlled subsequent transformations form formal [4+2]-annulation products of indoles and donor−acceptor cyclopropanes by stepwise bond migration, and hydrolysis/decarboxylation also occurs without loss of stereocontrol.

■ RESULTS AND DISCUSSION

The first task in this investigation was the preparation of enantioenriched donor−acceptor cyclopropanes. We chose to prepare these from 2-diazo-3-ketoesters and styrenes using dirhodium(II) catalysis (Scheme 3). A survey of catalysts revealed the formation of only one diastereomer (**3a**) whose structure as the dominant (1*S*, 2*S*)-enantiomer was confirmed by X-ray crystallography (Figure 1) and that the highest enantioselectivities in reactions with styrene were achieved with Rh_2(*S*-TBPTTL)$_4$ (80% *ee*)[9] and Rh_2(*S*-BTPCP)$_4$ (94% *ee*).[10] Reactions with these dirhodium(II) catalysts under standard conditions were sluggish, resulting in low conversion (see the SI for details), but optimization of the solvent produced the donor−acceptor cyclopropane in 87 and 93% yields, respectively. Substituted styrenes gave lower %*ee* values with these catalysts. Attempts to prepare these cyclopropane compounds with diazo esters having a larger ester group (benzyl or *tert*-butyl) using the Rh_2(*S*-BTPCP)$_4$ catalyst were not successful.

We selected 3-methylindole (**4a**) as our target substrate to investigate in detail its [3+2]-cycloaddition reaction with donor−acceptor cyclopropane **3a**. This indole or its *N*-methyl analogue is well known to undergo catalytic [3+2]-cycloaddition reactions with vinyldiazoacetates and with donor−acceptor cyclopropanes.[5,6] A range of Lewis acid catalysts was employed, from which $Ni(ClO_4)_2$ hexahydrate was the most suitable because of its overall conversion and retention of optical activity (see the SI for details). Reaction products were fully characterized spectroscopically (Scheme 4), and our assignments were confirmed with the X-ray structure of diastereomer (1*R*,3*R*)-**6a**, which is consistent with inversion of a configuration having occurred at the 2-position of **3a** (Figure 2).

Scheme 3. Enantioselective Cyclopropanation of Styrene with Methyl Aryloyldiazoacetates Using Chiral Dirhodium Carboxylates[a]



3a
A: 87% yield, 80% *ee*
B: 93% yield, 94% *ee*

3b
A: 78% yield, 72% *ee*
B: 90% yield, 97% *ee*

3c
A: 79% yield, 59% *ee*
B: 95% yield, 96% *ee*

3d
A: 82% yield, 70% *ee*
B: 92% yield, 93% *ee*

3e
A: 75% yield, 40% *ee*
B: 89% yield, 90% *ee*

3f
A: 83% yield, 61% *ee*
B: 91% yield, 93% *ee*

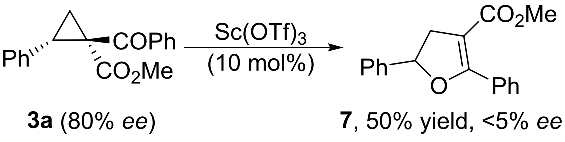
3g
A: 82% yield, 50% *ee*
B: 90% yield, 96% *ee*

3h
A: 80% yield, 70% *ee*
B: 96% yield, 93% *ee*

3i
A: 81% yield, 77% *ee*
B: 95% yield, 95% *ee*

[a]**Condition A**: To **2** (1.0 mmol, 5.0 equiv), [Rh_2(S-TBPTTL)$_4$] (5.0 mg, 1.0 mol %), and 4 Å MS (100 mg) in anhydrous DCM (1.0 mL) was added a solution of **1** (0.2 mmol) in anhydrous DCM (1.0 mL) *via* a syringe pump over 3 h at room temperature under an argon atmosphere; **Condition B**: to **2** (1.0 mmol, 5.0 equiv), [Rh2(S-BTPCP)4] (3.5 mg, 1.0 mol %), and 4 Å MS (100 mg) in toluene/TBME solvent (v:v = 4:1, 1.0 mL) was added a solution of **1** (0.2 mmol) in the same solvent (1.0 mL) *via* a syringe pump over 3 h at room temperature under an argon atmosphere. The yields are given in isolated yields after flash chromatography, and the ee values were determined by chiral HPLC analysis.

Intramolecular rearrangement of **3a** to its corresponding dihydrofuran (eq 1)[11] did not occur in the presence of **4a** under these reaction conditions, but **3a** was 50% converted to dihydrofuran **7** in the absence of **4a** over 12 h with virtually complete racemization (80% *ee* to 5% *ee*) of **3a**. The two diastereomers formed in the [3+2]-cycloaddition reaction point to a two-step cycloaddition involving initial nucleophilic attack from the indole-3-position on the phenyl-substituted carbon of **3a** and then the ring closure. The initial nucleophilic attack from **4a** fixes the absolute configuration at the phenyl-substituted carbon center of **5a** and **6a** as *R*. The fact that the loss of %*ee* from **3a** in the formation of diastereoisomer **5a** is negligible suggests that both **5a** and **6a** arose from S_N2 substitution on catalyst-activated **3a** by **4a**.

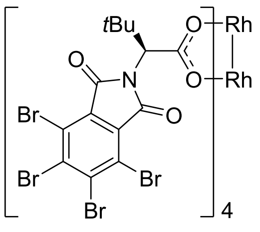


(1)

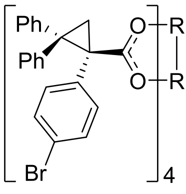
3a (80% *ee*) **7**, 50% yield, <5% *ee*

The fact that diastereomer **6a** has a lower %*ee* than **5a** was unexpected and prompted us to examine the retention of configuration in the individual diastereoisomers (**5a** and **6a**) under the same reaction conditions. The diastereomers were separated chromatographically, and each was treated with $Ni(ClO_4)_2$ hexahydrate under the same conditions and for the same amount of time as used for the initial reaction of **3a** with **4a** (Scheme 5). Diastereomer isomerization was observed with both diastereomers, suggesting that the ring-closing step in the [3+2]-cycloaddition step is reversible (Scheme 6), but the rate of isomerization for **6a** was greater than that for **5a**. However, while the %*ee* for **5a** remained the same, that for **6a** decreased, and the cause of this racemization is unknown. No other product was discernable in the reaction mixture after treatment with the Lewis acid catalyst. All attempts to trap an intermediate with potential dipoles (styrene, benzaldehyde, sulfur ylide, substituted indole) under the Lewis acid-catalyzed conditions were unsuccessful, and the starting material was recovered. Treatment of **5a**/**6a** with trifluoroethanol with and without the Lewis acid catalyst left the diastereoisomers unchanged.

For comparison, reactions of the *p*-methoxyphenyl (**3g**, 96% *ee*) and *p*-trifluoromethylphenyl (**3j**, 94% *ee*) analogues



Rh_2(*S*-TBPTTL)$_4$



Rh_2(*S*-BTPCP)$_4$

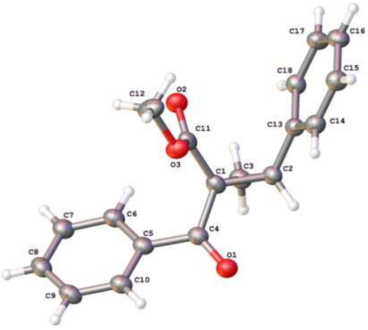
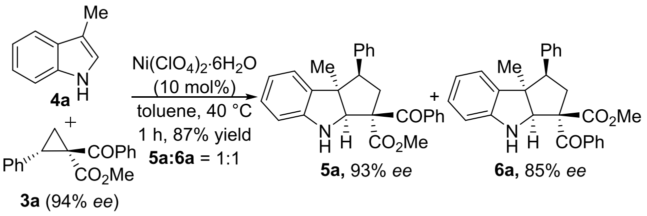


Figure 1. X-ray structure of (**1*S*,2*S***)-**3a** (CCDC: 2208962).

Scheme 4. [3+2]-Cycloaddition of 3-Methylindole with Non-Racemic Donor–Acceptor Cyclopropane 3a Using Nickel Perchlorate Catalysis



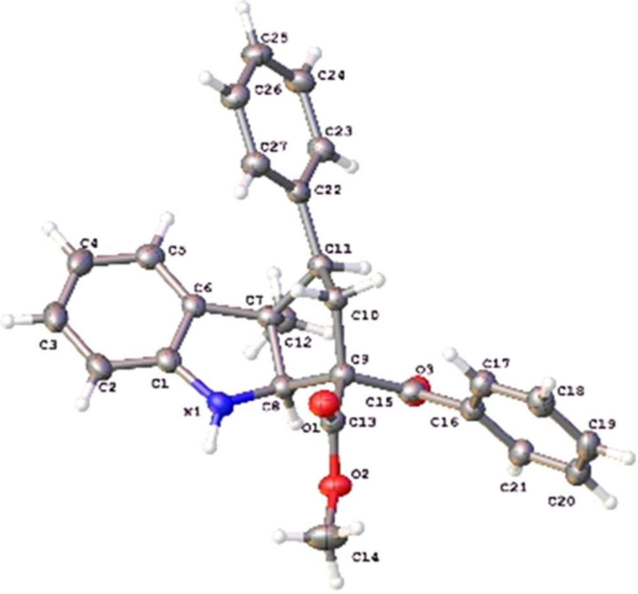
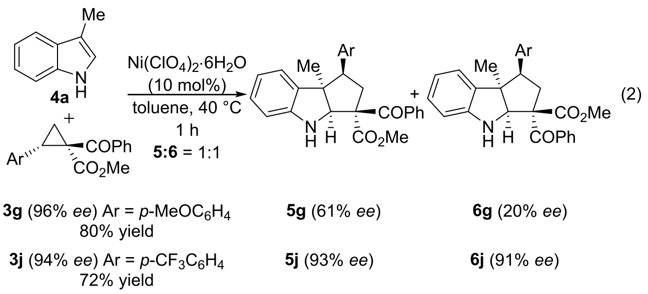


Figure 2. X-ray structure of **6a** (CCDC: 2208963) showing the *R*-configuration at C-12, consistent with inversion of configuration at C-2 of **3a**.

of donor–acceptor cyclopropane **3** with 3-methylindole also formed the corresponding [3+2]-cycloaddition products in good yields. A significant loss of enantioselectivity was found in the reaction with **3g**, but very high retention of enantiocontrol occurred in the reaction with **3j**, despite the lack of any diastereocontrol (eq 2).

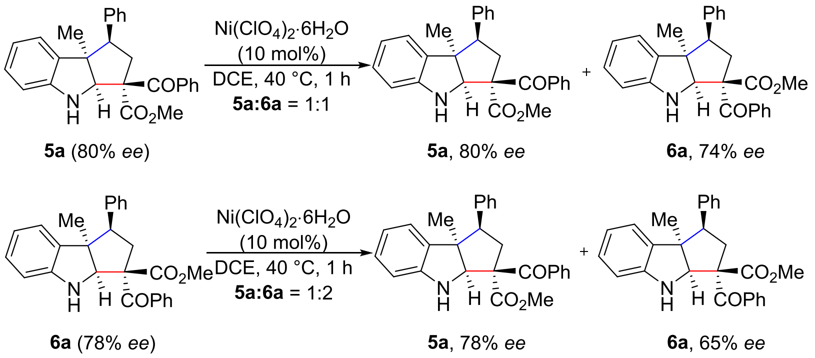


Because of the stepwise cycloaddition, diastereocontrol is lost in these reactions. Is there an indole that could undergo highly diastereoselective [3+2]-cycloaddition? To address this question, we surveyed the same reaction with representative substituted indoles, and the outcome is presented in Scheme 7. All of the 5-substituted-3-methylindoles underwent cycloaddition in high isolated yields and with high levels of enantiocontrol. Notably, although 5-methoxy-3-methylindole (**4b**), 6-methyl-3-methylindole (**4c**), and 4-methyl-3-methylindole (**4d**) gave the diastereomeric cycloaddition products **5** and **6** in a 1:1 ratio indicative of a stepwise cycloaddition process, its 5-chloro- (**4e**) and 5-bromo- (**4f**) analogues gave diastereomer **5** in a ratio greater than 10:1 over diastereoisomer **6**.

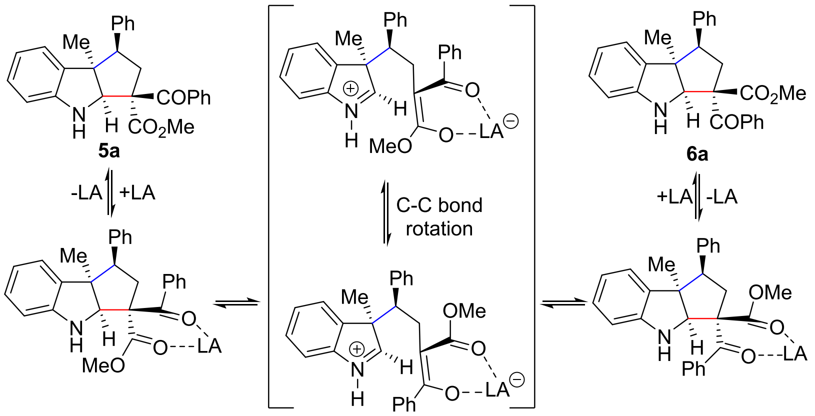
In initial investigations to determine suitable Lewis acids for cycloaddition, we discovered that several of the Lewis acids [Sc(OTf)$_3$, Cu(OTf)$_2$, and Fe(OTf)$_3$] produced a new compound (**8a**) in addition to the [3+2]-cycloaddition products. Previous reports have described a similar process for carbazole formation with donor–acceptor cyclopropanes and indoles but without the [3+2]-cycloaddition product as its precursor.[12] However, the formation of **8a** occurred in conjunction with the production of [3+2]-cycloaddition products **5a** and **6a**. Considering that the cycloaddition products could be precursors to **8a**, we prepared **5a**/**6a** (93/85% *ee*) from the Ni(ClO$_4$)$_2$-catalyzed cycloaddition and then treated the diastereomeric pair with Sc(OTf)$_3$ under the same conditions (Scheme 8), obtaining **8a** as the sole product with an enantiomeric excess of 85%. The formation of **8a** with the same enantiomeric excess as that of **6a** suggests that this rearrangement occurs from **6a** with isomerization of **5a** to **6a**, and a viable pathway to **8a** is described in Scheme 9. Diastereomer **6a** has the ketone carbonyl in close proximity with the basic nitrogen that allows 1,2-migration with concurrent C–C bond formation with the ketone carbonyl carbon followed by N to O Lewis acid/proton exchange and subsequent loss of water. If the alternative ring cleavage/readdition pathway[12] had occurred, the %*ee* of **8a** would have been the average of the %*ee* values of **5a** and **6a**.

To ascertain the breadth of indoles that would be suitable for cycloaddition, we monitored Sc(OTf)$_3$-catalyzed reactions between **3a** and 2-methylindole (**4g**), indole (**4h**), and *N*-methylindole (**4i**). As expected from prior investigations of vinyldiazo compounds or donor–acceptor cyclopropanes with 2-methylindole or its *N*-methyl derivatve,[7,13] formal C–H insertion (addition with 1,5-*H*-transfer) occurred at the indole-3-position to form a 1:1 diastereomeric mixture (**9**) with the two diastereomers enantiomerically enriched (eq 3).

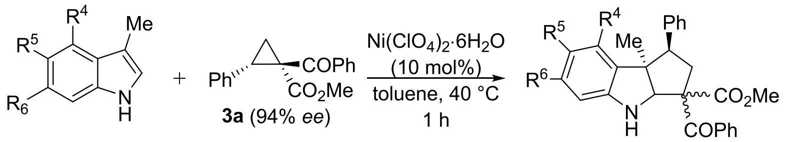
Scheme 5. Isomerization of 3-Methylindole [3+2]-Cycloaddition Products



Scheme 6. Proposed Reversibility of the Ring-Closing Step in the [3+2]-Cycloaddition of 3a with 3-Methylindole

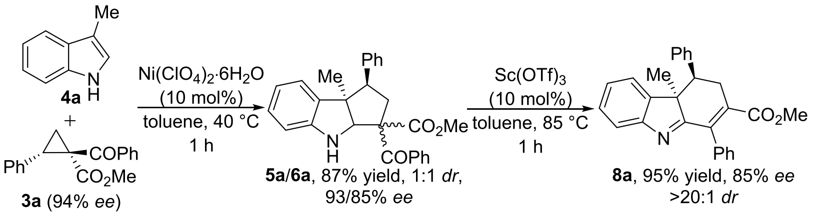


Scheme 7. [3+2]-Cycloaddition Reactions of Substituted 3-Methylindoles with 3a



4b: R^5 = MeO, R^4 = R^6 = H	80% yield	**5ba**:**6ba** = 1:1 = 93(91)% *ee*
4c: R^6 = Me, R^4 = R^5 = H	80% yield	**5ca**:**6ca** = 2:1 = 92(89)% *ee*
4d: R^4 = Me, R^5 = R^6 = H	81% yield	**5da**:**6da** = 2.5:1 = 92(88)% *ee*
4e: R^5 = Cl; R^4 = R^6 = H	88% yield	**5ea**:**6ea** = 15:1 = 93% *ee*
4f: R^5 = Br, R^4 = R^6 = H	85% yield	**5fa**:**6fa** = 12:1 = 93% *ee*

Scheme 8. [3+2]-Cycloaddition with 3-Methylindole and Subsequent Rearrangement



[3+2]-Cycloaddition of indole with **3a** occurred rapidly at 40 °C to form a 1:1 diastereomeric pair (**10**) with significant retention of enantiomeric purity. Diastereoisomers **10** were stable under these conditions for several hours but underwent rearrangement in refluxing 1,2-dichloroethane to yield dihydrocarbazole **11** in high overall yield (eq 4). With the absence of a methyl group at the indole-3-position, the reaction of indole (**4c**) undergoes cycloaddition to form **10**, elimination of water to yield the carbazole structure **11**, and its x-ray structure confirms the assignment. Finally, *N*-methylindole underwent the same transformations as indole and gave similar results (eq 5).

The influence of para substituents (Z) on the 2-aryl substituent of **3** was determined from various nickel perchlorate catalyzed cycloaddition reactions of 3-methylindole and for their subsequent scandium triflate catalyzed rearrangements, and this data is presented in Table 1. Both electron-donating and electron-withdrawing substituents have

Scheme 9. Mechanism for Rearrangement of 6a

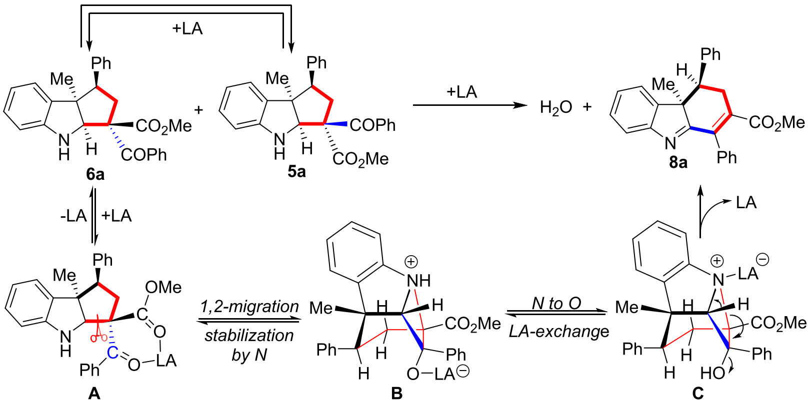
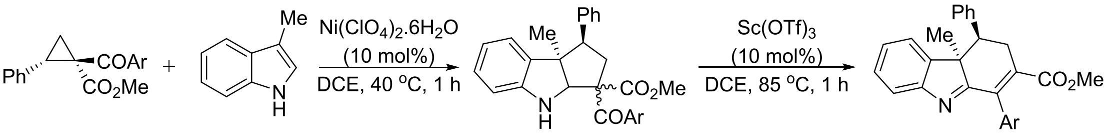


Table 1. Influence of Aroyl Substituents on Enantioselectivity and Yield in Carbazole (8) Formation[a]



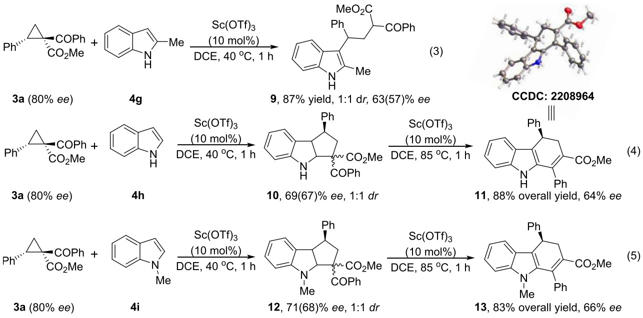
3 (Z, % *ee*, catalyst)	cycloaddition products **5** (% *ee*), **6** (% *ee*), *dr*	rearranged product **8** (% *ee*)	overall yield, %
3a (H, 94, Rh_2(S-BTPCP)$_4$)	**5a** (93), **6a** (85), 1:1	**8a** (85)	84
3b (MeO, 72, Rh_2(*S*-TBPTTL)$_4$)	**5b** (71), **6b** (72), 1:1	**8b** (60)	55[b]
3c (Me, 59, Rh_2(*S*-TBPTTL)$_4$)	**5c** (59), **6c** (55), 4:1	**8c** (48)	65
3d (Cl, 70, Rh_2(*S*-TBPTTL)$_4$)	**5d** (76), **6d** (77), 1.5:1	**8d** (74)	76
3e (CF_3, 40, Rh_2(*S*-TBPTTL)$_4$)	**5e** (50), **6e** (55), 1:1	**8e** (45)	71[b]

[a] Reactions were performed in toluene at 40 °C with $Ni(ClO_4)_2 \cdot 6H_2O$ for the formation of **5**/**6** and at 85 °C with $Sc(OTf)_3$ for the formation of **8**.
[b] 20 mol % of $Sc(OTf)_3$ was used.

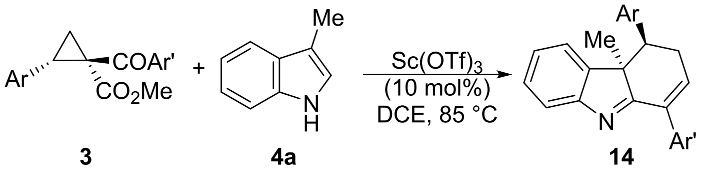
little effect on enantiomeric excess in the cycloaddition reaction, and electron-withdrawing substituents retain enantioselectivity in the rearrangement of **6** to **8**. However, cycloaddition product **6b** with an electron-donating methoxy substituent undergoes a significant loss of enantiomeric excess in the formation of **8b**, and this must have occurred with cleavage of the C−C bond between the indole-3-position and the adjacent aryl-substituted carbon.

The gain in %*ee* in the formation of their cycloaddition products (**5** and **6**) for the conversions of cyclopropane precursors having electron-withdrawing substituents (Table 1) was a matter of concern whose explanation was considered to be due to the influence of chiral products acting as ligands for the Lewis acid catalyst.[14] To test this hypothesis, we added 10 mol% of a 1:1 mixture of **5a** (93% *ee*):**6a** (85% *ee*) to the reaction mixture consisting of **3d** (70% *ee*), 3-methylindole **4a**, and 10 mol% $Ni(ClO_4)_2 \cdot 6H_2O$ in toluene (eq 6). The reaction was completed after 1 hour at 40 °C and produced a 1.5:1 mixture of **5d** (82% *ee*) and **6d** (81% *ee*), which was compared to **5d** (76% *ee*) and **6d** (77% *ee*) that was obtained without adding **5a**/**6a**. Obviously, the added **5a**/**6a** mixture enhanced enantiocontrol from that obtained without its presence.

For reactions of **5a**/**6a** performed in refluxing DCE under nitrogen without the rigorous exclusion of water, a new compound began to appear whose structure (**14a**) was consistent with hydrolysis and decarboxylation of **8a**. This transformation occurred slowly but was completed over a 50-h period. The surprising origin of this product was determined to be from **8a** *via* presumed hydrolysis and decarboxylation. No reaction occurs in the absence of water, but with the addition of only 2.0 equivalent amount of water, just twice the amount that is produced in the conversion of **6a** to **8a**, hydrolysis and decarboxylation is complete within 50 h (eq 7). The fact that water was involved was determined by deuterium labeling from the reaction performed in the presence of 99.9% D_2O, which formed **14a-D** with 80% deuterium incorporation (eq 8). Despite our attempts to remove all H_2O from the glassware and reaction solution, some sources of protons continued to donate hydrogen. When we used 99.4% D_2O, the same reaction gave **14a-D** with only 33% deuterium incorporation.

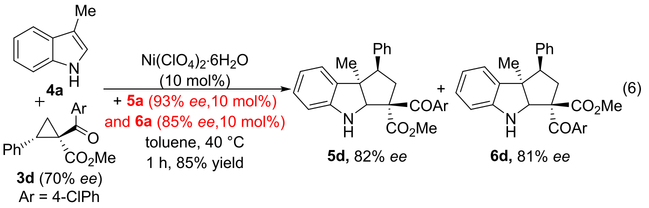


Scheme 10. Cycloaddition−Rearrangement−Hydrolysis−Decarboxylation from Reactions of Donor−Acceptor Cyclopropanes 3 and 3-Methylindole 4a



3a (80% *ee*): Ar = Ar' = Ph
3d (70% *ee*): Ar = Ph; Ar' = *p*-ClC_6H_4
3f (61% *ee*), Ar = Ph; Ar' = *p*-BrC_6H_4
3g (50% *ee*): Ar = *p*-$MeOC_6H_4$; Ar' = Ph
3h (70% *ee*): Ar = *p*-ClC_6H_4; Ar' = Ph
3i (77% *ee*): Ar = *p*-BrC_6H_4; Ar' = Ph

14a, 70% yield, 69% *ee*, >20:1 *dr*
14d, 68% yield, 57% *ee*, >20:1 *dr*
14f, 58% yield, 47% *ee*, >20:1 *dr*
14g, 67% yield, 0% *ee*, >20:1 *dr*
14h, 65% yield, 69% *ee*, >20:1 *dr*
14i, 68% yield, 76% *ee*, >20:1 *dr*



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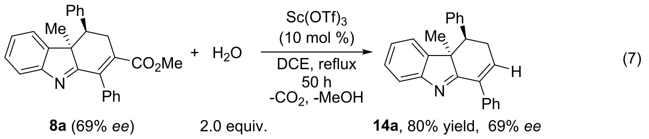
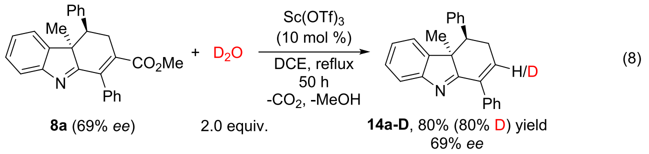


(7)



(8)

Decarboxylation reactions have been the subject of numerous chemical and biochemical studies,[15] most of which involve radical intermediates[16] or are catalyzed by transition metals.[17] With few exceptions,[18] decarboxylation reactions are generally carried out at high temperatures or with oxidants.[19] One of the exceptions is indole-3-carboxylic acid, which undergoes decarboxylation under mild conditions,[20] but **8a** undergoes both hydrolysis and decarboxylation under even milder conditions.

In an attempt to perform the multistep reaction to **14a** from donor−acceptor cyclopropane **3a** and 3-methylindole (**4a**) in one pot, the combined reagents with $Sc(OTf)_3$ were heated at reflux in 1,2-dichloroethane for 24 h without adding water to form **14a** in 70% yield with high retention of configuration in most cases. This transformation follows the cascade of steps catalyzed by the Lewis acid that begins with cycloaddition to **5a**/**6a**, then rearrangement of **6a** to **8a** that serves to produce an equivalent amount of water (Scheme 9), which facilitates hydrolysis of **8a** and, finally, decarboxylation. The same transformation was performed with a variety of non-racemic donor−acceptor cyclopropanes, and their outcomes are described in Scheme 10. As can be seen from the composite data, overall yields are moderate, and the retention of optical purity basically follows the enantiocontrol achieved in the formation of **6**.

CONCLUSIONS

[3+2]-Cycloaddition of chiral non-racemic donor−acceptor cyclopropane-1,1-dicarbonyl compounds with indoles can occur with high enantioretention but generally forms two diastereoisomers in nearly equivalent amounts, and $Ni(ClO_4)_2$ provides the highest levels of enantiocontrol of the Lewis acids that were examined. The stepwise transformation occurs with the inversion of configuration on the reactant donor−acceptor cyclopropane, and the second step in the cycloaddition process that forms the product diastereoisomers is generally reversible with low diastereocontrol. However, 3-methylindoles with electron-withdrawing substituents at the 5-position show high diastereocontrol. The stepwise reaction was assumed in prior studies using malonate-derived cyclopropane reactants,[6b,8,12a] but without evidence that is revealed in this study. The presence of the diastereomer whose ketone carbonyl is proximal to the indole nitrogen facilitates rearrangement with dehydration to generate a carbazole derivative with retention of configuration. Prior studies have reported carbazole formation from reactions of cyclopropane derivatives with indoles,[12] but their explanations did not reveal the [3+2]-cycloaddition product as an intermediate. Finally, the carbazole-carboxylate product was found to undergo catalytic hydrolysis and decarboxylation under very mild conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c05930.

- Experimental procedures and spectroscopic data for all new compounds (PDF)
- X-ray crystallographic data for **3a** (CIF)
- X-ray crystallographic data for **6a** (CIF)
- X-ray crystallographic data for **11** (CIF)

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Notes

The authors declare no competing financial interest.

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