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Asymmetric Carbocation Catalysis

Chiral Anion Directed Asymmetric Carbocation-Catalyzed Diels–Alder Reactions

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Abstract: In recent years the carbocation has re-emerged as a highly efficient Lewis acid catalyst for a variety of organic transformations. However, the goal of asymmetric carbocation catalysis has so far been out of reach mainly as a result of difficulties associated with the preparation of stable chiral carbocations. Here, we describe developments towards asymmetric carbocation catalysis based on the concept of chiral-anion-directed catalysis. Chiral tritylium salts can be conveniently prepared in situ by mixing trityl chloride derivatives with chiral phosphonate, phosphoramide, bis(sulfonyl)amide, and bis(sulfuryl)amide silver or sodium salts. It is shown that the bis(sulfuryl)amide/tritylium ion salt catalyzes the Diels–Alder reaction with an up to 53 % enantiomeric excess.

Introduction

Ever since its discovery[1] more then a century ago the triarylmethylium (trityl, Tr) ion has been well studied in terms of physical properties and reactivity.[2] Although trityl ions are highly versatile Lewis acids owing to their low-lying empty P_C-orbital, they have been almost completely neglected as Lewis acid catalysts,[3] except for a few elegant studies, mainly by Mukaiyama et al., 30 years ago.[4,5] In light of more recent work, the trityl ion has reemerged as a highly efficient Lewis acid catalyst for several different organic transformations.[6,7]

An intriguing quest in the field of carbocation Lewis acid catalysis is the development of asymmetric reactions. This is highly challenging as a result of the intrinsic problems associated with carbocation stability and reactivity. The rather unstable cationic carbon needs stabilization by at least two or three aryl groups. Furthermore, α-hydrogen atoms directly attached to the carbocation or in *ortho*- or *para*-positions on the pending phenyl ring are highly unstable as a result of E1 elimination, and α-tertiary alkyl groups can cause problems as a result of 1,2-alkyl shifts/elimination processes. These issues create difficulties about how to introduce a chiral environment in close proximity to the reaction center. So far, the few reported attempts have met with poor success.[8]

One alternative approach is to introduce enantioselectivity through asymmetric counter-anion-directed catalysis (ACDC) by means of a chiral anion that can potentially induce enantioselectivity in catalysis through a contact ion pair. This strategy has previously been applied successfully in organocatalysis and transition-metal catalysis.[9]

Recently, Luo et al. reported a most elegant study on chiral counterion/trityl ion directed catalysis.[7] They showed that enantioenriched trityl phosphates **1a**–**1c** could be used as a carbocation precursor for asymmetric Lewis acid catalysis. The labile C–O bond in trityl-phosphates **1a**–**1c** undergoes ionic dissociation upon interaction with a carbonyl electrophile to form catalytically a substrate–trityl oxonium ion/chiral anion pair, which can induce stereoselectivity through chiral counterion control. This strategy was demonstrated for the Michael addition reaction of indole and 3-methoxyphenol to activated α,β-unsaturated ketones, the hetero-Diels–Alder reaction, and the hetero-ene reaction with moderate to good enantioselectivity (Scheme 1).

In light of this excellent study we felt obliged to report our own results in this challenging area.

We have previously shown that the trityl cation (e.g. $TrBF_4$) is an outstanding catalyst for the Diels–Alder reaction of α,β-unsaturated aldehydes with un-activated dienes with catalyst loadings as low as 500 ppm.[6a,6c] During the past year we have addressed the challenge of developing an asymmetric catalytic version of this reaction. Here we present our attempts toward this goal based on asymmetric counter-anion directed catalysis (Scheme 2). We based our strategy on the in situ formation of a contact trityl cation/chiral anion pair from corresponding trityl chloride TrCl **2** and the silver or sodium salt of chiral phosphates **3**,[10] phosphoric amides **4**,[11] bis(sulfonyl)amide **5**,[12] or bis(sulfuryl)amide **6**[13] (Figure 1 and Figure 2). We anticipated that the chiral ion pair formed would be in equilibrium with the inactive covalent bound Tr-anion species (Scheme 2). Luo et al. showed that these types of equilibrium could be shifted to the left upon addition of a carbonyl substrate.[7] In the proposed catalytic cycle the dienophile, e.g. the free electron pair on α,β-unsaturated aldehyde **7**, attacks the trityl ion to form an intermediate oxonium ion/chiral anion pair. This lowers the

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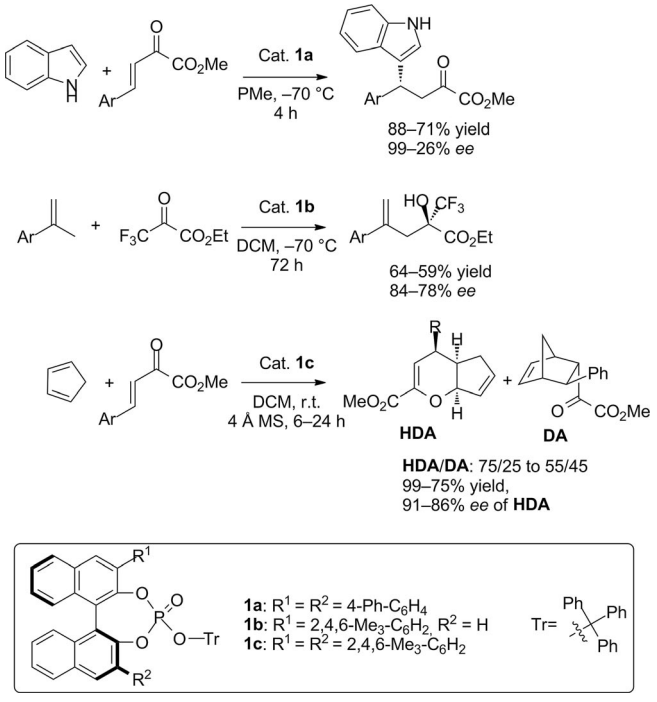
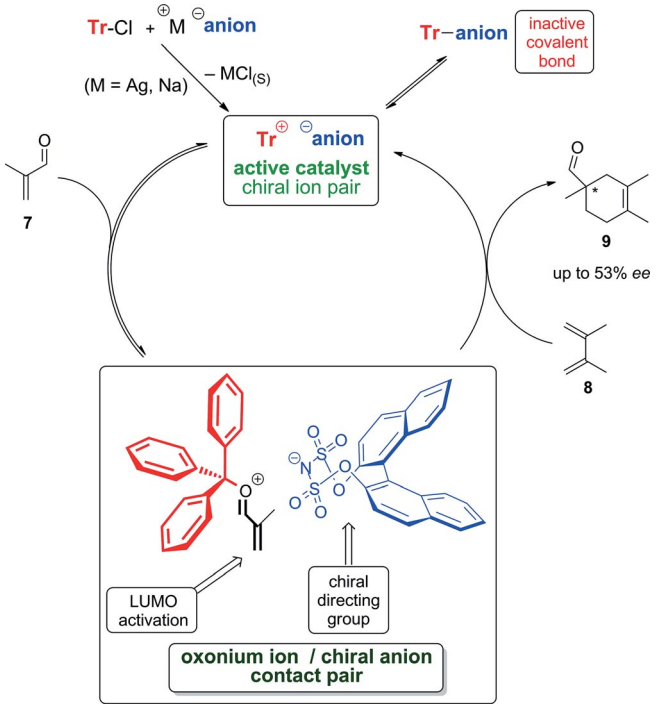


Scheme 1. Asymmetric catalysis using chiral trityl phosphate recently reported by Luo et al.[7]

LUMO of the substrate and enables the enantioselective cycloaddition reaction with diene **8** to give adducts **9**. By using binol-based bis(sulfuryl)amide **6a** we were able to catalyze the Diels–Alder reaction with up to 53 % enantiomeric excess.



Scheme 2. Strategy for a chiral anion directed asymmetric carbocation catalyzed Diels–Alder reaction.

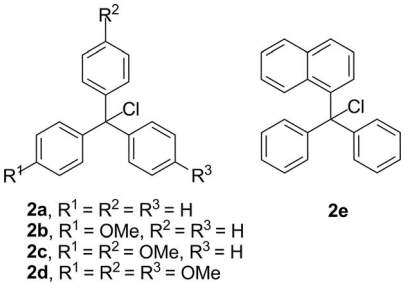


Figure 1. Trityl ion precursors.

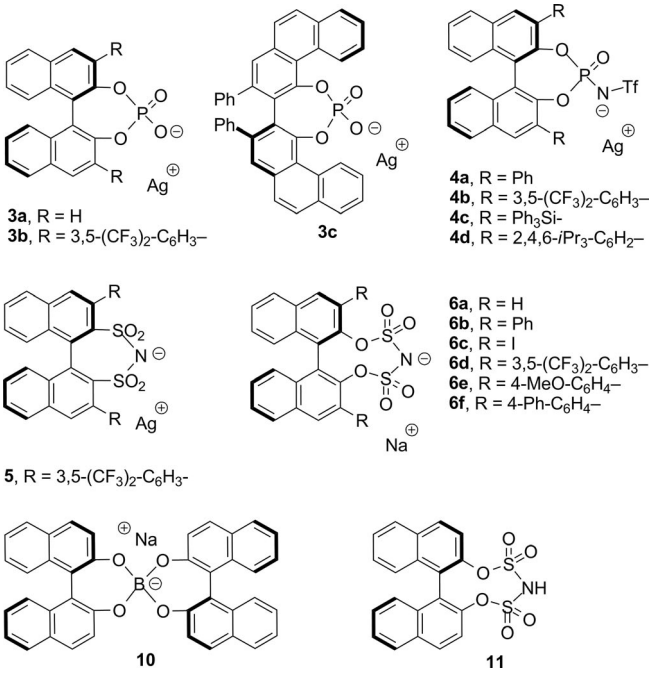


Figure 2. Chiral ions.

Results and Discussion

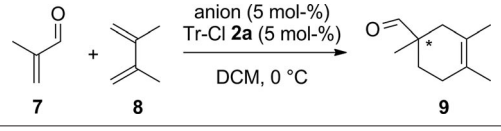
The silver and sodium salts of chiral phosphate **3**, phosphoric amides **4**, bis(sulfonyl)amide **5**, and bis(sulfuryl)amide **6** based on the binol scaffold are easily available chiral anions that have previously been successfully used in ACDC reactions (Figure 1).[9] Upon mixing of these salts with TrCl **2a** in CH_2Cl_2, an immediate precipitation of AgCl or NaCl occurred. These solutions were then directly used as catalysts for the Diels–Alder reaction of methacrylaldehyde **7** and 2,3-dimethylbutadiene **8** at 0 °C.

It should be noted that by mixing TrCl with bis(sulfonyl)-amide **5** and bis(sulfuryl)amide **6** heavily colored solutions resulted, which indicates the presences of trityl ion species. However, chiral phosphate **3** and phosphoric amide **4** gave colorless or very weakly colored solutions when mixed with TrCl, which indicates no or very low concentrations of free trityl ions.

From the screening of different counterion scaffolds we found that phosphoric amide **4a**, bis(sulfuryl)amide **6a**, and binol-derived borate ion **10**[14] resulted in the formation of potential catalysts for the Diels–Alder reaction of methacrylaldehyde (**7**) and 2,3-dimethylbutadiene (**8**) in the presence of TrCl

2a (Table 1, Entries 2, 4, 5, and 6). However, both phosphate **3a** and bis(sulfonyl)amide **5** resulted in very poor catalytic activity and low conversion into adduct **9** under the same reaction conditions (Table 1, Entries 1 and 3).

Table 1. Screening of the counterion motif.[a]



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Entry[a]	Anion	*t*	Conv.[b]	*ee*[c]
		[h]	[%]	[%]
1	**3a**	70	2	13
2	**4a**	100	40	4
3	**5**	26	5	5
4	**6a**	16	28	28
5	**6a**	**90**	**73**	**28**
6	**10**	91	23	0
7[d]	**6a**	68	0	–
8[e]	–	68	4	–
9[d]	**11**	23	40	11

[a] The anion (5 mol-%) and TrCl **2a** (5 mol-%) were dissolved in CH_2Cl_2. After 10 min the solution was cooled to the indicated temperature, methacrylaldehyde (**7**; 1 equiv.) and 2,3-dimethylbutadiene (**8**; 1 equiv.) were added (0.3 M) and the mixture was stirred for the indicated time. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral GC. [d] Reaction without TrCl **2a**. [e] Reaction without anion.

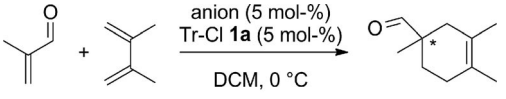
In terms of stereoselectivity bis(sulfuryl)amide **6a** was by far the best motif and gave Diels–Alder adduct **9** in 28 % *ee* (Table 1, Entry 5). Unfortunately, phosphoric amide **4a** and chiral borate ion **10** gave the Diels–Alder adduct with very poor and no stereoselectivity, respectively (Table 1, Entries 2 and 6).

In the absence of TrCl **2a** no reaction occurred (Table 1, Entry 7). Furthermore, in the abscess of anion reactivity slowed significantly and only 4 % conversion was observed after an extended reaction time, which indicates that TrCl **2a** is not responsible for any background catalysis (Table 1, Entry 8).

The trityl cation readily reacts with a number of rather weak nucleophiles and bases, such as water and olefins, and is also a reasonable hydride abstractor. Such processes would result in the formation of the corresponding acid of the anion, which would be a potent catalyst for the Diels–Alder reaction. However, there are strong preferences that trityl ion catalyzed Diels–Alder reactions do not operate through carbocation degradation and Brønsted acid catalysis.[5d,6a,6c] In addition, we found that the corresponding acid of **6a**, bis(sulfuryl)imide **11**, is a more efficient catalyst in terms of reactivity relative to the TrCl **2a**/Anion **6a** ion pair. However, for bis(sulfuryl)imide **11** enantioselectivity decreased significantly, which lead us to the conclusion that these reactions are not under Brønsted acid catalysis (Table 1, Entry 9).

Next, we turned our attention towards 3,3′-substitution of the binol motif with the expectation that increased steric bulk would have a positive influence on the enantioselectivity. 3,5-Bis(trifluoromethyl)phenyl-substituted phosphonate **3b** and TrCl **2a** gave only 13 % *ee* under the standard reaction conditions (CH_2Cl_2, 0 °C), which is the same selectivity that was observed for non-substituted phosphoric acid **3a** (Table 2, Entry 1 versus Table 1, Entry 1). For even bulkier VAPOL-phosphonate **3c** the reaction was almost completely inhibited and no enantioselectivity was observed (Table 2, Entry 2). Interestingly, for phosphoramides **4a**–**4d** we could observe a trend of increasing enantioselectivity with increasing bulk from 4 % *ee* for Ph- (**4a**) to 18 % *ee* for Ph_3Si- (**4c**) and tri-*i*Pr-Ph- groups (**4d**; Table 2, Entries 3–5 versus Table 1, Entry 2). What was most striking was the dramatic increase in reactivity that was observed for phosphoramide **4d** that resulted in complete conversion in 36 h (Table 2, Entry 5).

Table 2. Screening of binol motifs.[a]



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Entry[a]	Anion	*t* [h]	Conv.[b] [%]	*ee*[c] [%]
1	**3b**	70	10	13
2	**3c**	70	3	0
3	**4b**	64	18	8
4	**4c**	35	24	18
5	**4d**	36	<95	18
6	**6b**	20	45	2
7	**6c**	21	80	14
8	**6d**	26	5	5
9	**6e**	22	20	7
10	**6f**	19	24	6

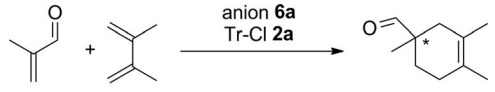
[a] The anion (5 mol-%) and TrCl **2a** (5 mol-%) were dissolved in CH_2Cl_2. After 10 min the solution was cooled to the indicated temperature, methacrylaldehyde (**7**; 1 equiv.) and 2,3-dimethylbutadiene (**8**; 1 equiv.) were added (0.3 M) and the mixture was stirred for the indicated time. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral GC.

For our best lead so far, bis(sulfuryl)amide **6a**, we were most disappointed to find that all attempts to increase the stereoselectivity of the Diels–Alder reaction by tuning the bulk of the binol scaffold failed and all substitutions made in the 3,3′-positions resulted in significant decreases in enantioselectivity (Table 2, Entries 6–10 versus Table 1, Entries 4 and 5). These observations are rather puzzling because binol-based organic acids that are non-substituted in the 3,3′-position generally shows poorer selectivity relative to their bulkier 3,3′-substitude counterparts in asymmetric catalysis.

Although discouraged, we continued our optimization based on the best lead so far, bis(sulfuryl)amide **6a**, and TrCl **2a**. Halogenated solvents are superior for this reaction with 1,2-dichloroethane (DCE) being the fastest (Table 3, Entries 1–3). The use of more apolar solvent toluene, which should favor a close contact ion pair, resulted in a significant decrease in rate and only 15 % *ee* under these conditions (Table 3, Entry 4). The use of a more polar solvent had a negative effect on the enantioselectivity (Table 3, Entries 5–7). As expected, an increase in catalyst loading led to an increase in extent of conversion, however, there was no effect on enantioselectivity (Table 3, Entries 8–11). A decrease the reaction temperature had some effect on enantioselectivity; at –20 °C, 35 and 34 % *ee* was obtained in CH_2Cl_2 and DCE, respectively, with DCE giving

the highest conversion (Table 3, Entries 12 and 13). At –70 °C in CH_2Cl_2, the *ee* increased to 40 %, but unfortunately with very low conversion (Table 3, Entry 15). It should be noted that the TrCl **2**/Anion **6** catalyzed reactions are very clean and only starting material or product are identified by ^1H NMR spectroscopy of the crude reaction mixture. The Diels–Alder reaction of methacrylaldehyde (**7**) and 2,3-dimethylbutadiene (**8**) catalyzed by bis(sulfuryl)amide **6a** and TrCl **2a** gave the corresponding Diels–Alder adduct in 75 % isolated yield and 29 % *ee* after 96 h reaction time (Table 3, Entry 3).

Table 3. Screening of reaction conditions.[a]



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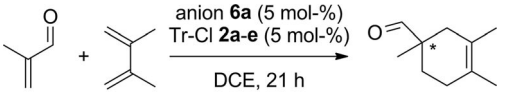
Entry[a]	Cat. [mol-%]	Solvent	*T* [°C]	*t* [h]	Conv.[b] [%]	*ee*[c] [%]
1	5	CH_2Cl_2	0	68	62	28
2	5	$CHCl_3$	0	68	29	21
3[d]	**5**	**DCE**	**0**	**68**	**78**	**29**
4	5	PhMe	0	68	10	15
5	5	THF	0	68	0	–
6	5	CH_3CN	0	68	17	4
7	5	CH_3NO_2	0	68	60	2
8	1	DCE	0	24	33	26
9	10	DCE	0	24	71	30
10	20	DCE	0	24	83	30
11	100	DCE	0	24	80	22
12	**5**	**CH_2Cl_2**	**–20**	**22**	**23**	**35**
13	**5**	**DCE**	**–20**	**22**	**41**	**34**
14	5	CH_2Cl_2	–20	70	37	35
15	5	CH_2Cl_2	–70	70	5	40

[a] Anion **6a** and TrCl **2a** were dissolved in CH_2Cl_2. After 10 min the solution was cooled to the indicated temperature, methacrylaldehyde (**7**; 1 equiv.) and 2,3-dimethylbutadiene (**8**; 1 equiv.) were added (0.3 M) and the mixture was stirred for the indicated time. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral GC. [d] Adduct **9** was isolated in 75 % yield and 29 % *ee* after 96 h reaction time.

The Lewis acidity of the trityl ion is easily tuned by variation of the electronic properties of the aromatic groups.[6a,6c,15] Thus, we wanted to see how this would affect the stereoselectivity of the Diels–Alder reaction. As expected from previous studies, the reactivity decreased as electron density on the aromatic groups increased e.g. as Lewis acidity of the carbocation decreased (Table 4, Entries 1–3). Tri-methoxy TrCl **2d** was too weak a Lewis acid to catalyze the Diels–Alder reaction under these conditions (Table 4, Entry 4). Unfortunately, the Lewis acidity had only a minor influence on enantioselectivity, although mono-methoxy TrCl **2b** gave a somewhat higher *ee* relative to TrCl **2a** and dimethoxy TrCl **2c** (Table 4, Entries 1–3). Bulkier carbocation 1-naphthyldiphenylmethylium ion **2e** did not influence the selectivity or the reactivity of the reaction (Table 4, Entry 5 versus Table 1, Entry 4).

Finally, the best selectivity for the Diels–Alder reaction was obtained with anion **6a** and TrCl **2b** at –70 in a 2:1 mixture of DCE/CH_2Cl_2, which gave the Diels–Alder adduct in 53 % *ee* but in only 9 % conversion after 45 h.

Table 4. Screening of TrCl derivatives.[a]



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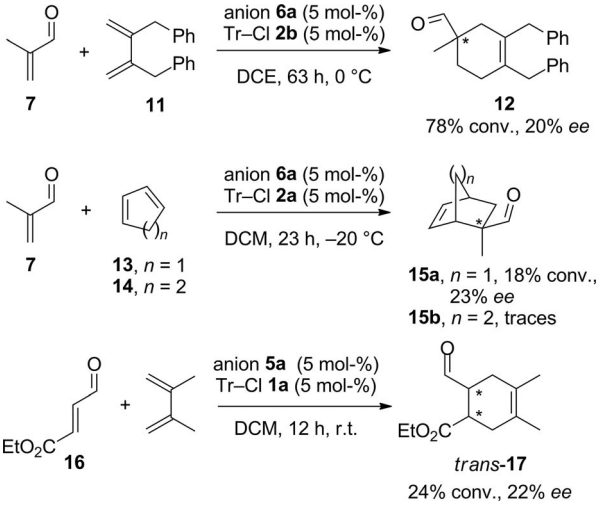
Entry	TrCl	*T* [°C]	Conv.[b] [%]	*ee*[c] [%]
1	**2a**	–20	41	34
2	**2b**	–20	23	39
3	**2c**	–20	4	36
4[d]	**2d**	–20	0	0
5[e]	**2e**	0	33	28
6[f, g]	**2b**	**–70**	**9**	**53**

[a] Anion **6a** (5 mol-%) and TrCl **2** (5 mol-%) were dissolved in CH_2Cl_2. After 10 min the solution was cooled to the indicated temperature, methacrylaldehyde (**7**; 1 equiv.) and 2,3-dimethylbutadiene (**8**; 1 equiv.) were added (0.3 M) and the mixture was stirred for the indicated time. [b] Determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral GC. [d] Reaction performed at 0 °C. [e] In CH_2Cl_2. [f] In DCE/CH_2Cl_2, 2:1. [g] Reaction time is 45 h.

Finally, we attempted the reaction with a few more dienes and dienophiles with limited success, although with substantial enantioselectivity demonstrates the concept of chiral-anion-directed carbocation catalysis (Scheme 3). 2,3-Dibenzylbutadiene (**11**) gave corresponding Diels–Alder adduct **12** in 20 % *ee* with anion **6a** and TrCl **2b**. Cyclopentadiene (**13**) gave the bicyclic adduct **15a** in 23 % *ee*, whereas 1,3-cyclohexadiene (**14**) did not react under these conditions. β-Substituted dienophile **16** gave *trans* adduct **17** in 22 % *ee*.



Scheme 3. Screening of different substrates for the chiral anion directed Diels–Alder reaction.

Conclusions

Here we have demonstrated that trityl cation/chiral anion contact pairs are catalytically active and capable of chiral induction in the Diels–Alder reaction with up to 53 % *ee* in accordance with the concept of chiral-anion-directed carbocation asymmetric catalysis. Although the results presented here are not of di-

rect synthetic value, they do provide an intriguing proof of concept to complement recent and more successful work by Luo et al.[7] in this area.

As a result of the exceptional Lewis acid properties of the carbocation and their recent application in catalysis for a variety of transformations, chiral anion directed asymmetric trityl ion catalysis has the potential to become a highly efficient strategy in organic synthesis.

We are continuing to explore the scope and limitations of chiral-anion-directed asymmetric trityl ion catalysis to gain further understanding of reactivity, to increase the enantioselectivity, and to extend the reaction scope. These results will be reported in due course.

Experimental Section

General: All reactions were performed in pre-dried solvents under a nitrogen atmosphere. Imidobis(sulfuryl chloride) was prepared in accordance with literature procedures.[13,16] The ^{1}H and ^{13}C NMR spectra were recorded at 500 or 400 MHz and 125 MHz, respectively. Chemical shifts are reported relative to $CHCl_3$ (δ = 7.26 ppm), [D_6]DMSO (δ = 2.50 ppm), and CD_3OD (δ = 3.32 ppm) resonances for ^{1}H NMR spectroscopy, and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Flash chromatography and column chromatography were carried out with Merck silica gel 60 (230–400 mesh).

General Procedures for the Preparation of Sodium 1,1′-Binaphthyl-2,2′-bis(sulfuryl)amides 6[13]

Method A. Exemplified by the Preparation of Sodium (R)-3,3′-Diiodo-1,1′-binaphthyl-2,2′-bis(sulfuryl)amide (6c): To a stirred solution of (*R*)-3,3′-diiodo-2,2′-dihydroxy-1,1′-binaphthyl (1.13 g, 2.10 mmol) in dry toluene (20 mL) was added sodium hydride (60 % in mineral oil, 265 mg, 6.62 mmol). The suspension was heated to 130 °C, and imidobis(sulfuryl chloride) (517 mg, 2.41 mmol) in dry toluene (10 mL) was added over a period of 30 min. The reaction mixture was stirred at 130 °C for 24 h. After cooling, the solution was poured into water (10 mL), and all volatile components were removed under reduced pressure to give a greenish, semisolid residue. Purification by flash chromatography (CH_2Cl_2/MeOH = 5:1) gave compound **6c** as a light yellow solid (736 mg, 50 %). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.68 (s, 2 H, Ar-H), 7.91 (d, J = 8.4 Hz, 2 H, Ar-H), 7.49 (t, J = 7.2 Hz, 2 H, Ar-H), 7.32 (t, J = 7.2 Hz, 2 H, Ar-H), 6.81 (d, J = 8.4 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 149.2, 142.2, 134.5, 134.2, 128.6, 128.27, 128.22, 127.9, 126.2, 90.3 ppm. HRMS (ESI): m/z = calcd. for $C_{20}H_{10}I_2NNa_2O_6S_2$ [M + Na]$^+$ 723.7834; found 723.7829.

Method B. Exemplified by the Preparation of Sodium (*R*)-3,3′-Diphenyl-1,1′-binaphthyl-2,2′-bis(sulfuryl)amide (6b): To a solution of sodium (*R*)-3,3′-diiodo-1,1′-binaphthyl-2,2′-bis(sulfuryl)amide **6c** (20.0 mg, 0.03 mmol) and $Pd(PPh_3)_4$ (3 mol-%, 1.0 mg, 0.009 mmol) in EtOH (0.1 M) were added phenylboronic acid (13.4 mg, 0.11 mmol) and Na_3PO_4 (24.6 mg, 0.15 mmol). The resulting mixture was heated to reflux temperatures until all of the starting material had reacted, then cooled to room temperature, and passed through a pad of Celite. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed with saturated aqueous NH_4Cl, water, and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to give the crude product. Subsequent purification by flash chromatography (CH_2Cl_2/MeOH = 15:1) gave compound **6b** as a white solid (12 mg, 66 %). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.08 (s, 2 H, Ar-H), 8.01 (d, J = 8.0 Hz, 2 H, Ar-H), 7.68 (d, J = 7.2 Hz, 4 H, Ar-H), 7.48 (t, J = 7.2 Hz, 2 H, Ar-H), 7.39 (t, J = 7.6 Hz, 4 H, Ar-H), 7.33–7.28 (m, 4 H, Ar-H), 7.02 (d, J = 8.4 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 147.2, 140.3, 137.3, 134.2, 133.6, 132.3, 130.7, 129.4, 129.15, 129.05, 128.1, 127.9, 127.4, 126.3 ppm. HRMS (ESI): m/z = calcd. for $C_{32}H_{20}NNa_2O_6S_2$ [M + Na]$^+$ 624.0527; found 624.0522.

General Procedure for Diels–Alder Reaction (screening conditions): Sodium bis(sulfuryl)amide **6** (0.0075 mmol) and TrCl **2** (0.0075 mmol) were dissolved in CH_2Cl_2 (0.3 mL). After 10 min, the solution was cooled to the indicated temperature and methacrylaldehyde (0.15 mmol) and 2,3-dimethylbutadiene (0.15 mmol) were added. The resulting mixture was stirred for the indicated time. Conversion into product was followed by ^{1}H NMR spectroscopy. The enantiomers were separated by GC on a CYCLOSIL-B column: temperature program: 60 °C (10 min)/2 °C min^{-1}/ 130 °C (30 min)/ 10 °C min^{-1}/ 180 °C (5 min). R_t (min): 40.9 (minor enantiomer); 41.8 (major enantiomer).

Preparation of 1,3,4-Trimethylcyclohex-3-ene-1-carbaldehyde (9): (Table 3, Entry 3). Sodium bis(sulfuryl)amide **6a** (17 mg, 0.0375 mmol) and TrCl **2a** (10 mg, 0.0375 mmol) were dissolved in DCE (2.5 mL). After 10 min, the solution was cooled to 0 °C and methacrylaldehyde (**7**; 62 µL, 0.75 mmol) and 2,3-dimethylbutadiene (**8**; 85 µL, 0.75 mmol) were added and the reaction mixture was stirred at 0 °C for 96 h. The reaction was quenched with a drop of water and directly purified by flash chromatography (pentane/Et_2O = 20:1) to give compound **9** as a colorless oil (85.0 mg, 75 %, 29 % *ee*). All characterization data was in accordance with those previously reported.[17] The enantiomers were separated by GC on a CYCLOSIL-B column: Temperature program: 60 °C (10 min)/ 2 °C min^{-1}/ 130 °C (30 min)/10 °C min^{-1}/ 180 °C (5 min). R_t (min): 40.9 (minor enantiomer); 41.8 (major enantiomer).

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