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ARTICLE

Regioselective molybdenum-catalysed allylic substitution of tertiary allylic electrophiles: methodology development and applications

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The first molybdenum-catalysed allylic sulfonylation of tertiary allylic electrophiles is described. The method utilizes a readily accesable catalyst ($Mo(CO)_6$/2,2′-bipyridine, both are commercially available) and represent the first example of the use of a group 6 transition metal-catalyst to substituted tertiary allylic electrophiles to form carbon-sulfur bonds. This atom economic and operationally simple methodology is charaterized by its relatively mild conditions, wide substrate scope, and excellent regioselectivity profile, thus unlocking a new platform to synthesize allylic sulfones, even at late stages and providing ample oppertunaties for further derivatization through traditional Suzuki cross-coupling reactions.

Introduction

The concept of π-allyl metal-complex was first formulated by Tsuji in 1965[1a] and, later, properly adopted by Trost in 1973.[1b] Since then, this technology has enabled organic chemists to create novel procedures for the synthesis of simple to complex molecules.[2] Among these is the development and utilization of heteroatom nucleophile reagents, such as oxygen, nitrogen, and or sulfur-based nucleophiles.[2,3] Despite the massive development that has been made in this area, there still remain untapped opportunities in the potential application of these heteroatom nucleophile reagents in transition metal-catalysed allylic substitution. For example, molybdenum-catalysed allylic substitution reactions of heteroatom nucleophiles are unknown and largely limited only to the carbon-carbon bond formation procedures (Figure 1A, left).[4] Furthermore, the substrate scope with respect to the allylic electrophile has also been unchanged and restricted to the ones that provide products containing a tertiary center at the allylic position.[5] Regardless of the longstanding interest in the formation of carbon-heteroatom bond with in the synthetic organic community, as well as the advancement of other transition-metal-catalysed reactions to provide heteroatom bearing quaternary and or tertiary allylic centers,[6] molybdenum-catalysed allylic substitution reactions that provide products containing such a stereocenter remain prominently absent from the literature and yet to be discovered (Figure 1A, right).[7]

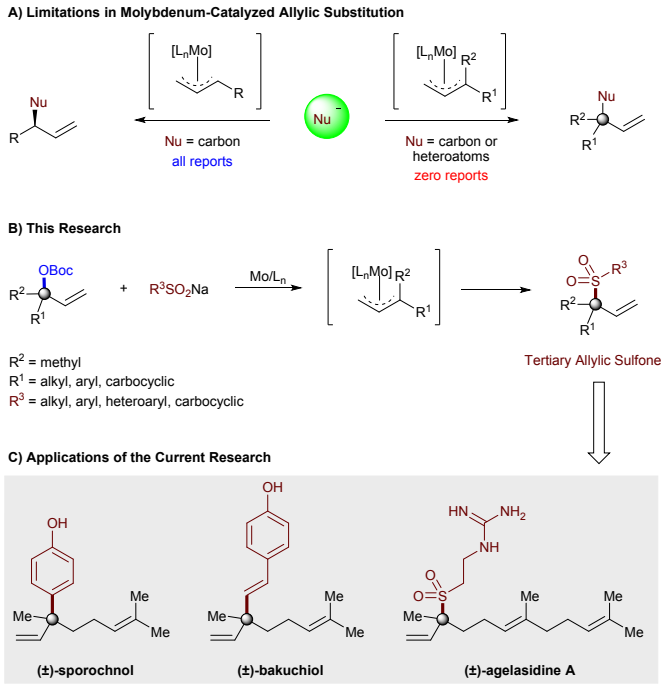

Fig. 1 (A) Limitations in molybdenum-catalysed allylic substitution, (B) our research, and (C) applications of the current research.

Due the high importance of allylic sulfones as pharmaceuticals[8] and synthetic candidates,[9] organic chemists have recently been tested to design catalytic C-S bond cleavage procedures as a new tool for carbon-carbon bond formation through Suzuki cross-coupling[10] and or allylic substitution reactions.[11] Despite the considerable development realized in this zone, allylic sulfone formation is still a challenging task and confined to the use of transition metal-catalysed allylic sulfonylation procedures.[12,13] However, using these procedures for the synthesis of allylic sulfone containing tetrasubstituted carbon centers are scarce and largely unexplored.[14] Therefore, at the beginning of our study it was

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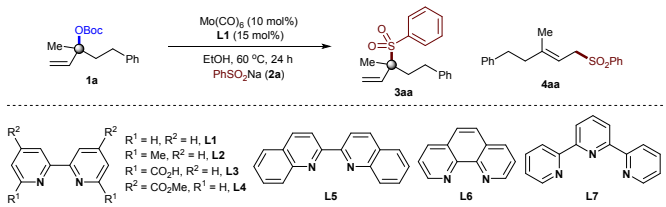
unclear whether a molybdenum-catalysed allylic substitution could ever be implemented with heteroatom (sodium sulfinate) nucleophile or even with α,α-disubstituted allylic precursors. If successful, such unexplored area of allylic substitution chemistry might not only provide opportunity to realize currently inaccessible chemical space (carbon-heteroatom bond formation) in molybdenum-catalysed allylic substitution, but also provide a new synthetic approach for rapidly generate quaternary all-carbon centers through Suzuki cross-coupling of the sulfone functionality. As part of our ongoing program in developing molybdenum-catalysed allylic substitution technology and our continued interest in the catalytic asymmetric synthesis of quaternary stereocenters,[14a, 15] we were attracted to this unmet challenge and report herein the successful implementation of this idea (Figure 1B). The salient features of this methodology are the atom-economic procedures, high regioselectivity, and excellent functional group tolerance for both sulfinate salt and tertiary allylic carbonates, even at late-stages. Furthermore, the high reactivity of tertiary allylic sulfones as a new class of electrophiles to yield structurally diverse products containing quaternary all-carbon centers through Suzuki cross-coupling are the special characteristic of this catalytic system (Figure 1C).[10a]

Table 1. Optimization of the reaction parameters[a]



Entry	Deviation in conditions	**3aa**/**4aa**[b]	**3aa** (%)[c]
1	none	99:1	92
2	**L2** was used instead of **L1**	99:1	87
3	**L3** was used instead of **L1**	99:1	35
4	**L4** was used instead of **L1**	99:1	52
5	**L5** was used instead of **L1**	25:1	16
6	**L6** was used instead of **L1**	--	0
7	**L7** was used instead of **L1**	--	>5
8	$(C_7H_8)_3Mo(CO)_3$ was used	99:1	82
9	THF was used as solvent	--	>5
10	Toluene was used as solvent	-	>5
11	DCE was used as solvent	25:1	35
12	^{i}PrOH was used as solvent	99:1	77
13	THF/EtOH (5:1) as solvent	25:1	25
14	DCE/EtOH (5:1) as solvent	25:1	63
15	Without Mo or **L1**	--	0

[a] Reaction conditions: Mo-catalyst (10 mol%), ligand (15 mol%), **1a** (0.2 mmol), $PhSO_2Na$ **2a** (0.3 mmol), solvent (1.0 mL, 0.2 M), 60 °C, 24 hours. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yields.

Results and discussion

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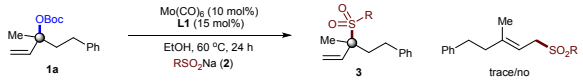
Our optimization began by evaluating the allylic substitution of tertiary allylic carbonate **1a**, readily prepared from the corresponding alcohol on a large scale, with sodium benzenesulfinate **2a** (Table 1). Interestingly, a disappointing amount of either **3aa** or **4aa** were detected under reaction conditions previously reported for other molybdenum-catalysed allylic substitution events.[4] After several experimentation,[16] we concluded that a combination of inexpensive commercially available $Mo(CO)_6$ precursor and 2,2′-bipyridyne as a ligand (**L1**)[17] in EtOH at 60 °C afforded **3aa** in 92% yield upon isolation with excellent branched to linear selectivity (**3aa**/**4aa** = > 99:1). Amongst all of the ligands utilized, 2,2′-bipyridine motifs were crucial for achieving the targeted transformation. While excellent reactivity towards **3aa** was found with 2,2′-bipyridines and 6,6′-dimethyl-2,2′-bipyridine, better yields were obtained for the first one (entries 1–7). Interestingly, the bench-stable terpyridine **L7** failed to provide product **3aa**. These results indicate that the coordination geometry of the ligand dictates the reactivity, with 2,2′-bipyridine ligands being particularly suited for the high yield and selectivity of **3aa**. Subtle changes on the molybdenum precursor, and or solvent, however, had a negative influence on the reaction to occur, consistently providing lower yields if any (entries 8-14). As expected, control experiments revealed that all of the reaction parameters were necessary for forging the sulfone moiety (entry 15).

Table 2. Sodium sulfinate substrate scope[a-c]



Entry	**2**	**3**[b]	yield (%)[c]
1	**2a** (R = Ph)	**3aa**	92
2	**2b** (R = 4-MeC_6H_4)	**3ab**	93
3	**2c** (R = 4-$MeOC_6H_4$)	**3ac**	90
4	**2d** (R = 4-ClC_6H_4)	**3ad**	87
5	**2e** (R = 4-FC_6H_4)	**3ae**	85
6	**2f** (R = 4-$NO_2C_6H_4$)	**3af**	75
7	**2g** (R = 4-CNC_6H_4)	**3ag**	72
8	**2h** (R = 2-FC_6H_4)	**3ah**	88
9	**2i** (R = 2-ClC_6H_4)	**3ai**	87
10	**2j** (R = 2-$OCF_3C_6H_4$)	**3aj**	72
11	**2k** (R = 3-BrC_6H_4)	**3ak**	82
12	**2l** (R = 3-CNC_6H_4)	**3al**	78
13	**2m** (R = 2,4-$MeOC_6H_3$)	**3am**	94
14	**2n** (R = 3,5-$CF_3C_6H_3$)	**3an**	95
15	**2o** (R = 2-MeO,5-BrC_6H_3)	**3ao**	84
16	**2p** (R = 3,4-ClC_6H_3)	**3ap**	87
17	**2q** (R = 2-naphthyl)	**3aq**	82

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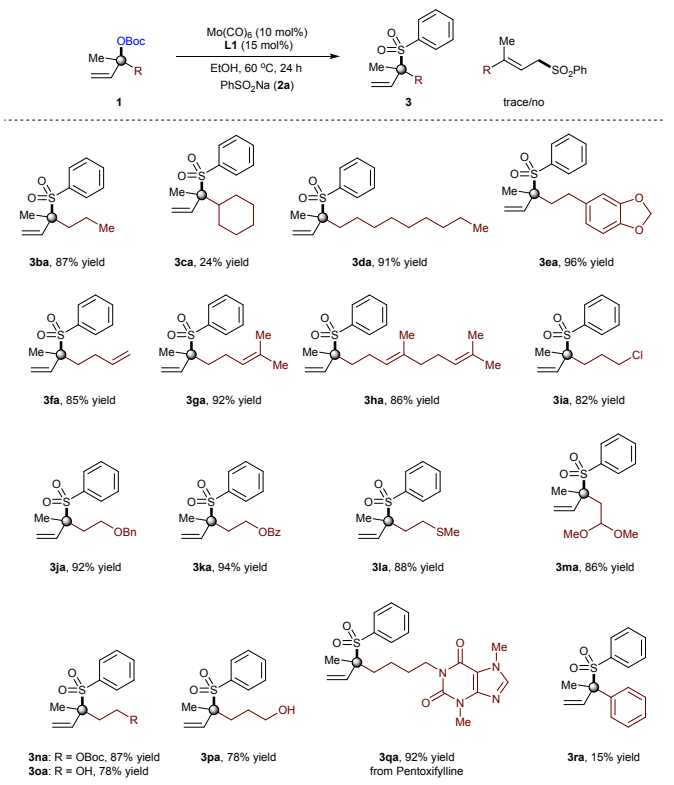
18	**2r** (R = 1-quinoline)	**3ar**	78
19	**2s** (R = 2,3-dihydrobenzofuran)	**3as**	92
20	**2t** (R = 3-pyridine)	**3at**	82
21	**2u** (R = 2-thiopene)	**3au**	86
22	**2v** (R = Me)	**3av**	72
23	**2w** (R = Et)	**3az**	78
24	**2x** (R = *i*Pr)	**3ax**	82
25	**2y** (R = cyclopropyl)	**3ay**	78
26	**2z** (R = $CH_3OCOCH_2CH_2$)	**3az**	72

[a] Reaction conditions: $Mo(CO)_6$ (10 mol%), **L1** (15 mol%), **1a** (0.2 mmol), RSO_2Na **2** (0.3 mmol), EtOH (1.0 mL, 0.2 M), 60 °C, 24 hours. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yields.

With reliable access to **3aa**, we next turned our attention to examine the generality of our newly developed molybdenum-catalysed regioselective sulfonylation of tertiary allylic electrophiles with sodium sulfinate by using Mo/**L1** catalyst system as shown in Table 2. In all cases analysed for sulfinate salts (**2**), excellent reactivity and selectivity was observed. Both the electron-withdrawing and electron-donating substituents on the aromatic ring of the sulfinate salts react smoothly with **1a**, affording the corresponding α,α-disubstituted allylic products in high yields (**3aa**-**3ap**). Sodium sulfinates with bulky naphthyl (**3aq**), quinoline (**3ar**), 2,3-dihydrobenzofuran (**3as**), and heteroaryl (**3at**, **3au**) moieties were also tolerated in the current optimized conditions. Likewise, the targeted tertiary allylic sulfone formation could be extended to sulfinate salts with alkyl substituents. Both primary and secondary alkyl substituted sodium sulfinates worked well to provide α,α-disubstituted allylic sulfones in high yields (72-82%). Furthermore, a more functionalized sodium sulfinate **2z**, when used as the sulfonylation partner, the branched product **3az** was obtained in 72% of isolated yield. The reaction leading to tertiary allylic sulfone **3aa** was easily scaled up to gram-scale without significance erosion in yield. Of particular note, almost in all cases, the reactions proceeded with excellent branched regioselectivity (> 99:1).

We then focused on investigating the scope of the α,α-disubstituted allylic carbonates and the results obtained were compiled in Table 3. Tertiary allylic carbonate with simple propyl substituent (**1b**) reacted efficiently with sodium benzenesulfinate (**2a**) to deliver the branched allylic sulfone **3ba** in high yield (87%). However, allylic carbonate with cyclohexyl moiety afforded the desired branched product in comparatively low yield (24%, **3ca**) due to the steric hindrance problem. While, with tertiary allylic carbonate (**1d**) having longer alkyl chain provided the desired product even at high yield (91%, **3da**). Tertiary allylic carbonates **1e**, **1f**, **1g** and **1h** with different groups in the alkyl chain were coupled with sulfinate salt **2a**, high yields of the branched allylic products were obtained (85–96%, **3ea**, **3fa**, **3ga** and **3ha**). Notably, various common functional groups such as Cl (**1i**), benzyl (**1j**), benzoyl (**1k**), thioether (**1l**), acetal (**1m**), and carbonate (**1n**) on the alkyl chain of the tertiary allylic carbonates were tolerated, and the sulfonylation branched products (**3ia**–**3na**) were isolated in high yields (82–94%). In addition, unprotected hydroxy group on the alkyl chain of the tertiary allylic carbonates **1o**, and **1p** do not interfere with productive tertiary allylic sulfones formation (**3oa** and **3pa**), thus providing opportunities for further derivatization. Notably, the reaction can be easily applied within the context of late-stages, supported by the formation of branched allylic sulfone **3qa**, derived from Pentoxyfylline. As expected, the allylic sulfonylation of phenyl substituted allylic carbonate occurred exclusively at the less-hindered position. The present optimized conditions were unsatisfactory with such substrate, provided the desired branched product (**3ra**) with low branched to linear ratio (b/l = 1:5); indicating some (steric) limitation of the current protocol. Besides methyl-substituted tertiary allylic substrates **1a**-**1r**, other alkyl or aryl substituted substrates return only starting materials when used under the optimized conditions, indicating some limitation of the present protocol.

Table 3. Allylic carbonate substrate scope[a-c]



[a] Reaction conditions: $Mo(CO)_6$ (10 mol%), **L1** (15 mol%), **1** (0.2 mmol), $PhSO_2Na$ **2a** (0.3 mmol), EtOH (1.0 mL, 0.2 M), 60 °C, 24 hours. [b] Regioselectivity was determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yields of the products.

In order to illustrate the synthetic utility of these elusive tertiary allylic sulfones, we focused on the reaction of α,α-disubstituted allylic carbonate (**1h**), and sodium sulfinate **2az**, to achieve the formal synthesis of (±)-agelasidine A.[18] The desired tertiary allylic sulfone **3haz** was isolated in 84% yield

under the standard conditions (Figure 1a). This compound (**3haz**) can be readily converted to (±)-agelasidine A by following the literature procedure.[13f] We further demonstrate that the current methodology can be utilize to prepare other related compounds containing sulfone-bearing quaternary carbon center.[19]

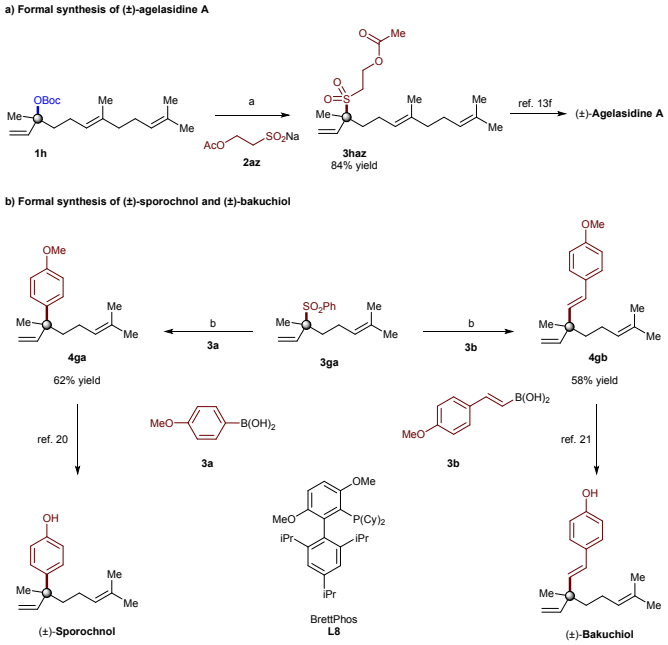


Fig. 2 Importance of current research towards the synthesis of agelasidine A, sporochnol, and bakuchiol. Reaction conditions: (a) $Mo(CO)_6$ (10 mol%), **L1** (15 mol%), **1h** (0.2 mmol), **2az** (0.3 mmol), EtOH (1.0 mL, 0.2 M), 60 °C, 24 hours. (b) $Ni(cod)_2$ (10 mol%) ligand **L8** (12 mol%), **3ga** (0.2 mmol), **3a** or **3b** (0.7 equiv), NaOEt (2.2 equiv), PhMe (0.2 M), 24h, 80 °C.

Due to their ambiphilic nature, allylic sulfones are synthetically important electrophiles and recently been utilized in Suzuki cross-coupling[10a] as well as allylic substitution reactions.[11d] However, selective cross-coupling of tertiary allylic sulfones remain highly challenging in Suzuki-Miyaura cross-coupling reactions.[10] Indeed, we employed our tertiary allylic sulfone product **3ga** along with typical boronic acids as a coupling partner, in order to achieved the formal synthesis of (±)-sporochnol,[20] and (±)-bakuchiol,[21] both of which are natural products possesses a quaternary all-carbon center. Our synthesis is illustrated in Figure 1b. The key step involves a previously reported Suzuki-Miyaura cross-coupling reaction of tertiary allylic sulfone **3ga** to afford **4ga**, and **4gb** efficiently with 62% and 58% of isolated yields respectively. Subsequent deprotection of phenol then could complete the formal synthesis of (±)-sporochnol and (±)-bakuchiol (Figure 1b).[20,21] Starting from **3ga** in 2 total steps indicating that our tertiary allylic sulfones can be used to prepare such natural products and other related compounds bearing all-carbon quaternary centers in a modular way.[22]

To gain mechanistic insight and the initial understanding on how the reaction works, we decided to study the reactivity of $[Mo^0L_n]$ species (Scheme 2). While $[Mo(bpy)(CO)_4]$ complex[23] was prepared on large scale by reacting $Mo(CO)_6$ and 2,2′-bipyridine (**L1**) in THF at 60 °C .[16] As show in Scheme 2, the structure was conformed and further analyzed.[24] Interestingly, $[Mo(bpy)(CO)_4]$ complex was found to be catalytically more efficient when used under the standard condition, supported by the formation of branched allylic sulfone product **3aa** in 96% yield. A small decline in yield of **3aa** under $[Mo(CO)_6]$/**L1** catalyst system, thus providing evidence and implicit that a $[Mo(bpy)(CO)_4]$ complex is likely the active precatalyst species in this allylic sulfonylation reaction.

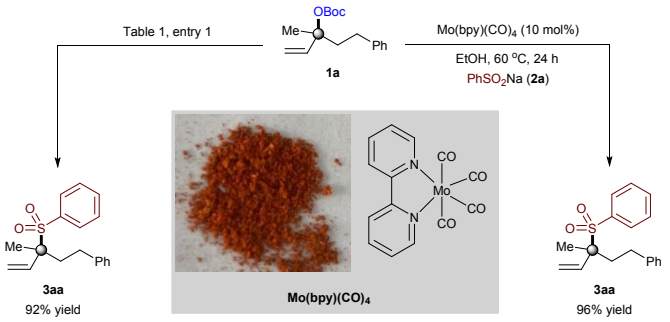


Fig. 3 Mechanistic experiments.

Conclusions

In conclusions we have developed a method for the allylic sulfonylation of α,α-disubstituted allylic electrophiles, using commercially available catalyst components ($Mo(CO)_6$/2,2′-bipyridine). To the best of our knowledge, the presented methodology is the first example of the use of sodium sulfinates as the heteroatom nucleophile reagents with tertiary allylic electrophiles to employ the group 6 catalyst in allylic substitution of tertiary allylic electrophiles to form C-S bonds. The process is characterized by its atom economic procedure, wide substrate scope, and excellent regioselectivity profile even at late stages, thus providing ample opportunities for further derivatization through traditional Suzuki cross-coupling reactions (as presented in Fig. 2b). Investigations of enantioselective reactions, mechanism and extension to other heteroatom nucleophiles are currently ongoing and will be reported in due course.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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7 The range of nucleophiles that has been used in molybdenum-catalysed allylic alkylations are limited to stabilized carbon nucleophiles, and is thus narrower than in the palladium- and iridium-catalysed reactions. However, to our knowledge there is no report available in literature on the use of heteroatom nucleophiles that provide access to tertiary and or secondary allylic products in Mo-catalysed allylic substitution reactions

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ARTICLE

Regioselective molybdenum-catalyzed allylic substitution of tertiary allylic electrophiles: methodology development and applications

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The first molybdenum-catalysed allylic sulfonylation of tertiary allylic electrophiles is described. The method utilizes a readily accesable catalyst ($Mo(CO)_6$/2,2′-bipyridine, both are commercially available) and represent the first example of the use of a group 6 transition metal-catalyst to substituted tertiary allylic electrophiles to form carbon-sulfur bonds. This atom economic and operationally simple methodology is charaterized by its relatively mild conditions, wide substrate scope, and excellent regioselectivity profile, thus unlocking a new platform to synthesize allylic sulfones, even at late stages and providing ample oppertunaties for further derivatization through traditional Suzuki cross-coupling reactions.

Introduction

The concept of π-allyl metal-complex was first formulated by Tsuji in 1965[1a] and, later, properly adopted by Trost in 1973.[1b] Since then, this technology has enabled organic chemists to create novel procedures for the synthesis of simple to complex molecules.[2] Among these is the development and utilization of heteroatom nucleophile reagents, such as oxygen, nitrogen, and or sulfur-based nucleophiles.[2,3] Despite the massive development that has been made in this area, there still remain untapped opportunities in the potential application of these heteroatom nucleophile reagents in transition metal-catalysed allylic substitution. For example, molybdenum-catalysed allylic substitution reactions of heteroatom nucleophiles are unknown and largely limited only to the carbon-carbon bond formation procedures (Figure 1A, left).[4] Furthermore, the substrate scope with respect to the allylic electrophile has also been unchanged and restricted to the ones that provide products containing a tertiary center at the allylic position.[5] Regardless of the longstanding interest in the formation of carbon-heteroatom bond with in the synthetic organic community, as well as the advancement of other transition-metal-catalysed reactions to provide heteroatom bearing quaternary and or tertiary allylic centers,[6] molybdenum-catalysed allylic substitution reactions that provide products containing such a stereocenter remain prominently absent from the literature and yet to be discovered (Figure 1A, right).[7]

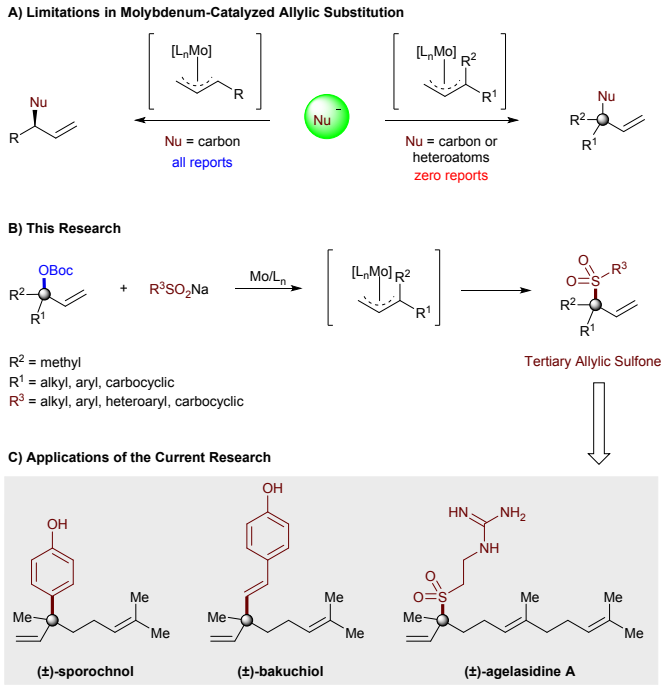

Fig. 1 (A) Limitations in molybdenum-catalysed allylic substitution, (B) our research, and (C) applications of the current research.

Due the high importance of allylic sulfones as pharmaceuticals[8] and synthetic candidates,[9] organic chemists have recently been tested to design catalytic C-S bond cleavage procedures as a new tool for carbon-carbon bond formation through Suzuki cross-coupling[10] and or allylic substitution reactions.[11] Despite the considerable development realized in this zone, allylic sulfone formation is still a challenging task and confined to the use of transition metal-catalysed allylic sulfonylation procedures.[12,13] However, using these procedures for the synthesis of allylic sulfone containing tetrasubstituted carbon centers are scarce and largely unexplored.[14] Therefore, at the beginning of our study it was

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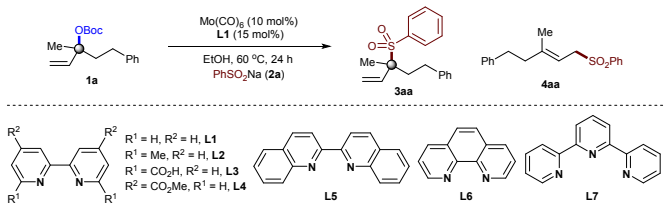
unclear whether a molybdenum-catalysed allylic substitution could ever be implemented with heteroatom (sodium sulfinate) nucleophile or even with α,α-disubstituted allylic precursors. If successful, such unexplored area of allylic substitution chemistry might not only provide opportunity to realize currently inaccessible chemical space (carbon-heteroatom bond formation) in molybdenum-catalysed allylic substitution, but also provide a new synthetic approach for rapidly generate quaternary all-carbon centers through Suzuki cross-coupling of the sulfone functionality. As part of our ongoing program in developing molybdenum-catalysed allylic substitution technology and our continued interest in the catalytic asymmetric synthesis of quaternary stereocenters,[14a, 15] we were attracted to this unmet challenge and report herein the successful implementation of this idea (Figure 1B). The salient features of this methodology are the atom-economic procedures, high regioselectivity, and excellent functional group tolerance for both sulfinate salt and tertiary allylic carbonates, even at late-stages. Furthermore, the high reactivity of tertiary allylic sulfones as a new class of electrophiles to yield structurally diverse products containing quaternary all-carbon centers through Suzuki cross-coupling are the special characteristic of this catalytic system (Figure 1C).[10a]

Table 1. Optimization of the reaction parameters[a]



Entry	Deviation in conditions	**3aa**/**4aa**[b]	**3aa** (%)[c]
1	none	99:1	92
2	**L2** was used instead of **L1**	99:1	87
3	**L3** was used instead of **L1**	99:1	35
4	**L4** was used instead of **L1**	99:1	52
5	**L5** was used instead of **L1**	25:1	16
6	**L6** was used instead of **L1**	--	0
7	**L7** was used instead of **L1**	--	>5
8	$(C_7H_8)_3Mo(CO)_3$ was used	99:1	82
9	THF was used as solvent	--	>5
10	Toluene was used as solvent	-	>5
11	DCE was used as solvent	25:1	35
12	^{i}PrOH was used as solvent	99:1	77
13	THF/EtOH (5:1) as solvent	25:1	25
14	DCE/EtOH (5:1) as solvent	25:1	63
15	Without Mo or **L1**	--	0

[a] Reaction conditions: Mo-catalyst (10 mol%), ligand (15 mol%), **1a** (0.2 mmol), $PhSO_2Na$ **2a** (0.3 mmol), solvent (1.0 mL, 0.2 M), 60 °C, 24 hours. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yields.

Results and discussion

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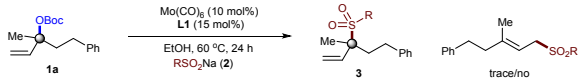
Our optimization began by evaluating the allylic substitution of tertiary allylic carbonate **1a**, readily prepared from the corresponding alcohol on a large scale, with sodium benzenesulfinate **2a** (Table 1). Interestingly, a disappointing amount of either **3aa** or **4aa** were detected under reaction conditions previously reported for other molybdenum-catalysed allylic substitution events.[4] After several experimentation,[16] we concluded that a combination of inexpensive commercially available $Mo(CO)_6$ precursor and 2,2′-bipyridyne as a ligand (**L1**)[17] in EtOH at 60 °C afforded **3aa** in 92% yield upon isolation with excellent branched to linear selectivity (**3aa**/**4aa** = > 99:1). Amongst all of the ligands utilized, 2,2′-bipyridine motifs were crucial for achieving the targeted transformation. While excellent reactivity towards **3aa** was found with 2,2′-bipyridines and 6,6′-dimethyl-2,2′-bipyridine, better yields were obtained for the first one (entries 1–7). Interestingly, the bench-stable terpyridine **L7** failed to provide product **3aa**. These results indicate that the coordination geometry of the ligand dictates the reactivity, with 2,2′-bipyridine ligands being particularly suited for the high yield and selectivity of **3aa**. Subtle changes on the molybdenum precursor, and or solvent, however, had a negative influence on the reaction to occur, consistently providing lower yields if any (entries 8-14). As expected, control experiments revealed that all of the reaction parameters were necessary for forging the sulfone moiety (entry 15).

Table 2. Sodium sulfinate substrate scope[a-c]



Entry	**2**	**3**[b]	yield (%)[c]
1	**2a** (R = Ph)	**3aa**	92
2	**2b** (R = 4-MeC_6H_4)	**3ab**	93
3	**2c** (R = 4-$MeOC_6H_4$)	**3ac**	90
4	**2d** (R = 4-ClC_6H_4)	**3ad**	87
5	**2e** (R = 4-FC_6H_4)	**3ae**	85
6	**2f** (R = 4-$NO_2C_6H_4$)	**3af**	75
7	**2g** (R = 4-CNC_6H_4)	**3ag**	72
8	**2h** (R = 2-FC_6H_4)	**3ah**	88
9	**2i** (R = 2-ClC_6H_4)	**3ai**	87
10	**2j** (R = 2-$OCF_3C_6H_4$)	**3aj**	72
11	**2k** (R = 3-BrC_6H_4)	**3ak**	82
12	**2l** (R = 3-CNC_6H_4)	**3al**	78
13	**2m** (R = 2,4-$MeOC_6H_3$)	**3am**	94
14	**2n** (R = 3,5-$CF_3C_6H_3$)	**3an**	95
15	**2o** (R = 2-MeO,5-BrC_6H_3)	**3ao**	84
16	**2p** (R = 3,4-ClC_6H_3)	**3ap**	87
17	**2q** (R = 2-naphthyl)	**3aq**	82

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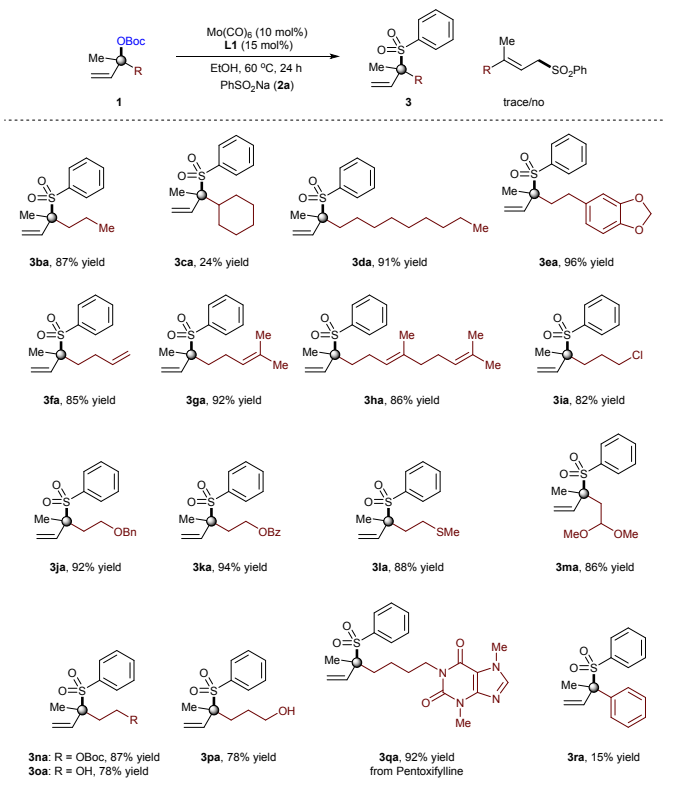
18	**2r** (R = 1-quinoline)	**3ar**	78
19	**2s** (R = 2,3-dihydrobenzofuran)	**3as**	92
20	**2t** (R = 3-pyridine)	**3at**	82
21	**2u** (R = 2-thiopene)	**3au**	86
22	**2v** (R = Me)	**3av**	72
23	**2w** (R = Et)	**3az**	78
24	**2x** (R = *i*Pr)	**3ax**	82
25	**2y** (R = cyclopropyl)	**3ay**	78
26	**2z** (R = $CH_3OCOCH_2CH_2$)	**3az**	72

[a] Reaction conditions: $Mo(CO)_6$ (10 mol%), **L1** (15 mol%), **1a** (0.2 mmol), RSO_2Na **2** (0.3 mmol), EtOH (1.0 mL, 0.2 M), 60 °C, 24 hours. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yields.

With reliable access to **3aa**, we next turned our attention to examine the generality of our newly developed molybdenum-catalysed regioselective sulfonylation of tertiary allylic electrophiles with sodium sulfinate by using Mo/**L1** catalyst system as shown in Table 2. In all cases analysed for sulfinate salts (**2**), excellent reactivity and selectivity was observed. Both the electron-withdrawing and electron-donating substituents on the aromatic ring of the sulfinate salts react smoothly with **1a**, affording the corresponding α,α-disubstituted allylic products in high yields (**3aa**-**3ap**). Sodium sulfinates with bulky naphthyl (**3aq**), quinoline (**3ar**), 2,3-dihydrobenzofuran (**3as**), and heteroaryl (**3at**, **3au**) moieties were also tolerated in the current optimized conditions. Likewise, the targeted tertiary allylic sulfone formation could be extended to sulfinate salts with alkyl substituents. Both primary and secondary alkyl substituted sodium sulfinates worked well to provide α,α-disubstituted allylic sulfones in high yields (72-82%). Furthermore, a more functionalized sodium sulfinate **2z**, when used as the sulfonylation partner, the branched product **3az** was obtained in 72% of isolated yield. The reaction leading to tertiary allylic sulfone **3aa** was easily scaled up to gram-scale without significance erosion in yield. Of particular note, almost in all cases, the reactions proceeded with excellent branched regioselectivity (> 99:1).

We then focused on investigating the scope of the α,α-disubstituted allylic carbonates and the results obtained were compiled in Table 3. Tertiary allylic carbonate with simple propyl substituent (**1b**) reacted efficiently with sodium benzenesulfinate (**2a**) to deliver the branched allylic sulfone **3ba** in high yield (87%). However, allylic carbonate with cyclohexyl moiety afforded the desired branched product in comparatively low yield (24%, **3ca**) due to the steric hindrance problem. While, with tertiary allylic carbonate (**1d**) having longer alkyl chain provided the desired product even at high yield (91%, **3da**). Tertiary allylic carbonates **1e**, **1f**, **1g** and **1h** with different groups in the alkyl chain were coupled with sulfinate salt **2a**, high yields of the branched allylic products were obtained (85–96%, **3ea**, **3fa**, **3ga** and **3ha**). Notably, various common functional groups such as Cl (**1i**), benzyl (**1j**), benzoyl (**1k**), thioether (**1l**), acetal (**1m**), and carbonate (**1n**) on the alkyl chain of the tertiary allylic carbonates were tolerated, and the sulfonylation branched products (**3ia**–**3na**) were isolated in high yields (82–94%). In addition, unprotected hydroxy group on the alkyl chain of the tertiary allylic carbonates **1o**, and **1p** do not interfere with productive tertiary allylic sulfones formation (**3oa** and **3pa**), thus providing opportunities for further derivatization. Notably, the reaction can be easily applied within the context of late-stages, supported by the formation of branched allylic sulfone **3qa**, derived from Pentoxyfylline. As expected, the allylic sulfonylation of phenyl substituted allylic carbonate occurred exclusively at the less-hindered position. The present optimized conditions were unsatisfactory with such substrate, provided the desired branched product (**3ra**) with low branched to linear ratio (b/l = 1:5); indicating some (steric) limitation of the current protocol. Besides methyl-substituted tertiary allylic substrates **1a**-**1r**, other alkyl or aryl substituted substrates return only starting materials when used under the optimized conditions, indicating some limitation of the present protocol.

Table 3. Allylic carbonate substrate scope[a-c]



[a] Reaction conditions: $Mo(CO)_6$ (10 mol%), **L1** (15 mol%), **1** (0.2 mmol), $PhSO_2Na$ **2a** (0.3 mmol), EtOH (1.0 mL, 0.2 M), 60 °C, 24 hours. [b] Regioselectivity was determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yields of the products.

In order to illustrate the synthetic utility of these elusive tertiary allylic sulfones, we focused on the reaction of α,α-disubstituted allylic carbonate (**1h**), and sodium sulfinate **2az**, to achieve the formal synthesis of (±)-agelasidine A.[18] The desired tertiary allylic sulfone **3haz** was isolated in 84% yield

under the standard conditions (Figure 1a). This compound (**3haz**) can be readily converted to (±)-agelasidine A by following the literature procedure.[13f] We further demonstrate that the current methodology can be utilize to prepare other related compounds containing sulfone-bearing quaternary carbon center.[19]

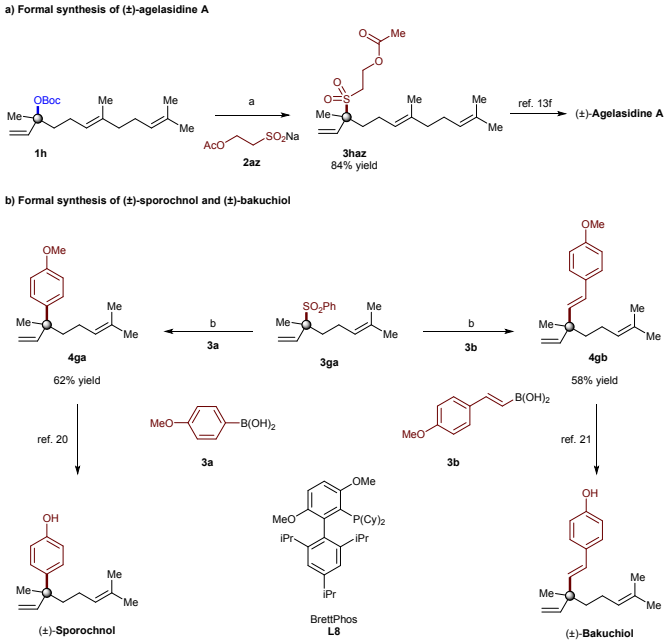


Fig. 2 Importance of current research towards the synthesis of agelasidine A, sporochnol, and bakuchiol. Reaction conditions: (a) $Mo(CO)_6$ (10 mol%), **L1** (15 mol%), **1h** (0.2 mmol), **2az** (0.3 mmol), EtOH (1.0 mL, 0.2 M), 60 °C, 24 hours. (b) $Ni(cod)_2$ (10 mol%) ligand **L8** (12 mol%), **3ga** (0.2 mmol), **3a** or **3b** (0.7 equiv), NaOEt (2.2 equiv), PhMe (0.2 M), 24h, 80 °C.

Due to their ambiphilic nature, allylic sulfones are synthetically important electrophiles and recently been utilized in Suzuki cross-coupling[10a] as well as allylic substitution reactions.[11d] However, selective cross-coupling of tertiary allylic sulfones remain highly challenging in Suzuki-Miyaura cross-coupling reactions.[10] Indeed, we employed our tertiary allylic sulfone product **3ga** along with typical boronic acids as a coupling partner, in order to achieved the formal synthesis of (±)-sporochnol,[20] and (±)-bakuchiol,[21] both of which are natural products possesses a quaternary all-carbon center. Our synthesis is illustrated in Figure 1b. The key step involves a previously reported Suzuki-Miyaura cross-coupling reaction of tertiary allylic sulfone **3ga** to afford **4ga**, and **4gb** efficiently with 62% and 58% of isolated yields respectively. Subsequent deprotection of phenol then could complete the formal synthesis of (±)-sporochnol and (±)-bakuchiol (Figure 1b).[20,21] Starting from **3ga** in 2 total steps indicating that our tertiary allylic sulfones can be used to prepare such natural products and other related compounds bearing all-carbon quaternary centers in a modular way.[22]

To gain mechanistic insight and the initial understanding on how the reaction works, we decided to study the reactivity of $[Mo^0L_n]$ species (Scheme 2). While $[Mo(bpy)(CO)_4]$ complex[23] was prepared on large scale by reacting $Mo(CO)_6$ and 2,2′-bipyridine (**L1**) in THF at 60 °C .[16] As show in Scheme 2, the structure was conformed and further analyzed.[24] Interestingly, $[Mo(bpy)(CO)_4]$ complex was found to be catalytically more efficient when used under the standard condition, supported by the formation of branched allylic sulfone product **3aa** in 96% yield. A small decline in yield of **3aa** under $[Mo(CO)_6]$/**L1** catalyst system, thus providing evidence and implicit that a $[Mo(bpy)(CO)_4]$ complex is likely the active precatalyst species in this allylic sulfonylation reaction.

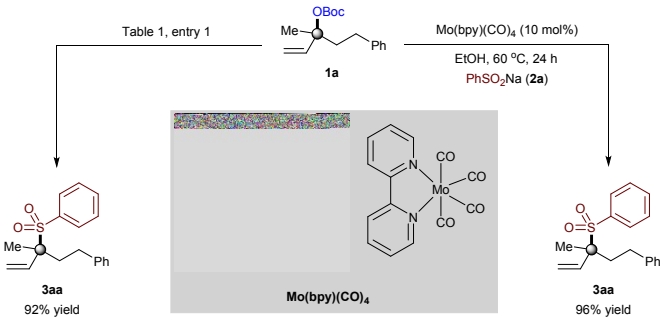


Fig. 3 Mechanistic experiments.

Conclusions

In conclusions we have developed a method for the allylic sulfonylation of α,α-disubstituted allylic electrophiles, using commercially available catalyst components ($Mo(CO)_6$/2,2′-bipyridine). To the best of our knowledge, the presented methodology is the first example of the use of sodium sulfinates as the heteroatom nucleophile reagents with tertiary allylic electrophiles to employ the group 6 catalyst in allylic substitution of tertiary allylic electrophiles to form C-S bonds. The process is characterized by its atom economic procedure, wide substrate scope, and excellent regioselectivity profile even at late stages, thus providing ample opportunities for further derivatization through traditional Suzuki cross-coupling reactions (as presented in Fig. 2b). Investigations of enantioselective reactions, mechanism and extension to other heteroatom nucleophiles are currently ongoing and will be reported in due course.

Conflicts of interest

The authors declare no conflicts of interest.

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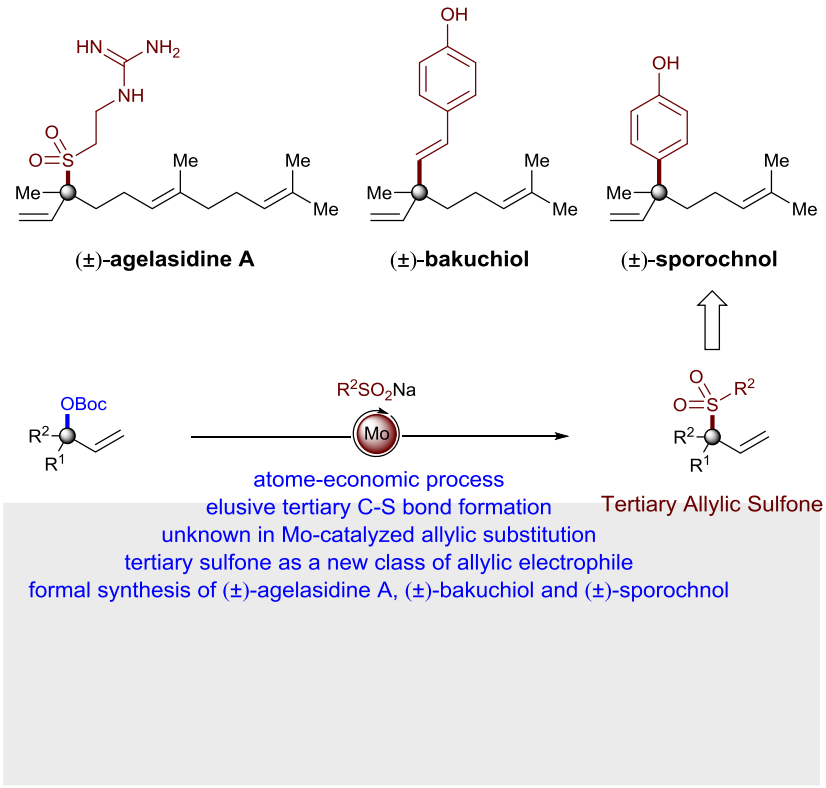

The first general example of molybdenum-catalyzed allylic sulfonylation of tertiary allylic electrophile provides an efficient and direct way to form tetrasubstituted carbon-sulfur bonds, thus unlocking a new platform to synthesize tertiary allylic sulfones, even at late stages and providing ample opportunities for further derivatization through traditional Suzuki cross-coupling.