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Asymmetric Catalysis |*Hot Paper*|

Enantiopure Sulfinyl Aniline as a Removable and Recyclable Chiral Auxiliary for Asymmetric C(sp^3)–H Bond Activation

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Abstract: An original and recyclable chiral bidentate aniline-sulfoxide-based directing group has been developed. This auxiliary allows challenging stereoselective Pd-catalyzed direct functionalization of small cycloalkanes through C–aryl and C–alkyl bond formation. Although moderate diastereoselectivities are observed, both optically pure enantiomers of the highly functionalized products can be obtained separately by simple silica gel chromatography and cleavage of the chiral auxiliary. This strategy was further applied to the preparation of enantiomerically pure 1,2,3-trisubstituted cyclopropane carboxylic acid derivatives, with three stereogenic centers and bearing both alkyl and aromatic substituents. These molecular scaffolds are not yet reported in the literature. The synthetic utility of this approach is validated by the chiral auxiliary being readily cleaved and recovered posteriori to the C–H activation step, without deterioration of its optical purity. Finally, an unprecedented palladacycle intermediate generated through C–H activation of the cyclopropane moiety has been isolated and fully characterized. Initial DFT calculations shed additional light on the reactivity of this original intermediate.

Introduction

The extraordinary advances achieved over the last decade in the field of C–H bond activation render this approach a truly useful strategy for the synthesis of complex molecules from simple and non-prefunctionalized starting materials.[1,2] In clear contrast, the stereoselective outcome of such transformations has remained a niche topic for years and it is only recently that this field has been attracting a growing interest from the scientific community.[3] Accordingly, several catalytic systems have been devised to allow, for example, the generation of axially chiral,[4] planar-chiral,[5] and stereogenic spirocyclic-type molecules[6] by means of C(sp^2)–H bond activation. The direct functionalization of aliphatic C–H bonds is recognized to be more challenging than those of aromatic ones and therefore, accessing stereogenic carbons by means of asymmetric C(sp^3)–H bond activation presents an additional difficulty.[7] The initial key achievements in C(sp^3)–H activation concerned mainly intramolecular reactions in which a chiral catalyst, preinstalled on a molecule, was prompted to differentiate two stereotopic aliphatic motifs.[8] Intermolecular catalytic systems in which a chiral induction is attained by differentiation of stereotopic protons of a methylene bridge are even more challenging. To achieve this goal, several research groups focused on the functionalization of chiral amino acid derivatives, imposing the chiral induction by the presence of a proximal stereogenic center.[9] Yu discovered that monoprotected amino acids may also play the role of chiral ligands in the enantioselective transformations occurring through a Pd^{II}/Pd^0 mechanism.[10] Recently, enantioselective functionalization of cyclopropylmethylamine cores was achieved by Yu using monoprotected amino acids,[11] and Duan reported functionalization of aliphatic linear substrates by employing phosphoric amides ligands.[12] As the monoprotected amino acids clearly stand out as a privileged chirality source in asymmetric C–H activation, Hong astutely installed this motif directly on a substrate as a directing group, targeting diastereoselective reactions.[13]

With regard to the widely recognized potential of bicoordinating directing groups to facilitate challenging functionalization of aliphatic substrates,[14] the conception of original chiral bidentate directing groups, implying different sources of chirality from the commonly used amino acid scaffolds, is highly appealing.[15] However, when designing a synthetically useful system, it is essential to use a chiral inductor/directing group that may be easily installed and cleaved posteriori to the functionalization event (Figure 1). Ideally, the chiral auxiliary should also be recyclable without alteration of its optical purity. Notably, generation of diastereomeric products gives a unique opportunity for their convenient separation while allowing isolation of the desired product with a total optical purity. If these conditions were met, such a diastereoselective transformation

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would be synthetically as appealing as an enantioselective reaction, because no additional steps are required and the chiral source is regenerated. Considering these criteria and encouraged by our recent work showing the potential of a sulfoxide moiety to allow highly atropo-diastereoselective C–H activation,[4a–d] we designed a 2-(*p*-tolylsulfinyl)aniline (**1**) moiety as a precursor for an original bicoordinating directing group (Figure 2). The chiral induction might be anticipated by coordination of the stereogenic sulfur atom to the Pd-catalyst. We expect that the primary amine motif would allow its handy installation on a carboxylic acid derived substrate through amide coupling (Path A) and ensure a second coordination site. Alternatively, the aliphatic amide-sulfoxide derivatives may be constructed in two steps (Path B), 1) preparation of *N*-(2-*b*romophenyl)-aliphatic carboxamide, followed by 2) lithium/bromine exchange and an electrophilic trapping with an enantiopure sulfoxide precursor.

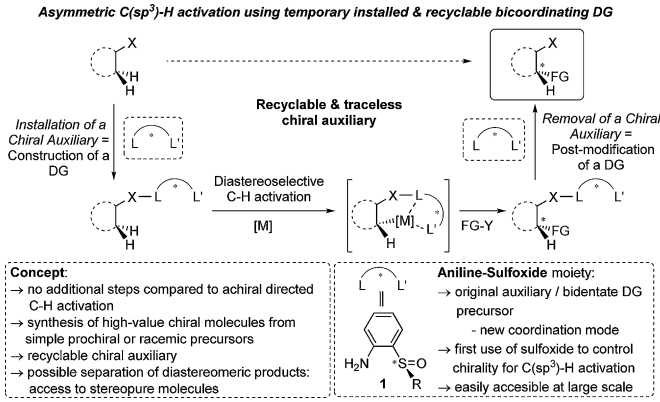


Figure 1. Diastereoselective C–H activation using a traceless and recyclable chiral DG.

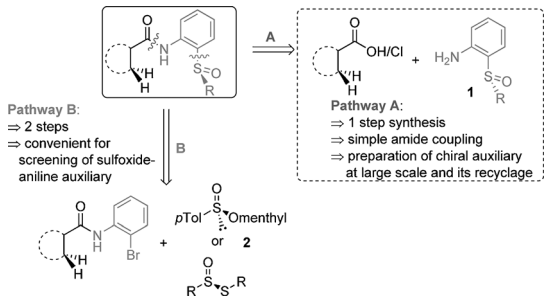
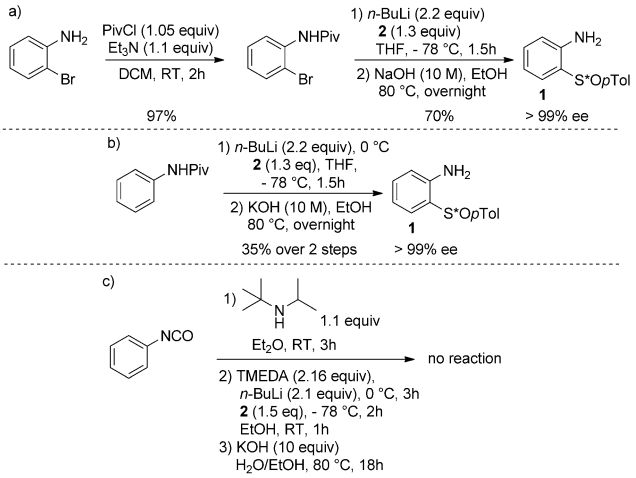


Figure 2. Retrosynthetic pathways for the preparation of aliphatic substrates bearing the chiral aniline-sulfoxide-based DG.

Results and Discussion

Our work commenced with the preparation of (*S*)-2-(*p*-tolylsulfinyl)aniline **1**. As no general synthetic pathway to access a chiral primary sulfinyl aniline was known in the literature,[16] we evaluated three different strategies, using (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (**2**) as an easily accessible precursor (Scheme 1). The first strategy applying bromine/lithium exchange of *N*-(2-bromophenyl)pivalamide, followed by an electrophilic trapping with **2**, and deprotection, afforded **1** in 70% yield (Scheme 1 A). Targeting a more atom-economical pathway, a sequence of directed *ortho*-lithiation of *N*-phenylpivalamide/electrophilic trapping with **2** was evaluated, but under these conditions, **1** was isolated in a lower yield of 35% over 2 steps. The third approach, inspired by Lloyd-Jones and Booker-Milburn,[17] consisted of a one-pot generation of a urea derivative, followed by *ortho*-lithiation and quenching with **2**. However, no product formation was observed.

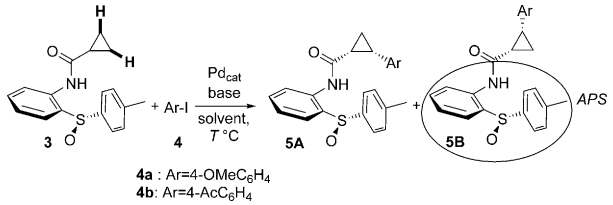


Scheme 1. Synthesis of enantiopure **1** (Tol = tolyl).

With the enantiopure **1** in hand, we embarked on an evaluation of its potential for the direct asymmetric activation of cyclopropane derivatives,[18] because they are important scaffolds in pharmaceutical and agrochemical industry.[19] Accordingly, *N*-[2-(*p*-tolylsulfinyl)phenyl]cyclopropanecarboxamide (**3**) was prepared by amide coupling between **1** and cyclopropanecarbonyl chloride (retrosynthetic pathway A, Figure 2) in quantitative yield. Notably, the alternative approach (retrosynthetic pathway B, Figure 2) based on an initial construction of *N*-(2-bromophenyl)cyclopropanecarboxamide, followed by lithium/bromine exchange and an electrophilic trapping with **2** was also effective, delivering enantiopure **3** in 71% yield.

Promisingly, the first attempt of a direct functionalization of **3**, using $Pd(OAc)_2$ catalyst, AgOAc as base (OAc = acetate), 4-iodoanisole (**4a**, 4 equiv) as coupling partner, and conducting the reaction in toluene at 120 °C, showed the formation of the desired product **5**, but in trace amounts (Table 1, entry 1). A significantly higher reactivity was observed when an electron-poor aryl iodide, such as 4-iodoacetophenone (**4b**), was employed. The arylation occurred with 80% conversion and 64:36 diastereomeric ratio, together with 3% of the biarylated side product (Table 1, entry 2). Replacing the toluene solvent by dichloromethane or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) allowed for a decrease in the reaction temperature to 100 and 80 °C, respectively, but maintained the high conversion (Table 1, entries 3–4). The addition of 0.5 equiv of NaTFA (TFA = trifluoroacetate) resulted in a further improvement of

Table 1. Optimization of the diastereoselective arylation of **3**.[a]



4a : Ar=4-OMeC$_6$H$_4$
4b: Ar=4-AcC$_6$H$_4$

Entry	**4**	Base	Solvent	*T* [°C]	Conversion [%][b]	**5A**:**5B**[c]	Mono: biarylation [%][c]
1	**4a**	AgOAc	PhMe	120	13	nd	nd
2	**4b**	AgOAc	PhMe	120	80	64:36	97:3
3	**4b**	AgOAc	DCM	100	60	65:35	96:4
4	**4b**	AgOAc	HFIP	80	88	63:37	96:4
5[d]	**4b**	AgOAc	HFIP	80	100	61:39	95:5
6	**4b**	Ag_2CO_3	HFIP	80	78	61:39	97:3
7	**4b**	AgTFA	HFIP	80	40	52:48	96:4
8[e]	**4b**	AgOAc	HFIP	100	80	66:34	97:3
9[f]	**4b**	AgOAc	HFIP	100	85	64:36	97:3

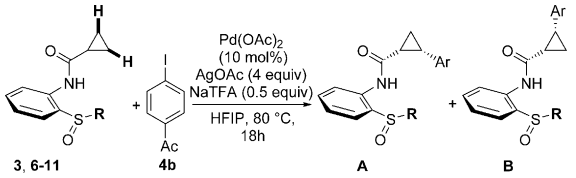
[a] General reaction conditions: **3** (0.15–0.30 mmol), **4** (4 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (4 equiv), solvent (0.15 M), 18 h. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC; nd = not determined. [d] 0.5 equiv of NaTFA was added. [e] $Pd(TFA)_2$. [f] $Pd(OPiv)_2$. Ac = acetyl, Piv = pivaloyl.

the reactivity of this catalytic system allowing full consumption of **3** (Table 1, entry 5). Neither solvent nor temperature significantly impacted the diastereoselectivity of this transformation. Also, no improvement was evidenced when modifying the palladium catalyst or silver salt (Table 1, entries 6–9). Undesired biarylation could be avoided by lowering the excess of the iodoarene partner **4**.

Considering that the chiral information is transferred from the stereogenic sulfoxide moiety, we speculated that a modification of the steric hindrance on the sulfur atom should directly impact the diastereoselectivity of this transformation (Table 2). Thus, several racemic *N*-[2-(sulfinyl)phenyl)]cyclopropanecarboxamide substrates **6**–**11** were synthesized (retrosynthetic pathway B, Figure 2). Replacement of the *p*-tolyl substituent of the sulfoxide by other aromatics, such as 2,4,6-trimethylbenzene (**6**), 3,5-dimethylbenzene (**7**), or 4-*tert*-butylbenzene (**8**) only slightly improved the stereoselectivity (Table 2, entries 2–4). In contrast, arylation of the substrates **10**–**11**, with sulfoxide moieties bearing more sterically hindering aliphatic substituents, such as cyclohexyl and *tert*-butyl, occurred with high diastereoselectivities of 85:15 and 90:10 respectively, but with dramatically decreased yields (30–35%, Table 2, entries 6–7). Disappointingly, an extensive optimization study did not improve the reactivity of **11** towards this C–H functionalization.

Considering both the antagonism between efficiency and stereoselectivity of this catalytic system and the formation of diastereomeric products easily separable by simple silica-gel column chromatography, we decided to evaluate the scope of this transformation using **3** with the 2-(*p*-tolylsulfinyl)aniline (APS) auxiliary as the standard substrate. Unexpectedly, when 4-iodoacetophenone coupling partner **4b** was replaced by methyl 4-iodobenzoate (**4c**) the desired arylated product was generated in trace amounts. Rewardingly, a more robust

Table 2. Influence of steric hindrance of the chiral auxiliary.[a]



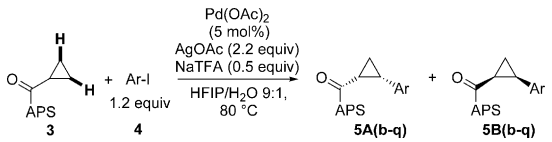
Entry	Substrate	R	Conversion [%][b]	**A**:**B**[c]
1	**3**	*p*-tolyl	90	60:40
2	**6**	2,4,6-mesityl	45	70:30
3	**7**	3,5-xylyl	70	65:35
4	**8**	*p*-*t*-buylphenyl	55	65:35
5	**9**	isopropyl	42	70:30
6	**10**	cyclohexyl	35	85:15
7	**11**	*t*-butyl	30	90:10

[a] General reaction conditions: **3** (0.15–0.30 mmol), **4** (1.5 equiv), $Pd(OAc)_2$ (10 mol%), NaTFA (0.5 equiv), AgOAc (4 equiv), HFIP (0.15 M), 80 °C, 18 h. [b] Determined by ^{1}H NMR. [c] Determined by ^{1}H NMR.

system was obtained by adding a small amount of water as co-solvent. Use of this solvent mixture also permitted the reduction of catalyst and silver salt loadings (down to 5 mol% and 2.2 equiv, respectively). Under these reoptimized reaction conditions, the direct arylation of **3** using a large panel of iodoarenes **4** was performed (Table 3). When *para*-substituted aryl iodides were employed, the chiral cyclopropane compounds were usually generated in high yields but with modest diastereoselectivities of approximately 60:40 (Table 3, entries 1–6). However, both diastereoisomers could be isolated separately, thus allowing access to optically pure enantiomeric compounds. Importantly, the steric hindrance of the aryl cou-

pling partner also influences the stereoselectivity of the overall transformation; Ar–I bearing a nitro- or chloro- substituent in the *meta* position (**4i**, **4k**) or ester or aldehyde functionalization in the *ortho* position (**4n**, **4o**) delivered the functionalized cyclopropanes with significantly improved diastereoselectivity of 80:20 (Table 3, entries 8, 10, 13, 14). Remarkably, several synthetically useful functionalities were well tolerated, such as ester or chloro motifs. Additionally, iodoarenes bearing substituents such as trifluoromethyl (Table 3, entry 4) or nitro (Table 3, entries 6, 8, 12, 15), which can be considered as an amine precursor, important motifs in agrochemistry and pharmaceutical industry, also worked well under our reaction conditions. 4-bromoiodobenzene (**4f**) could also be used as the coupling partner (Table 3, entry 5), generating a product equipped to undergo further functionalization, albeit in significantly lower yield.

Table 3. Scope of the arylation of **3**.[a]



Entry	Ar	d.r.[b] (crude)	5A(a–q) yield [%][c]	5B(a–q) yield [%][c]	Total yield [%][d]
1	**4b**: 4-Ac-C_6H_4	60:40	54	36	90
2	**4c**: 4-CO_2Me-C_6H_4	60:40	54	37	91
3	**4d**: 4-CN-C_6H_4	60:40	52	33	85
4	**4e**: 4-CF_3-C_6H_4	65:35	45	17[e]	62
5	**4f**: 4-Br-C_6H_4	60:40	26	nd	26
6	**4g**: 4-NO_2-C_6H_4	60:40	54	28	82
7	**4h**: 3-Ac-C_6H_4	70:30	55	22	77
8	**4i**: 3-NO_2-C_6H_4	80:20	70	21	91
9	**4j**: 3-CF_3-C_6H_4	70:30	55	25[e]	80
10	**4k**: 3-Cl-C_6H_4	80:20	56	18[e]	74
11	**4l**: 3,5-di-Cl-C_6H_3	70:30	32	11[e]	43
12	**4m**: 3,5-di-NO_2-C_6H_3	70:30	41	17	58
13	**4n**: 2-CO_2Me-C_6H_4	80:20	45 (A + B mixture)		45
14	**4o**: 2-CHO-C_6H_4	80:20	40	13	53
15	**4p**: 2-NO_2-C_6H_4	70:30	66	12[e]	88
16	**4q**: C_6H_5	60:40	31	17	48

[a] General reaction conditions: **3** (0.23 mmol), **4** (1.2 equiv), $Pd(OAc)_2$ (5 mol%), NaTFA (0.5 equiv), AgOAc (2.2 equiv), HFIP:H_2O 9:1 (0.1 M), 80 °C, 8–24 h. [b] Determined by ^1H NMR. [c] Isolated yield. [d] Total isolated yield of A + B. [e] Isolated together with a small amount of **3**; for details, see the Supporting Information.

Notably, this arylation reaction is equally efficient on gram scale, rendering it synthetically applicable in multistep synthesis. Using standard reaction conditions, non-distilled solvent and under air, we were pleased to isolate the desired **5Ab** and **5Bb** in the unchanged yields of 54 and 36%, respectively.

To assign the absolute configuration of the major and minor products obtained, **5Ab** was recrystallized from a mixture of DCM:$CHCl_3$:Et_2O, providing monocrystals. The X-ray diffraction analysis showed a ($S_sR_{C15}S_{C17}$) configuration of **5Ab**.[20] The absolute configuration for the other products was attributed accordingly (Figure 3).

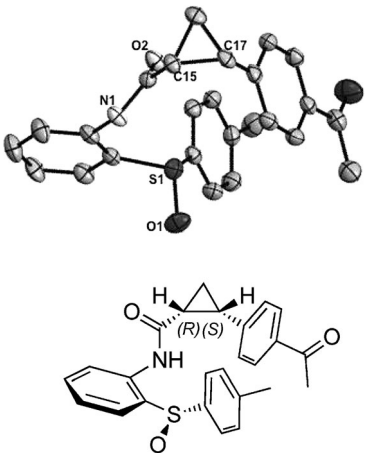
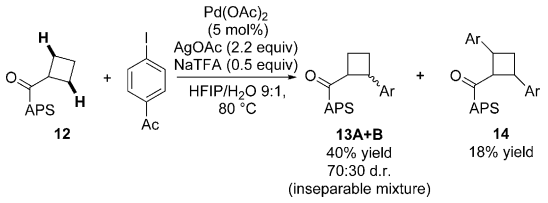


Figure 3. ORTEP-type diagram of the structure of ($S_sR_{C15}S_{C17}$)-**5Ab**.

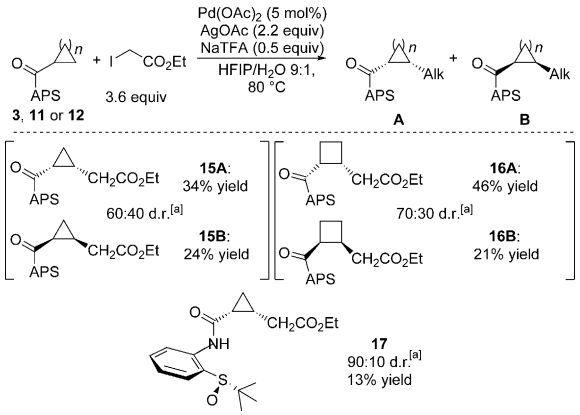
The APS-based bicoordinating directing group also allows a direct arylation of a cyclobutane derivative **12** (Scheme 2). In this case, however, a selective monofunctionalization turned out to be more challenging. Under the standard reaction conditions, the coupling with 4-iodoacetophenone (**4b**) afforded the monoarylated **13** in 40% yield and a moderate diastereoselectivity of 70:30, together with the diarylated compound **14** in 18% yield.



Scheme 2. Arylation of cyclobutane derivative **12**.

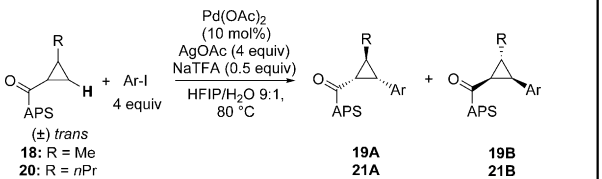
The cyclohexane substrate also underwent direct arylation under the optimized reaction conditions with a diastereoselectivity of 70:30. Nevertheless, considering that both *cis* and *trans* cyclopalladations occur,[21] four separable products were obtained in a combined yield of 57% (*cis* products: 23 and 16% yield, *trans* products: 10 and 8% yield).[22]

Although direct arylation by means of C–H activation is amongst the most frequently studied transformations, closely related alkylations are much more challenging. In particular, examples of C(sp^3)–H activation/C(sp^3) couplings are scarce. Thus, we pursued our study by investigating the alkylation reaction of small cyclic substrates bearing our aniline-sulfoxide-derived directing group (APS) (Scheme 3). Remarkably, in the presence of ethyl iodoacetate, the alkylation of **3** occurred smoothly yielding diastereomeric products **15A** and **15B** in 34% and 24% yield, respectively, (overall yield of 58% and 60:40 d.r. of the crude mixture; d.r. = diastereomeric ratio). Moreover, cyclobutane substrate **12** was also compatible with this transformation and, contrary to the C–Ar coupling, selec-



Scheme 3. C(sp^3)–H alkylation. [a] d.r. of crude product measured by ^{1}H NMR.

Table 4. Scope of the arylation of *trans*-alkyl-substituted cyclopropane acid derivatives.[a]



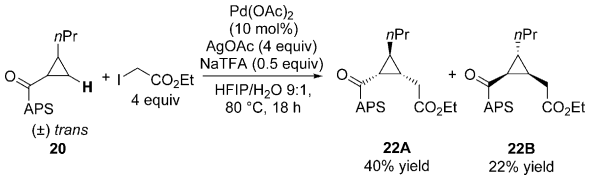
Entry	R	Product	**A** yield [%][b]	**B** yield [%][b]	Total yield [%][c]
1	Me	**19b**: 4-Ac-C_6H_4	52	31	83
2	Me	**19h**: 3-Ac-C_6H_4	56	36	92
3	Me	**19i**: 3-NO_2-C_6H_4	54	31	85
4	Me	**19q**: Ph	50	36	86
5	*n*Pr	**21b**: 4-Ac-C_6H_4	56	34	90
6	*n*Pr	**21g**: 4-NO_2-C_6H_4	47	40	87

[a] General reaction conditions: **16** (0.23 mmol), **4** (4 equiv), $Pd(OAc)_2$ (10 mol%), NaTFA (0.5 equiv), AgOAc (4 equiv), HFIP:H_2O 9:1 (0.1 M), 80 °C, 24 h; [b] Isolated yield. [c] Total isolated yield of **A** and **B**.

tive monofunctionalization was effective, yielding separately both diastereomers of **16** in 46% and 21% yield, respectively. Remarkably, although the diastereoselectivity remains moderate (70:30), this reaction is, to the best of our knowledge, the first example of the direct C(sp^3)–C(sp^3) coupling of cyclobutane derivative. Noteworthy is the significant increase of the diastereoselectivity observed using a more sterically demanding chiral directing group. Alkylation of **11** occured with high 90:10 chiral induction but, as observed with the arylation, the product **17** was isolated in a low yield of 13%.

Regarding the high reactivity of our catalytic system and the usually very convenient separation of the two diastereomeric products, this approach seems to be particularly well adapted to prepare both enantiomers of optically pure 1,2,3-trisubstituted cyclopropane carboxylic acid derivatives from racemic precursors. Notably, cyclopropane carboxylic acids bearing both alkyl and aryl substituents are key biologically active scaffolds, used as epoxide hydrolase inhibitors involved in cardiovascular disease treatment and pyrethroid insecticides.[23,24] Additionally, they may be applied as conformationally restricted peptide isosters.[25] However, in spite of their importance, synthesis of such scaffolds with *cis* configuration between the carboxylic acid and an aromatic ring and *trans* configuration relative to the alkyl moiety remains, to the best of our knowledge, unexplored not only in enantioselective but also in a racemic manner.[26] Notably, because of the potential biological and agrochemical reactivity of such a scaffold, straightforward access to both enantiomers is highly desirable. Accordingly, the direct C–H arylation of *trans*-2-alkylcyclopropane-1-carboxylic acid derivatives bearing the APS auxiliary, could pave the way towards such a challenging goal.

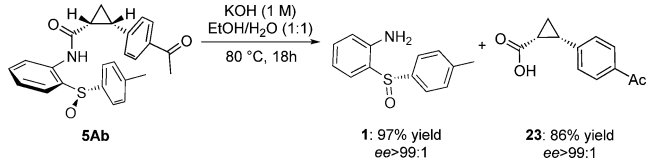
Following this target, *trans*-(*S*)-2-methyl-*N*-(2-(*p*-tolylsulfinyl)-phenyl)cyclopropane-1-carboxamide (**18**),[27] was prepared in one step from a racemic *trans*-2-methylcyclopropane-1-carboxylic acid and our chiral auxiliary **1**. Although under our standard conditions the reaction failed, increasing the amount of the aryliodide **4b**, the loading of the palladium catalyst (up to 10 mol%), and the silver salt allowed the formation of the expected product **19b** in 83% yield, and, as expected, as two diastereomers (Table 4, entry 1). Importantly, **19Ab** and **19Bb** were separated by a simple silica-gel column chromatography, affording enantiomerically pure compounds containing three C-stereocenters, in 52 and 31% yields, respectively. Subsequently, the generality of this challenging transformation was illustrated by performing the coupling with several different iodoarenes **4**. In all cases, the reactions occur smoothly, delivering both diastereomers separately in decent yields. Moreover, other aliphatic substituent on the cyclopropane ring, such as an *n*-propyl chain, was also well tolerated (Table 4, entries 5-6); the arylated product **21b** and **21g** were generated in total yields of 90 and 87%, respectively. Both diastereomers **21Ab** and **21Bb** were isolated in respective yields of 56 and 34%, whereas **21Ag** and **21Bg** were isolated in 47 and 40% yields, respectively. In addition, trisubsituted 2,3-dialkyl-cyclopropane carboxylic acid may also be prepared employing our approach. Alkylation of **20** with iodoethylacetate afforded **22** in a total yield of 62%, isolated as **22A** and **22B** in respective yields of 40 and 22% (Scheme 4).



Scheme 4. Direct alkylation of the substituted cyclopropane substrate **20**.

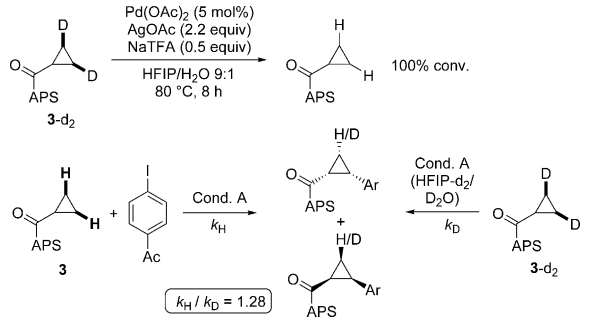
Finally, the essential prerequisite rendering the present strategy synthetically useful involves a straightforward cleavage of the APS directing group and its recovery without alteration of its optical purity. As expected, the removal of the sulfinyl aniline auxiliary **1** from **5Ab** occurred readily using 1 M KOH solution in EtOH at 80 °C. Rewardingly, this mild deprotection allows the isolation and separation of both the enantiopure,

highly functionalized cyclopropane carboxylic acid **23** and the chiral inductor **1** in high yields by a simple acido-basic workup (86 and 97% respectively). Notably, as **1** was isolated without loss of its chiral purity, this moiety can indeed be considered as a truly recyclable chiral source (Scheme 5).



Scheme 5. Deprotection of the functionalized carboxylic acid and recovery of the chiral auxiliary **1**.

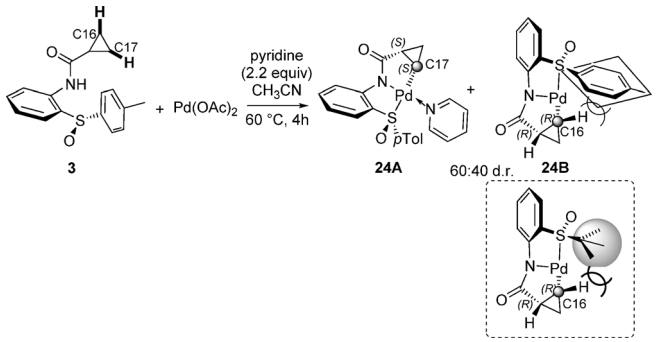
As the sulfoxide-aniline moiety has never been used before in the context of the asymmetric activation of C(sp^3)–H bonds, we have subsequently undertaken some mechanistic investigations (Scheme 6). Targeting kinetic isotope effect studies, we first focused on the preparation of the *cis*-1,2-deuterated substrate **3**-d_2. Remarkably, this original molecule could be synthesized very easily using the C–H activation strategy. When **3** was reacted with $Pd(OAc)_2$ catalyst (5 mol%) and deuterated acetic acid, in [D_3]acetonitrile, a double *cis*-deuteration proceeded efficiently, providing **3**-d_2 in 88% yield, with >99% *cis*-D purity. **3**-d_2 was then subjected to our standard arylation reaction in the absence of the Ar–I coupling partner. Total deuterium/proton exchange was observed in only 8 h suggesting a reversible character of this metallation step. In parallel, the initial rates of the arylation of **3** and **3**-d_2 were measured. The k_H/k_D ratio of 1.28 further suggests that in our catalytic system, the C(sp^3)–H bond cleavage is probably not the rate determining step.



Scheme 6. Study of the reversibility of the C–H activation step and determination of the kinetic isotope effect.

Regarding the smooth deuteration of **3** in acetonitrile and the strongly coordinating nature of our bidentate DG, we speculated that isolation of a metallacyclic intermediate could be possible. The isolation and characterization of such an organometallic compound is undeniably appealing, as only very few examples of palladacyclic species resulting from C(sp^3)–H activation are described in the literature.[28] In particular, no cyclopropane-based palladacycle has been reported. In our initial attempts, the substrate **3** was reacted with a stoichiometric amount of $Pd(OAc)_2$ in acetonitrile at 60 °C. Encouragingly, formation of the palladacyclic intermediates was confirmed by ^{1}H NMR, but a mixture of OAc- and CH_3CN-ligated complexes was evidenced. The addition of pyridine displaced weakly coordinating ligands and the expected organometallic molecule was formed cleanly as a mixture of two diastereoisomers in an approximate 60:40 ratio. **24** is surprisingly stable and could be purified by silica gel chromatography. Furthermore, ($R_sS_{C15}S_{C17}$)-**24** afforded monocrystals and its structure could be further confirmed by X-Ray diffraction analysis.[20]

At this point, different hypothesis can be proposed to rationalize the modest diastereoselectivity observed. Firstly, the X-Ray structure of **24A** (Figure 4, view b), shows that the *p*-tolyl group on the sulfinyl moiety is orientated above the cyclopropane core. Therefore, the steric interaction with protons on C17 is minimized compared to the interaction with protons at C16, yet favoring formation of **24A** (Scheme 7). In line with this, a significantly more sterically demanding *tert*-butyl group on the sulfinyl auxiliary leads to more pronounced steric congestion with the proton on C16, clearly disfavoring this intermediate and resulting in an improved diastereoselectivity of 90:10 (Table 2, entry 7). Nevertheless, as the C–H activation step is reversible, the overall stereoselectivity may also result from the different rates of oxidative addition and reductive elimination steps (for the proposed catalytic cycle, see Figure 6 ahead). In particular, the clear improvement of the diastereoselectivity for the arylation with 2-substituted iodoarenes **4n** and **4o** (Table 3, entries 13, 14) further supports this hypothesis.



Scheme 7. Formation of diastereoisomeric palladacyclic species **24A** and **24B** (for clarity, the pyridine ligand is not represented for **24B**) and proposed origin of diastereoselectivity.

This crystallographic data provides key information about the original cyclopropane-derived palladacycle. Firstly, the bidentate character of the APS directing group is proven and the amide group coordinates through its deprotonated form. Moreover, although the sulfoxide moiety contains potentially two chelating atoms, that is, O and S, the Pd–S coordination is favored resulting in the formation of 5,5-bicyclic species. Importantly, the rare examples of isolated palladacycle intermediates generated through C(sp^3)–H activation of aliphatic, linear

substrates bearing quinolin-8-amine derived *N,N*-bicoordinating (QA) DG show related 5,5-bicyclic structures.[28a,b] A rapid comparison of **24 A** with the literature-reported structures indicates that APS moiety leads to formation of a larger metallacyclic species; for **24 A** the amide–Pd bond is 2.014 Å, whereas for the QA intermediate, the values of 1.971[28b] and 1.969 Å[28a] were determined (Figure 4). In addition, the S–Pd bond of 2.329 Å is significantly longer than the N(quinoline)–Pd linkages (2.126[28b] and 2.124 Å[28a]). In contrast, the Pd–C bond in **24** is shorter in comparison to its quinolin-8-amine congeners (2.001 vs. 2.023[28b] and 2.012 Å[28a]). The N(1)-Pd-C(17) angle of 83.1° shows distortion from an idealized square planar geometry at the palladium center, which is coherent with the literature.[28a] In addition, slight torsion of the second ring is observed, as suggested by the S(1)-Pd-N(1) angle of 84.09 Å, and S(1)-C(8)-C(13) and C(8)-C(13)-N(1) angles of 118.92° and 117.09° respectively, together with the S(1)-C(8)-C(13)-N(1) torsion of −0.90°.

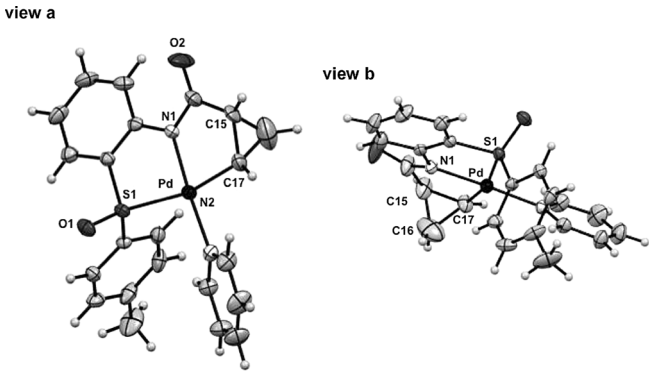


Figure 4. Ortep-type diagram of the structure of **24 A** with full atom numbering. Ellipsoids are drawn at the 30% level. Selected interatomic distances (Å) and angles (deg): S1–Pd1 2.3289(13), O1–S1 1.477(4), N2–Pd1 2.065 (4), N1–Pd1 2.014(4), C17–Pd1 2.001(6), C16–C17 1.471(11), C8–C13 1.409(7), N1-Pd1-S1 84.09(13), C17-Pd1-N1 83.1(2), C17-Pd1-S1 165.81(17), N1-Pd1-N2 176.12(18).

Furthermore, preliminary density functional theory (DFT-D) computations were carried out without thorough investigation of the reaction energy profile (Figure 5). Given the conditions required for the catalysis to take place and the central role of palladacyclic intermediates in the overall process, a mere comparison of the energies of metallacycles **24 A** and **24 B** that are formed indicated that they were almost all isoenergetic within 2 kcal mol^{-1} (gas phase ground state geometries at 298.15 K, ZORA-PBE-D3(BJ)[29,30]/all electron TZP), with a slight bias in favour of the tridentate complex **24 A** depicted in Figure 4 in which the cyclopropyl methylene orientation is antara-facial with respect to the sulfoxide oxygen atom. As a matter of fact, in the present stage of the study, it was not possible to confirm that the deprotonation of the amidic NH position that leads to neutral **24 A** took place before the cyclopalladation step or after.

Computation of the energies of the two low-lying tridentate palladium acetate chelates, i.e., the precursors of **24 A**,**B**

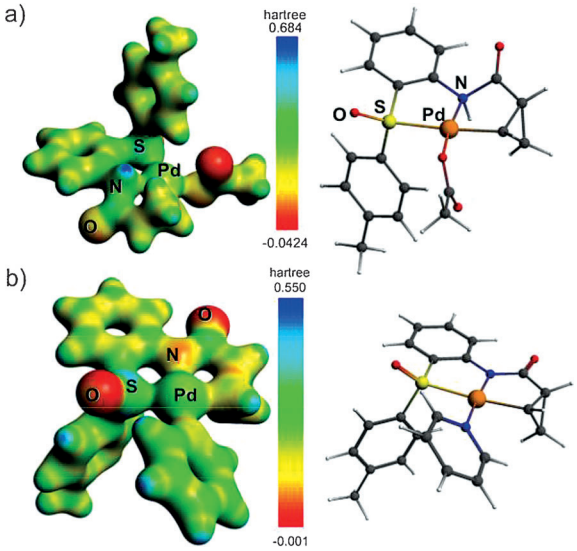


Figure 5. Maps of electrostatic potential (MEP) drawn on an isosurface of the electron density (0.06 e/bohr^3) and the related gas phase singlet ground state geometries (ZORA-PBE-D3(BJ)/all electron TZP) of **pre-24 A** (a) and **24 A** (b). The MEP of **pre-24 A** was drawn on a flipped (rotated) geometry to emphasize the peculiar charge density depletion around the amide H atom. Carbon and hydrogen atoms are colored in grey and white, respectively, in the right hand side drawn geometries. Selected interatomic distances (Å) for **pre-24 A**: Pd–N 2.133, Pd–C 2.028, Pd–S 2.369, Pd–O 2.043, C–O 1.210, S–O 1.496. Selected interatomic distances (Å) for **24 A**: Pd–N 2.032, Pd–C 2.035, Pd–S 2.323, Pd–N_{py} 2.073, C–O 1.237, S–O 1.507.

(noted **pre-24 A**,**B**), indicates, however, that the N-bound proton bears a rather high positive charge that makes it potentially prone to abstraction by any moderate base such as the acetate. This can be intuitively noted from the map of electrostatic potential drawn in Figure 5 a, which denotes a dark blue colored isosurface area indicative here of an important charge density depletion at the amide proton. Deprotonation of this position is key to the stabilization of the palladacycle as it releases the nitrogen lone electron pair leading to enhanced electron conjugation and planarization of the whole chelate. Natural charges [extracted from Natural Bonding Orbital (NBO)-Natural Population analysis[31]] clearly support the acidic character of this position ($q(H_{amide}) = +0.43$, $q(H)_{average} \sim +0.22$) in **pre-24 A**. When comparing relevant interatomic distances around the central Pd atom in going from **pre-24 A** to **24 A**, one can note that the largest variation of distance is observed by order of importance for the N_{amide}–Pd bond (shortening by 0.10 Å), the S–Pd bond (shortening by 0.05 Å) and the C–Pd bond (shortening by 0.01 Å). As a consequence the amide C–O and sulfoxide S–O distances undergo a slight elongation by about 0.010-0.020 Å. Further NBO analysis of **24 A** indicates that in the assumed Lewis structure, the lowest bond electron populations around the Pd center are found for the S–Pd and $N_{pyridine}$–Pd bonds, which fall below the detection threshold of 1.7 e. Their Wiberg bond indices (NBO), *w*, are w(S–Pd) = 0.14 and $w(N_{pyridine}–Pd) = 0.05$, respectively. Interestingly, in the computed NBO Lewis structure, the bonds that actually seem to support the chelate are the N_{amide}–Pd and $C_{cyclopropyl}$–Pd, which are both computed as the following linear combinations of

atom-centered orbitals: $\psi(N_{amide}\text{–Pd})$ (1.89 e) = $0.90(sp^{2.99})_N + 0.43(sd^{0.95})_{Pd}$, $w(N_{amide}\text{-Pd}) = 0.10$; $\psi(C_{cyclopropyl}\text{–Pd})$ (1.83 e) = $0.78(sp^{3.54})_C + 0.62(sd^{1.21})_{Pd}$, $w(C\text{–Pd}) = 0.53$.

On the basis of this study and in accordance with literature precedents, a simplified catalytic scenario can be proposed (Figure 6). A substrate binding to the metal by coordinating S- and N-atoms is believed to initiate the overall transformation.

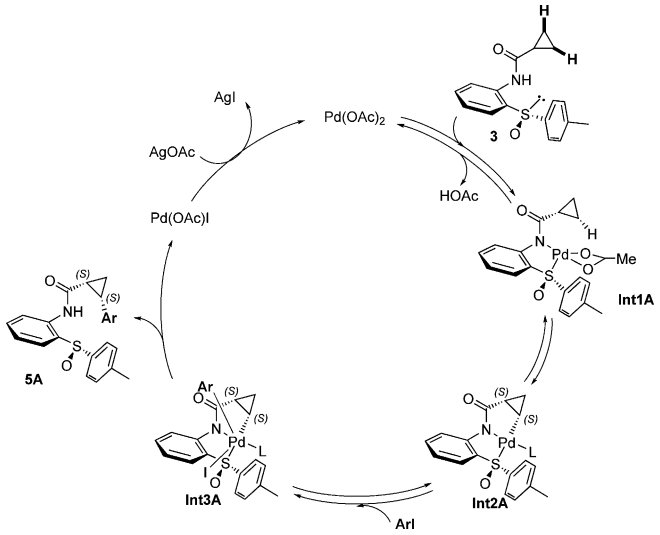


Figure 6. Proposed catalytic cycle.

The chelation with the deprotonative amide group bearing a negative charge, enhances formation of Pd-intermediate **Int1** bearing one anionic acetate ligand and allows the C–H preactivation through favorable Pd-CH agostic geometry.[32] However, the order of the elemental steps of NH-deprotonation and palladation, remains ambiguous. Subsequently, the reversible C–H activation takes place, probably through a concerted metallation-deprotonation pathway, enhanced in the presence of NaTFA additive. This metallation step is believed to be stereodeterminant, because the same diastereomeric ratio of the palladacyclic intermediates **Int2** and the arylated products were usually observed. Subsequent oxidative addition of Ar–I leads to the formation of Pd^{IV} intermediates **Int3** and a final reductive elimination delivers both diastereomers of the product and the catalyst is regenerated in the presence of AgOAc. Notably, the scope of the arylation of **3** clearly indicates that the diastereoselectivity is improved when *meta*- and *ortho*-substituted iodoarenes **4** are used (Table 3, entries 8, 10, 13–14). It can be hypothesized that when more sterically demanding **4** variants are used, the rate of the oxidative addition of **Int2 A** and **Int2 B** and/or reductive elimination from the two diastereomeric metallacyclic **Int3** is different. Accordingly, one diastereomer of **Int3** is converted into the final product more rapidly and the reversibility of the previous steps allows the re-equilibration of the ratio **Int3 A**:**Int3 B**. Therefore, in this case, the overall stereoinduction would be impacted by both the diastereoselectivity of the C–H activation step and the rate of the oxidative addition/reductive elimination from the two diastereomeric intermediates.

Conclusion

In summary, we have devised an original and truly recyclable chiral auxiliary, (*S*)-2-(*p*-tolylsulfinyl)aniline (**1**) to construct a stereogenic bidentate directing group. This original enantiopure N,S-coordinating moiety allows Pd-catalyzed diastereoselective direct functionalization of aliphatic C–H bond of cyclopropane and cyclobutane carboxylic acid derivatives. Both arylation and more challenging alkylation reactions have been investigated and moderate to good levels of diastereoselectivity are observed. However, the formation of diastereomeric products easily separable by simple silica-gel column chromatography allows isolation of both diastereomers separately, thus giving access to both optically pure enantiomers in synthetically useful yields. Subsequently, this approach paved the way towards preparation of unique, enantiomerically pure 1,2,3-trisubstituted cyclopropane carboxylic acid derivatives containing three stereocenters by functionalization of racemic precursors. Targeting the mechanistic studies, the first palladacyclic intermediate resulting from the C–H activation of the cyclopropane core has been isolated, showing unambiguously N,S-bicoordinating character of our APS auxiliary. APS chiral auxiliary, which is easy to install, to cleave and to recover is therefore a unique tool for challenging asymmetric $C(sp^3)$–H activations and synthesis of unprecedented chiral cyclopropane scaffolds with possible biological and agrochemical applications.

Experimental Section

To a Schlenk flask were added compound **3** (0.23 mmol, 1 equiv), coupling partner **4** (0.28 mmol, 1.2 equiv), silver(I) acetate (86 mg, 0.52 mmol, 2.2 equiv), sodium trifluoroacetate (17 mg, 0.12 mmol, 0.5 equiv), and palladium(II) acetate (2.6 mg, 0.012 mmol, 5 mol%). HFIP (2 mL) and water (0.2 mL) were then added and the mixture was stirred at 80 °C during the appropriate time (typically between 8 and 18 h) under air. The mixture was then allowed to cool to room temperature, diluted with EtOAc, filtered over celite and evaporated in vacuo. The crude was purified by column chromatography on silica gel with cyclohexane/EtOAc to obtain the two diastereomers of the title compound as pure enantiomers.

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Keywords: C–H activation · chiral auxiliaries · cyclopropane · sulfoxide

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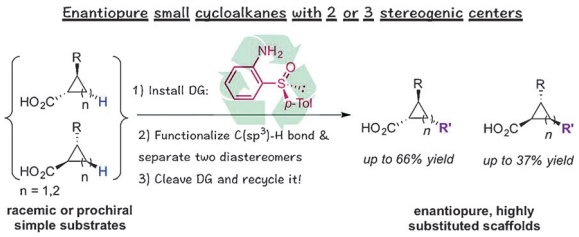

APS: ***A***symmetric cyclo***P***ropane ***S***ynthesis via C–H activation strategy has been achieved using new stereogenic bicoordinating, sulfoxide-based directing group. Enantiopure small cycloalkanes with up to three carbon stereocenters were constructed with concomitant recovery of the chiral directing group.

Asymmetric Catalysis

S. Jerhaoui, F. Chahdoura, C. Rose, J.-P. Djukic, J. Wencel-Delord, F. Colobert**

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Enantiopure Sulfinyl Aniline as a Removable and Recyclable Chiral Auxiliary for Asymmetric C(sp^3)–H Bond Activation