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## A convergent fragment coupling strategy to access quaternary stereogenic centers†

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The formation of quaternary stereogenic centers *via* convergent fragment coupling is a longstanding challenge in organic synthesis. Here, we report a strategy for the formation of quaternary stereogenic centers in polycyclic systems based upon the semi-pinacol reaction. In the key transformation, two fragments of a similar size and complexity are joined by a 1,2-addition of an alkenyl lithium to an epoxy ketone, and the resulting epoxy silyl ether undergoes a semi-pinacol rearrangement catalyzed by *N*-(trimethylsilyl)bis(trifluoromethanesulfonyl)imide (TMSNTf<sub>2</sub>) or trimethylsilyl trifluoromethanesulfonate (TMSOTf). Polycyclic scaffolds were generated in high yields and the reaction conditions tolerated a variety of functional groups including esters, silyl ethers, enol ethers, and aryl triflates. This method provides a useful strategy for the synthesis of complex polycyclic natural product-like scaffolds with quaternary stereogenic centers from simplified fragments.

Convergent fragment coupling is a strategic approach that can rapidly generate complex molecules by joining fragments of a similar size and complexity.<sup>1</sup> The independent synthesis of each fragment can be completed in parallel and this approach reduces the potential for competitive functional group reactivity. Many elegant syntheses have been developed utilizing a fragment coupling as a key strategic disconnection, often employing well established chemistry such as the Michael addition, the Diels–Alder reaction, transition metal-catalyzed cross-coupling, and 1,2-nucleophilic addition.<sup>2</sup> A major limitation to these approaches is the challenge of accessing stereogenic quaternary carbons, which are common motifs in natural products.<sup>3</sup> Stereocontrol at attached-ring quaternary centers represents an especially difficult task due to the lack of well-defined stereocontrol elements, in contrast to the more rigid ring topologies of bridging, spirocyclic, and fused ring systems.<sup>4</sup>

A powerful method to form quaternary stereogenic centers is the semi-pinacol rearrangement, a stereospecific reaction that can convert epoxy alcohols to  $\alpha$ -quaternary ketones (Fig. 1a).<sup>5</sup> The strategic application of the semi-pinacol rearrangement in total synthesis has predominately focused on skeletal rearrangement (for example, Fig. 1b) rather than as part of a fragment coupling tactic.<sup>6,7</sup> There have been relatively few applications of the semi-pinacol rearrangement as fragment coupling strategies in total synthesis,<sup>8</sup> which motivated us to

develop a general set of conditions based upon our work towards the C19 diterpenoid alkaloids (Fig. 1c).<sup>8b</sup>

Our initial studies began with the investigation of the semi-pinacol rearrangement of epoxide **2a-OH**, an intermediate in our synthesis of the diterpenoid alkaloid (–)-talatisamine.<sup>8b</sup>

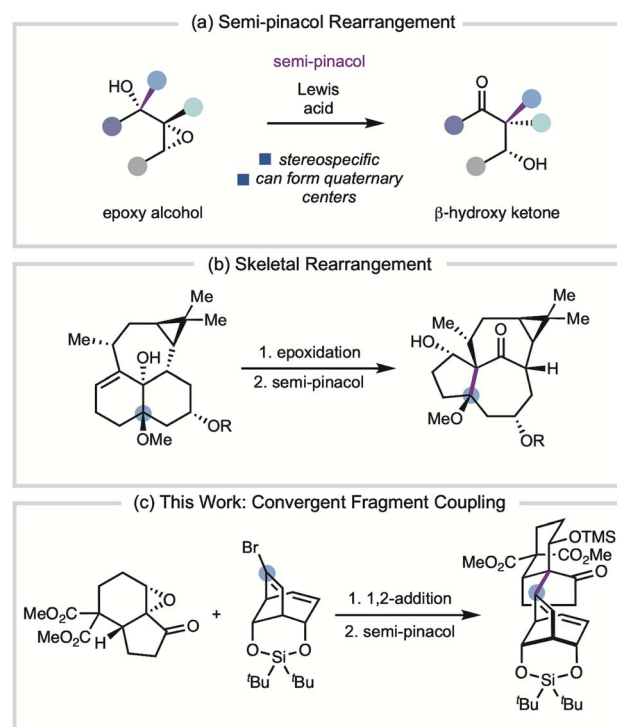


Fig. 1 Synthetic strategies using the semi-pinacol rearrangement.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data (<sup>1</sup>H and <sup>13</sup>C NMR, HRMS, FTIR) for all new compounds (PDF). See DOI: <https://doi.org/10.1039/d2sc07023e>

Treatment alcohol **2a-OH** with 1.2 equiv. of TMSOTf at  $-10^{\circ}\text{C}$  resulted only in silylation of the tertiary alcohol to give **2a** in 97% yield (Table 1a, entry 1). However, performing the reaction with 1.5 equiv. of TMSOTf at  $21^{\circ}\text{C}$  provided  $\beta$ -silyoxyketone **3a** in 33% yield along with several other side products (entry 2). Although the yield of **3a** was low, this result did confirm the feasibility of migrating the bicyclic fragment.

Since migration occurred after silyl ether formation when excess TMSOTf was used, we posited that use of **2a** as a substrate in conjunction with a stronger Lewis acid could allow the reaction to be conducted at low temperature, and could potentially improve the yield of **3a** (Table 1b).<sup>9</sup> When **2a** was treated with 1.0 equiv. of TMSNTf<sub>2</sub> at  $-78^{\circ}\text{C}$  for 45 minutes, starting material was consumed, but low yields of **3a** were again observed (entry 1). Close monitoring of the reaction at early timepoints revealed that the reaction was very fast; indeed, stopping the reaction after 60 seconds improved the yield to 50% (entry 2). Further improvement was obtained by lowering the reaction temperature to  $-94^{\circ}\text{C}$  and quenching 10 seconds after addition of TMSNTf<sub>2</sub> (entry 3). Although we were pleased with this discovery, it was not well suited for up-scaling.

Given that the use of silyl ether **2a** negated the need for stoichiometric TMSNTf<sub>2</sub>, we evaluated using this Lewis acid catalytically. Gratifyingly, treatment of **2a** with 10 mol% TMSNTf<sub>2</sub> at  $-78^{\circ}\text{C}$  and then warming to  $0^{\circ}\text{C}$  over 2.5 hours gave **3a** in 99% yield (entry 4). The optimal conditions for gram scale were treatment of **2a** with 10 mol% TMSNTf<sub>2</sub> at  $-78^{\circ}\text{C}$  for

15 minutes without warming, which provided semi-pinacol product **3a** in a 97% yield (entry 5). To our knowledge, TMSNTf<sub>2</sub> has not previously been used as a catalyst for the semi-pinacol reaction.

Table 1 Optimization of the reaction conditions

**a**

Entry	Lewis Acid (Equiv.)	Temperature	Product	Yield (%)
1	TMSOTf (1.2)	$-10^{\circ}\text{C}$	<b>2a</b>	97
2	TMSOTf (1.5)	$21^{\circ}\text{C}$	<b>3a</b>	33

**b**

Entry	Equiv. LA	Temperature	Time	Yield (%)
1	1.0	$-78^{\circ}\text{C}$	45 min	25
2	1.0	$-78^{\circ}\text{C}$	60 sec	50
3	1.0	$-94^{\circ}\text{C}$	10 sec	90
4 <sup>a</sup>	0.1	$-78^{\circ}\text{C}$ to $0^{\circ}\text{C}$	2.5 h	99
5 <sup>b</sup>	0.1	$-78^{\circ}\text{C}$	15 min	97

**2a-OH**

**R=**

<sup>a</sup> 110 mol% of 2,6-(*t*-Bu)<sub>2</sub>-4-MePyr. <sup>b</sup> 110 mol% of 2,6-(*t*-Bu)<sub>2</sub>-4-MePyr on 4.3 g scale.

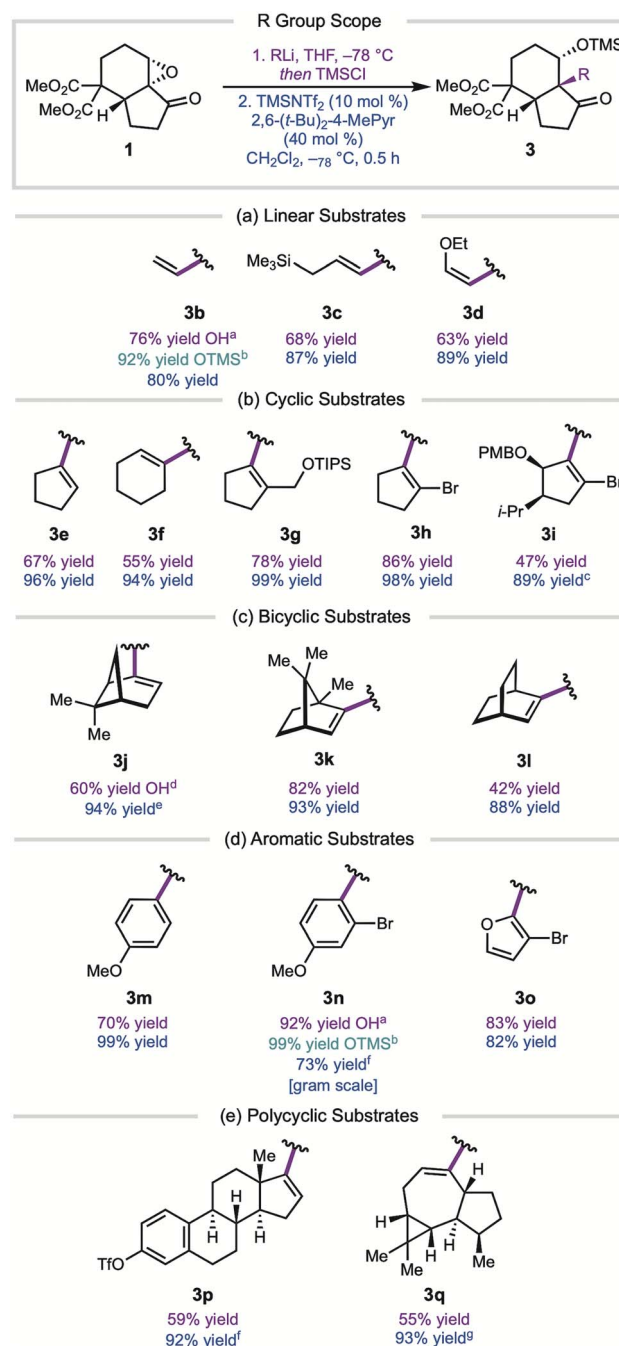
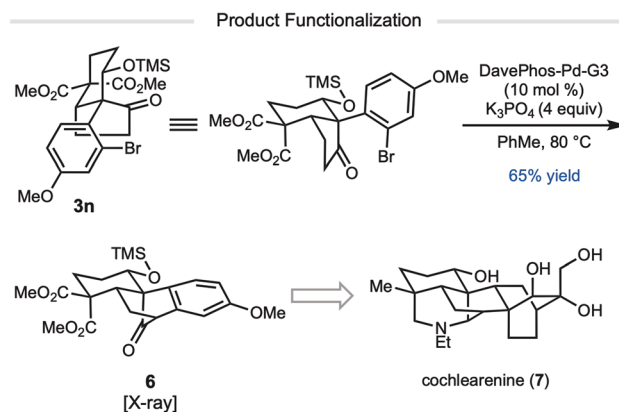


Fig. 2 Scope of migrating group. Isolated yields of 1,2-addition product in purple, isolated yield of silylation (if separate step) in teal, isolated yields of semi-pinacol product in blue. <sup>a</sup>Yield of 1,2-addition from Grignard reagent without TMSCl trapping. <sup>b</sup>Yield of TMS protection. <sup>c</sup>50 mol% TMSNTf<sub>2</sub>, 110 mol% 2,6-(*t*-Bu)<sub>2</sub>-4-MePyr,  $-78^{\circ}\text{C}$ , 4 h. <sup>d</sup>Yield of 1,2-addition from alkenyl lithium without TMSCl trapping. <sup>e</sup>TMSOTf (5 equiv), Et<sub>3</sub>N (6 equiv.),  $0^{\circ}\text{C}$  to  $21^{\circ}\text{C}$ , 1 h. <sup>f</sup>50 mol% TMSNTf<sub>2</sub>, 110 mol% 2,6-(*t*-Bu)<sub>2</sub>-4-MePyr,  $0^{\circ}\text{C}$ , 0.5 h. <sup>g</sup>30 mol% TMSNTf<sub>2</sub>, 100 mol% 2,6-(*t*-Bu)<sub>2</sub>-4-MePyr,  $-78^{\circ}\text{C}$ , 4 h.

With optimized conditions in hand, we examined the scope of the convergent fragment coupling strategy (Fig. 2). Although the yields of the alkenyl lithium 1,2-addition were substrate dependent, the semi-pinacol rearrangement gave consistently high yields. Simple linear alkenes, including an allylic silane and enol ether, migrated with high yields (**3c**, **3d**). Cyclic and bicyclic alkenyl substrates also provided the rearrangement products (**3e–3l**) in excellent yields, showcasing the ability for this reaction to form attached-ring motifs bearing hindered quaternary centers. The fragment coupling tolerated substrates bearing TIPS- and PMB-protected alcohols (**2g**, **2i**), functional groups that could be useful in natural product synthesis applications. Aromatic substrates were also found to be viable in this reaction, with products **3m–3o** obtained in high yields. In addition to the gram scale reaction of **2a**, the semi-pinacol rearrangement of aryl bromide **2n** was carried out on gram scale, providing **3n** in 73% yield. We were able to effect the migration of large polycyclic alkenes (**3p–3q**) in yields greater than 90%. Notably, these conditions are relatively mild and tolerated allyl ethers and enol ethers (**3d**, **3g**, **3i**), which are often reactive under common semi-pinacol rearrangement conditions.<sup>7c,10</sup> A small additive screen found that the reaction tolerates acetal and ester functional groups, while an *N*-*t*-butyl-carboxylate-protected amine inhibited product formation (see ESI†).

We also investigated simpler monocyclic ketones for their ability to rearrange using TMSNTf<sub>2</sub> as the Lewis acid (Fig. 3). Using 10 mol% TMSNTf<sub>2</sub>, cyclopentanone **5a** was prepared in 93% yield. Although the cyclohexyl substrate was less reactive, by increasing the catalyst loading to 50 mol%, the semi-pinacol product **5b** was obtained in 79% yield.

Several of the products prepared by this method contained alkenyl or aryl bromide substituents (e.g. **3h**, **3i**, **3n**, and **3o**), which can allow for further functionalization of the product. For example, treatment of ketone **3n** with DavePhos-Pd-G3 in the presence of K<sub>3</sub>PO<sub>4</sub> at 80 °C resulted in clean enolate arylation to



Scheme 1 Intramolecular enolate arylation of **3n**.

give tetracycle **6** (Scheme 1).<sup>11</sup> We anticipate that tetracycle **6** could serve as an intermediate for the synthesis of the denudatine-type diterpenoid alkaloids.<sup>12</sup>

## Conclusions

In summary, a convergent fragment coupling approach was developed to access a variety of quaternary centers in polycyclic substrates in high yields. This method is compatible with a variety of functional groups including sterically hindered alkenes, enol ethers, silyl ethers, alkenyl halides, aryl halides, and allyl silanes. The total syntheses of talatisamine and other C19 diterpenoid alkaloids have been enabled using this strategy to produce **3a** in high yields on gram scale.<sup>8b</sup>

## Data availability

Experimental procedures and characterization data (<sup>1</sup>H and <sup>13</sup>C NMR) for all new compounds are provided in the ESI†

## Author contributions

Project conceptualization: A. R. W., V. W. M., and S. E. R. Funding acquisition: S. E. R. Experimental design and investigation: J. K. K., A. R. W., V. W. M., and S. E. R. Manuscript writing and editing: J. K. K. and S. E. R.

## Conflicts of interest

There are no conflicts to declare.

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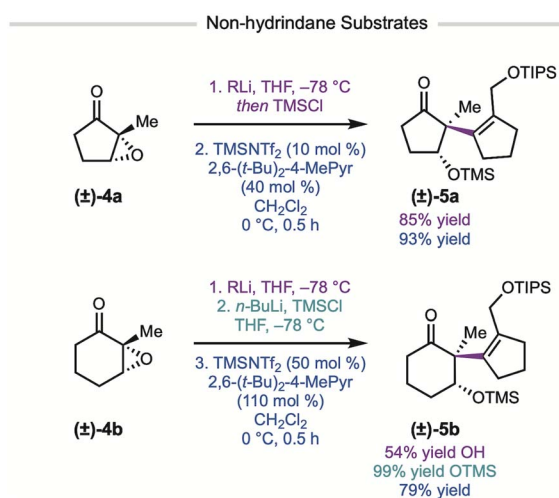


Fig. 3 Substrates derived from simple epoxyketones. Isolated yields of 1,2-addition product in purple, isolated yield of silylation (if separate step) in teal, isolated yields of semi-pinacol product in blue.



of Chemistry and Chemical Engineering is acknowledged for their help in acquisition of HRMS data with instrumentation purchased by funds from DOW Next Generation Instrumentation and the NSF CRIF program (CCEC.DOWINSTR-1-GRANT.DOWINSTR). Dr M. Takase and L. Henling are acknowledged for acquiring the X-ray diffraction data. Funding: Fellowship support was provided by the Natural Sciences and Engineering Research Council (NSERC) of Canada (PGS-D fellowship to J. K. K., grant PGSD3-532535-2019), and the NSF (DGE-1144469 to A. R. W. and V. W. M.). S. E. R. acknowledges financial support from the NIH (R35GM118191).

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