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COMMUNICATION

Trapping of chiral enolates generated by Lewis acid promoted conjugate addition of Grignard reagents to unreactive Michael acceptors by various electrophiles

Denisa Vargová, a,b Juana M. Pérez, a Syuzanna R. Harutyunyan, b and Radovan Šebest a

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Trapping reactions were discovered by Feringa in 1997, when he reported the first tandem asymmetric conjugate addition (CA)-aldol reaction. Since then, many groups were intrigued by the concept of one-pot reactions, which becomes more relevant in view of green chemistry. The trapping reactions take advantage of a chiral enolate formed in-situ, which can react with an electrophile, to form a product with two or more new stereogenic centers. The chiral enolate can be formed by an asymmetric Cu-catalyzed CA of an organometallic reagent to a Michael acceptor. A variety of substrates was utilized such as enones, esters, thioesters, and lactones. A large variety of electrophilic reagents was used for enolate trapping. We showed the trapping of Zr and Mg-enolates by carbocations. Highly enantioselective protocols for CAs of Grignard reagents to less reactive, but highly valuable amides, and heteroarenes prompted us to investigate the enolate intermediates of these reactions in electrophilic trapping reactions with carbocations, and other less utilized electrophiles. Aza-enolates derived from Lewis acid promoted CA to alkenyl-heteroarenes can be trapped with Michael acceptors as electrophiles.

Here we show a simple one-pot CA-trapping protocol that leads to functionalized molecules starting from unreactive Michael acceptors (Scheme 1). This domino reaction of enamides with carbocation ions afforded compounds featuring useful and non-trivial substituent motives.

We started our investigation with amide 1a, using previously optimized conditions for the CA. Tropylionium 4 was chosen as the first cation (Scheme 2). Tropylionium derivatives are desired structural motives, such as in stimuli-responsive dyes. The model reaction in DCM afforded the product 3a in promising 19% yield (Table 1, entry 1). To improve the solubility of the cation, we added a polar additive, 1,3-dimethylimidazolidin-2-one (DMEU) (entry 2). Other polar solvents such as DMF, N,N-dimethylpropylene urea (DMPU), or NMP could also be used with comparable results (Table S1; see ESI). We continued the optimization with DMEU as it afforded the highest conversion (43%). Data in Table S2 show that DCM is the most suitable solvent for the trapping reaction. Coordinating solvents such as THF, and 2-Me-THF could dissolve the cation, so no additive was needed, but conversions did not improve (37% in THF, and 11% in 2-Me-THF). Decreased reactivity in coordinating solvents can be attributed to more effective solvation of cations in these solvents.

As we observed higher conversion in less coordinating solvents, we added minimum amount of coordinating additive. Indeed, yield increased from 27 to 59% (entries 2 and 3). Unfortunately, larger amount of tropylionum NTf2 (4, 2 equiv.) led to a less clean reaction, and a lower yield of the tandem product (entries 3 and 4). We also tried BF3 contraion for the cation because it can release a more reactive enolate by attacking the silyl moiety. In this case, 50% conversion was observed, and the product 3a was obtained in 36% yield (entry 5). To improve the selectivity, we have tested the reaction at a lower temperature. However, the reaction slowed down,
affording the product in only 17\% yield (entry 6). As before, a larger amount of the cation 4 did not restore the yield of 3a (entry 7). Diastereoselectivity of the reaction was poor, and neither the amount of tropolium 4, nor the reaction temperature had any effect. The use of BF3·Et2O instead of TMSOTf led to the formation of only a trace amount of product 3a (entry 8), probably due to an undesired interaction between the excess LA and cation 4.

Table 1. Optimization of reaction conditions for the reaction of silyl ketene aminal 2a with tropolium cation 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv.</th>
<th>mol % DMEU</th>
<th>Conversion(%)</th>
<th>Yield(%)</th>
<th>dr(^a)</th>
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<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>-</td>
<td>25</td>
<td>19</td>
<td>59:41</td>
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<tr>
<td>2</td>
<td>1.3</td>
<td>4.4</td>
<td>45</td>
<td>27</td>
<td>54:46</td>
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<tr>
<td>3</td>
<td>1.1</td>
<td>0.6(^c)</td>
<td>75</td>
<td>59</td>
<td>57:43</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>0.6</td>
<td>41</td>
<td>21</td>
<td>55:45</td>
</tr>
<tr>
<td>5</td>
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<td>0.6(^c)</td>
<td>50</td>
<td>36</td>
<td>52:48</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>0.6(^c)</td>
<td>31</td>
<td>17</td>
<td>56:44</td>
</tr>
<tr>
<td>7</td>
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<td>0.6(^c)</td>
<td>39</td>
<td>9</td>
<td>54:46</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>0.6(^c)</td>
<td>trace</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\(^a\) Determined by analysis of the crude \(^1\)H NMR spectra; \(^b\) Isolated yield after column chromatography; \(^c\) Amount required to dissolve 4; \(^d\) Tropolium BF3 was added to the mixture directly; \(^e\) -50 °C to 13 °C gradually over 1h; \(^f\) BF3·Et2O was used as Lewis acid.

Next, we changed the steric demands of the silyl group of enolate 2. However, the diastereoselectivity was not affected if TESOTf, TIPSOTf, TBOSOTf, and TBDPSTOF were used. We further observed a rapid decrease in the yield of 3a, as the groups got bulkier (Table S3).

With the optimized conditions (Table 1, entry 3), we focused on the scope of the reaction. We evaluated cations 5-8 of diverse structures (Scheme 3). Cation 5 afforded 52\% conversion and 25\% isolated yield of 3b. Such sulfur-containing derivatives afforded by reactions with benzenthiolium 5 and ditinanium 6 cations can serve as synthetic equivalents for other transformations.\(^14\) This reaction did not require any additive. Ditinanium ion 6 and Eschenmoser’s salt 7 gave less than 30\% conversions. The problem with the cation 7 was its low solubility in DCM, even with DMEU as a co-solvent. Low conversion with the tritylum ion 8 can be attributed to its high steric demands. Neither Pd-allyl cation (9, generated from allyl bromide and Pd[(PPh3)2]) did not afford any trapping product under variety of conditions.

We have altered the steric demands of the amide moiety by using diallylamino group (Scheme 3c). However, the diastereomeric ratio of 10, after ring-closing metathesis was 61:39. We have also assessed N,N’-phenyl(benzyl) amide, but it did not afford any trapping product. This finding together with the silyl group variation suggests that steric hindrance close to the reaction center has negative impact on the yield. A variation on the side chain showed that products with the aromatic ring 3g and 3h were obtained with high dr (up to 94:6) (Scheme 3b).

We have investigated trapping of aza-enolates derived from CA of Grignard reagents to alkanyl heteroarenes 11 (Scheme 5). For the benzoxazole substrate 11a, we obtained the trapping product 12a with tropolium ion 4 in high yield. Interestingly, the use of BF3·Et2O with amide 1a led to almost no conversion, on the other hand with the benzoxazole substrate 11a the reaction with cation 4 proceeded with high conversion. A possible reason for this difference is that only 1.2 equiv. of BF3·Et2O was needed for the activation of the benzoxazole substrate 11a, compared to two equivalents for 1.
It is possible to use both Lewis acids, but its higher excess interferes with the trapping reaction. Interestingly, with sulfur-containing cations 5 and 6, only one diastereomer of the products 12b,c was isolated. Two conditions were used for these products differing by the Lewis acid. With TMSOTf, nearly racemic products 12b,c were obtained but in good yields. On the other hand, BF₃·Et₂O gave the products in high enantiomeric purities, but only low conversions were observed. It was also possible to obtain the pyridine-containing product 12d, but the conversion was low due to unreactivity of this substrate. Reactions of the pyridine-substrate with the sulfur-containing cations 5 and 6 gave less than 20% conversions. Absolute configuration of compound 12b was determined as (2R,3S) by X-ray crystallographic analysis (see Supplementary information). Other products were assigned by analogy.

We tried to trap the silyl ketene aminal 2 with activated alkenes (Scheme 5). Only alkenes activated by two EWGs afforded trapping products 15. (Ethene-1,1-diyldisulfonyl)di benzene afforded the product 15a in high yield, but medium dr of 61:39. 2-Benzylidenemalononitrile gave the product 15b in low yield, presumably due to steric hindrance. (Vinylsulfonyl)benzene and methacrylonitrile did not react.

We evaluated α-bromination of silyl ketene aminals with NBS. α-Bromoamides are useful for further functionalization, e.g. asymmetric cross-couplings. The α-bromination of amide 1a proceeded with 50% conversion and afforded the corresponding α-brominated amide 15c (Scheme 6b).

Overall yields of the trapping reactions 15-65% may seem modest but applying Jørgensen’s YRF (yield per bond formed). These are typically between 40-80%. We hypothesized that incomplete conversions are caused by low reactivity of silyl enolates compared to metal enolates, which are obtained in CAs of organometallics. Surprisingly, base-

Scheme 4. Conversions and dr were determined by 1H NMR of crude reaction mixtures. Conditions A: 5 mol% CuBr·SMe₂, 6 mol% L2, 1.2 equiv BF₃·Et₂O, 4h, -78 °C; Conditions B: 10 mol% CuBr·SMe₂, 12 mol% L2, 3 equiv TMSOTf, DCM, 18h, -78 °C. X-ray structure of compound (2R,3S)·12b. CCDC 1937210 contains the supplementary crystallographic data.

Scheme 5. Trapping by activated alkenes, and bromination. Conversions and dr were determined by 1H NMR of crude reaction mixtures.

Scheme 6. Trapping reactions of the silyl ester-enolate. Conversions were determined by analysis of the crude 1H NMR spectra, yields are after column chromatography. Relative configuration was determined by analogy with 12b. **18b was obtained as an inseparable mixture with the CA product.

Overall yields of the trapping reactions 15-65% may seem modest but applying Jørgensen’s YRF (yield per bond formed). These are typically between 40-80%. We hypothesized that incomplete conversions are caused by low reactivity of silyl enolates compared to metal enolates, which are obtained in CAs of organometallics. Surprisingly, base-
generated Li-enolate afforded 26% conversion, in comparison with silyl enolate 2a, which afforded 31%. This observation suggests that the reactivity of silyl enolate 2 would not improve by transmetalation (Scheme 7).

Silyl ketene aminals 2 do not have nucleophilic parameters determined,18 but related silyl ketene acetics have N between 8-12.19 Therefore, we can estimate nucleophilicity of silyl ketene aminals to around 10. We calculated HOMO energies and natural charges at the enolate C-2 carbon for relevant nucleophiles from this study (Scheme 7b). Li-enamide should be the most nucleophilic, and silyl ketene aminal and acetal are roughly the same. Benzoxazole substrate seems quite nucleophilic, which correlates with our results. According to Mayr-Patz equation, useful reactions between nucleophiles and electrophiles have E+N between 10 and -5.20 Therefore, silyl ketene aminals should react effectively with carbocation ions 4-9, which have electrophilicities ranging from 0.5 to -10.18,21 However, our experiments suggest that other factors should also be considered. Our results also show that trapping reactions highly depend on the structure of electrophile.

In conclusion, we showed that chiral silyl ketene aminals and related enolates from carboxylic acids and alkenylenoacycetals could be trapped by various electrophiles. Trapping by carbocations was compatible with the excess of TMSOTf and Grignard reagent, which are required for the effective CA to unreactive Michael acceptors. Experiments showed that steric factors were responsible for reactions outcomes. Trapping reaction on alkenylenoacycetals allowed use of BF₃.OEt₂ and TMSOTf. By this one-pot procedure, we obtained multiple-functionalized products, which are not accessible by other methods. This work was supported by the Slovak Research and Development Agency (grant APVV-18-0242). Slovak Academic Information Agency is acknowledged for a research scholarship to D.V.J.M.P. thanks to the European Commission for an Intra-

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Conflicts of interest
There are no conflicts to declare.

Notes and references