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

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

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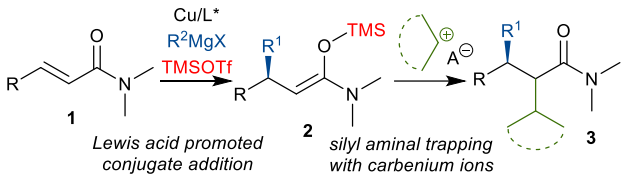
Here we show trapping of chiral enolates with carbenium ions, Michael acceptors, and bromine. Silyl ketene aminals, disilyl acetals, and aza-enolates were obtained via Lewis acid mediated enantioselective conjugate addition of Grignard reagents to unsaturated amides, carboxylic acids and alkenyl heterocycles.

Trapping reactions were discovered by Feringa in 1997,[1] 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.[2] The chiral enolate can be formed by an asymmetric Cu-catalyzed CA of an organometallic reagent to a Michael acceptor.[3] A variety of substrates was utilized such as enones, esters,[4] thioesters,[5] and lactones.[6] A large variety of electrophilic reagents was used for enolate trapping.[7] We showed the trapping of Zr and Mg-enolates by carbocations.[8] Highly enantioselective protocols for CAs of Grignard reagents to less reactive, but highly valuable amides,[9] and heteroarenes,[10] prompted us to investigate the enolate intermediates of these reactions in electrophilic trapping reactions with carbocations, and other lesser utilized electrophiles. Aza-enolates derived from Lewis acid promoted CA to alkenyl-heteroarenes can be trapped with Michael acceptors as electrophiles.[11]

Here we show a simple one-pot CA-trapping protocol that leads to functionalized molecules **3** starting from unreactive Michael acceptors (Scheme 1). This domino reaction of enamides **2** with carbenium ions **4-8** afforded compounds **3** featuring useful and non-trivial substituent motives.



Scheme 1. One-pot CA of Grignard reagents to α,β-unsaturated amides **1**, catalyzed by Cu/L* complex, followed by trapping of silyl ketene aminals **2** with carbocations.

We started our investigation with amide **1a**, using previously optimized conditions for the CA.[9] Tropylium ion **4** was chosen as the first cation (Scheme 2). Tropylium derivatives are desired structural motives, such as in stimuli-responsive dyes.[12] The model reaction in DCM afforded the product **3a** in a promising 19% yield (Table 1, entry 1). To improve the solubility of the cation **4**, 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 tropylium NTf_2 (**4,** 2 equiv.) led to a less clean reaction, and a lower yield of the tandem product (entries 3 and 4). We also tried BF_4 contraion for the cation because it can release a more reactive enolate by attacking the silyl moiety.[13] 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,

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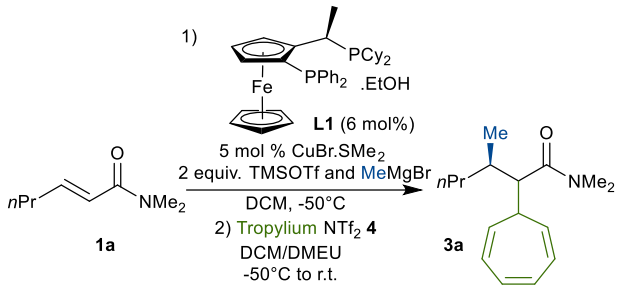
Electronic Supplementary Information (ESI) available: additional optimization results, experimental procedures and characterization data for all compounds, pictures of NMR spectra and HPLC chromatograms; CCDC 1937210 contains the supplementary crystallographic data for this paper. See DOI: 10.1039/x0xx00000x

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 tropylium **4**, nor the reaction temperature had any effect. The use of $BF_3.Et_2O$ 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**.



Scheme 2. Initial experiments with trapping of the enamide with tropylium ion **4**.

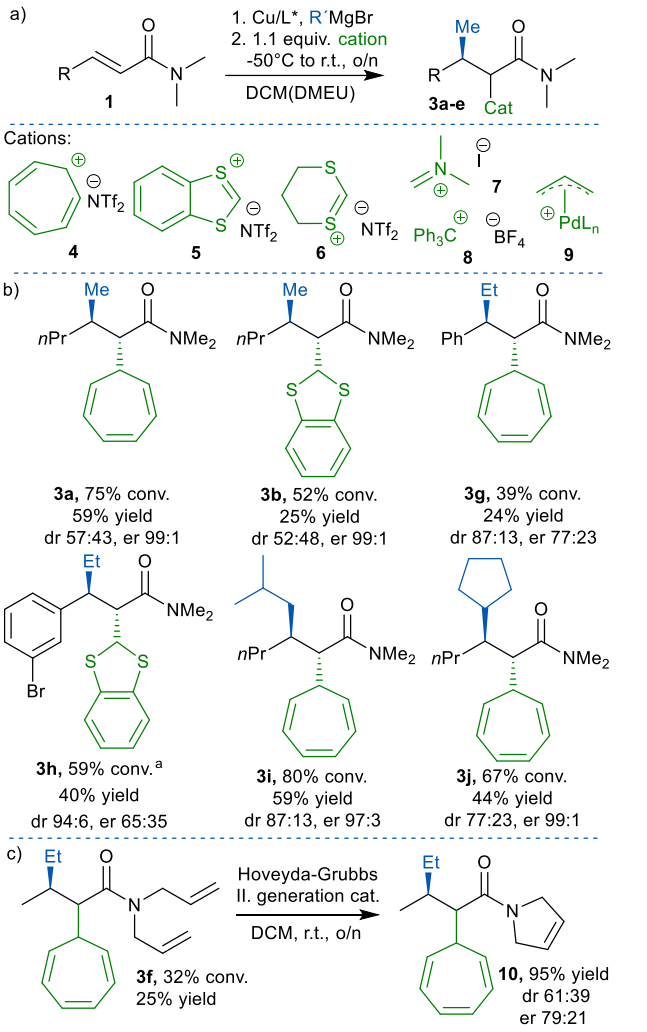
Table 1. Optimization of reaction conditions for the reaction of silyl ketene aminal **2a** with tropylium cation **4**.

Entry	Equiv. of **4**	mol % DMEU	Conversion[a] (%)	Yield[b] (%)	dr[a]
1	1.1	-	25	19	59:41
2	1.3	4.4	45	27	54:46
3	1.1	0.6[c]	75	59	57:43
4	2.0	0.6	41	21	55:45
5	1.1	0.6[c,d]	50	36	52:48
6	1.1	0.6[e]	31	17	56:44
7	1.5	0.6[e]	39	9	54:46
8	1.1	0.6[c,f]	trace	n.d.	n.d.

[a] Determined by analysis of the crude ^{1}H NMR spectra; [b] Isolated yield after column chromatography; [c] Amount required to dissolve **4**; [d] Tropylium BF_4 was added to the mixture directly; [e] -50 °C to 13 °C gradually o/n; [f] $BF_3.Et_2O$ 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, TBSOTf, and TBDPSOTf were used. Furthermore, we 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 benzodithiolium **5** and ditianium **6** cations can serve as synthetic equivalents for other transformations.[14] This reaction did not require any additive. Ditianium 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 tritylium ion **8** can be attributed to its high steric demands. Neither Pd-allyl cation (**9**, generated from allyl bromide and $Pd(PPh_3)_4$) did not afford any trapping product under variety of conditions.

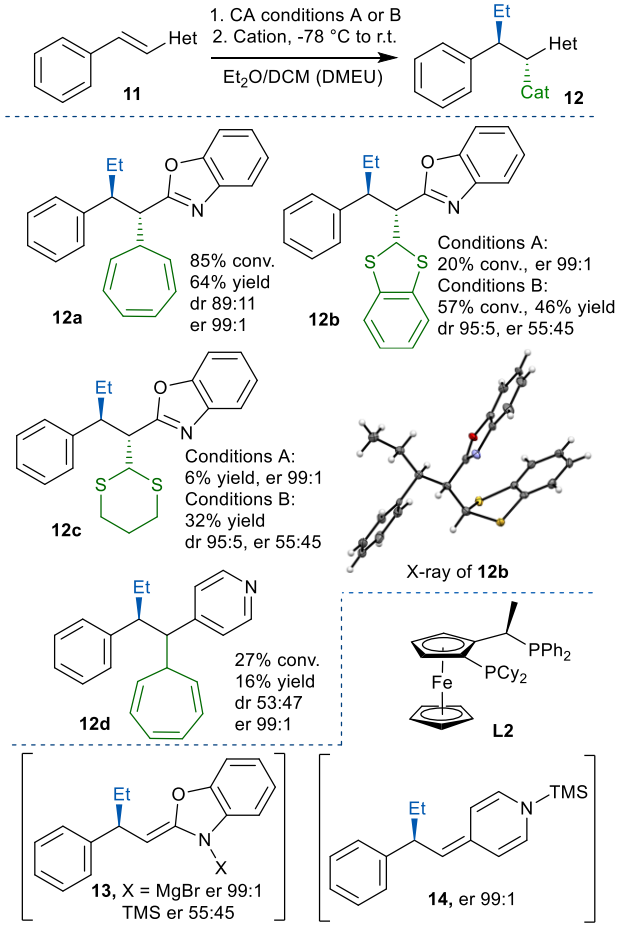


Scheme 3. a) Screening of cations **4-9** in the trapping of enamides **2**. Conversions and dr were determined by ^{1}H NMR of crude reaction mixtures; b) variations on the side chain; c) trapping reaction on a bulkier amide. [a] Two equiv. of cation **5** were used.

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 alkenyl heteroarenes **11** (Scheme 5). For the benzoxazole substrate **11a**, we obtained the trapping product **12a** with tropylium ion **4** in high yield. Interestingly, the use of $BF_3.Et_2O$ 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 $BF_3.Et_2O$ was needed for the activation of the benzoxazole substrate **11a**, compared to two equivalents for **1**.

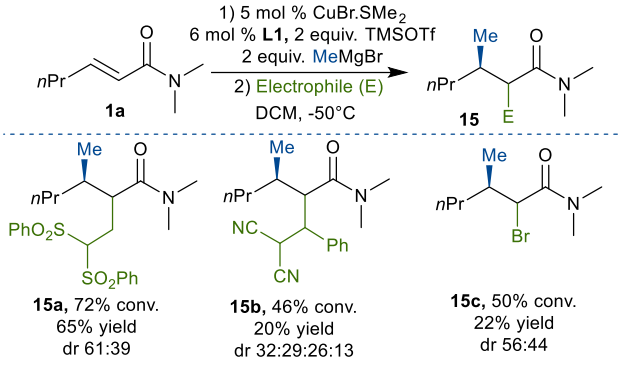
It is possible to use both Lewis acids, but its higher excess interferes with the trapping reaction. Interestingly, with sulfur-containing cations **5** and **6**, only one diastereomer of the products **12b,c** was isolated. Two conditions were used for these products differing by the Lewis acid. With TMSOTf, nearly racemic products **12b**,**c** were obtained but in good yields. On the other hand, $BF_3.Et_2O$ 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 (2*R*,3*S*) by X-ray crystallographic analysis (see Supplementary information). Other products were assigned by analogy.



Scheme 4. Conversions and dr were determined by ^{1}H NMR of crude reaction mixtures. Conditions A: 5 mol% $CuBr_2.SMe_2$, 6 mol% **L2**, 1.2 equiv. $BF_3.Et_2O$, 1.2 equiv. EtMgBr, Et_2O, 4h, -78˚C; Conditions B: 10 mol% $CuBr_2.SMe_2$, 12 mol% **L2**, 3 equiv. TMSOTf, 3 equiv. EtMgBr, DCM, 18h, -78˚C. X-ray structure of compound (2*R*,3*S*)-**12b**. CCDC 1937210 contains the supplementary crystallographic data.

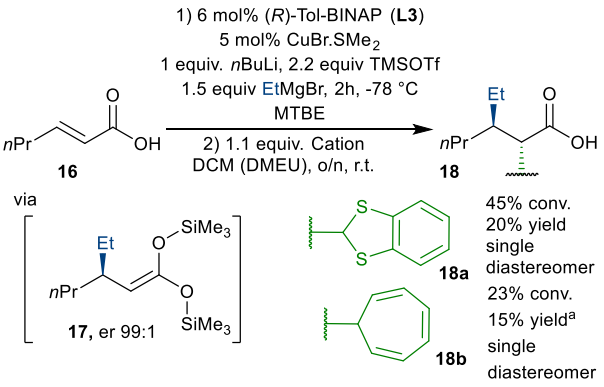
We tried to trap the silyl ketene aminal **2** with activated alkenes (Scheme 5). Only alkenes activated by two EWGs afforded trapping products **15**. (Ethene-1,1-diyldisulfonyl)dibenzene afforded the product **15a** in high yield, but medium dr of 61:39. 2-Benzylidenemalononitrile gave the product **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.[15] The α-bromination of amide **1a** proceeded with 50% conversion and afforded the corresponding α-brominated amide **15c** (Scheme 6b).



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

We also applied this methodology to the protocol recently developed in our group for conjugate addition of Grignard reagents to α,β-unsaturated carboxylic acids (Scheme 6).[16] Gratifyingly, we obtained the corresponding tandem products **18a,b**. In a comparative experiment with the corresponding TBS-ester intermediate, which was treated with LDA at -78˚C, and then with the tropylium ion **4**, only a trace amount (3%) of product **18b** was found in the crude mixture. This finding suggests that the bulky TBS group blocks the α-carbon, preventing the reaction.

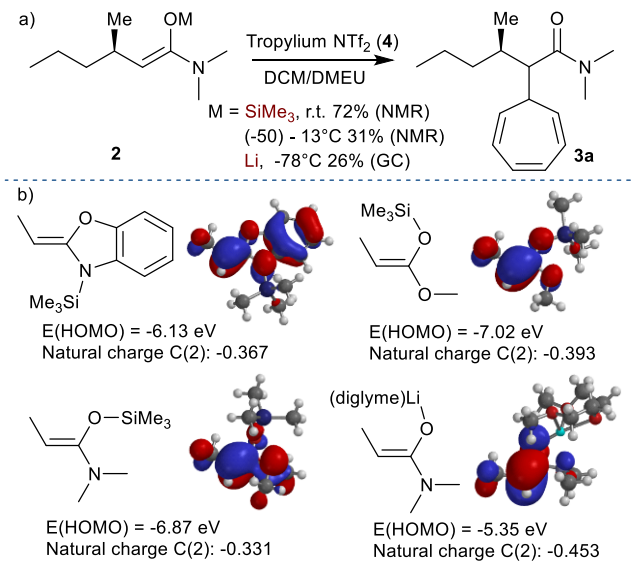


Scheme 6. Trapping reactions of the silyl ester-enolate. Conversions were determined by analysis of the crude ^{1}H NMR spectra, yields are after collumn chromatography. Relative configuration was determined by analogy with **12b**.; [a] **18b** was obtained as an inseparable mixture with the CA product.

Overall yields of the trapping reactions 15-65% may seem modest but applying Jorgensen´s Y_{PBF} (yield per bond formed),[17] 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 nucleophilicity parameters determined,[18] but related silyl ketene acetals 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 carbenium 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.



Scheme 7. a) Comparison of the reactivity of silyl ketene aminal with lithium enolate; b) HOMO energies and C-2 natural charges calculated at ωB97X-D/6-31G*//M06-2X/6-311+G**level.

In conclusion, we showed that chiral silyl ketene aminals and related enolates from carboxylic acids and alkenylheterocycles 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 alkenylheterocycles allowed use of $BF_3.OEt_2$ 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-european Marie Curie fellowship (grant 746011–ChirPyr). We thank Folkert de Vries for the X-ray measurements.

Conflicts of interest

There are no conflicts to declare.

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