JOC The Journal of Organic Chemistry

Michael additions catalyzed by a #-diketiminate-supported aluminum complex

Zhizhou Liu, and Dragoslav Vidovic

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00434 • Publication Date (Web): 13 Apr 2018

Michael additions catalyzed by a β-diketiminate-supported aluminum complex

Zhizhou Liu[a], Dragoslav Vidović[b,*]

[a]Department of Chemistry, South University of Science and Technology of China, Shenzhen 518055, China.

[b]School of Chemistry, Monash University, 3800 Australia.

*Corresponding author. E-mail: drasko.vidovic@monash.edu

Supporting Information Placeholder

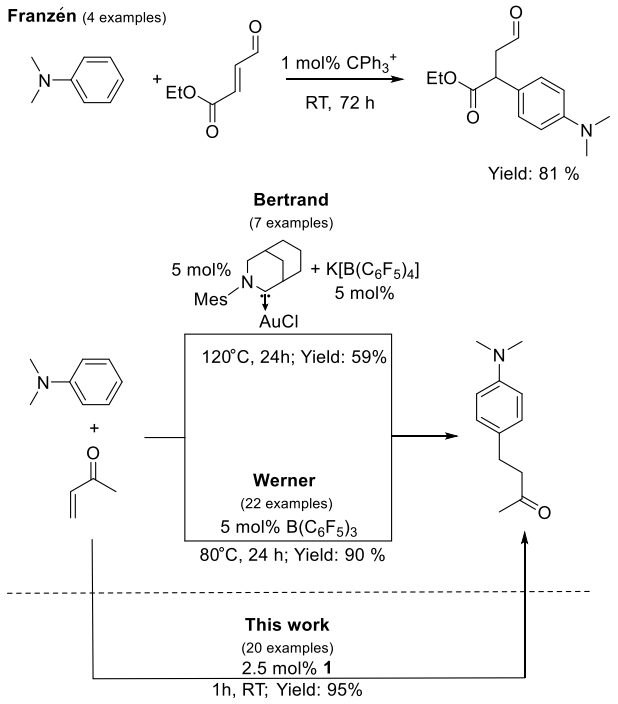
ABSTRACT: A β-diketiminate-supported aluminum bistriflate complex (^{Dip}LAl(OTf)$_2$·Na[BAr$^{Cl}_4$]; ^{Dip}L = CH(CMe)$_2$(N-C$_6$H$_3$-^{i}Pr$_2$)$_2$; Tf = O$_2$SCF$_3$; Ar^{Cl} = 3,5-Cl$_2$-C$_6$H$_3$), has been identified as an efficient Lewis acid catalyst for Michael additions involving numerous electron rich (hetero)aromatic substrates and several α,β-unsaturated carbonyl compounds. In a vast majority of the attempted Michael reactions our catalytic system was significantly superior over the currently used methods for the same transformations in terms of reaction times and temperatures, catalyst loadings, isolated product yields and/or selectivity.

C-C bond formation is arguably the most important process in the field of organic chemistry.[1] Numerous synthetic protocols were developed that describe the formation of both single and double C-C bonds for which efforts several prominent chemists received Nobel prizes.[2] Among this vast research field, Michael reactions or Michael additions are considered as one of the most effective and efficient processes for C-C bond formations due to versatility, high functional group tolerance and quantitative atom economy.[3] It is, then, not surprising that these transformations (including heteroatom Michael additions) have been extensively used, for example, in various aspects of synthetic chemistry as well as material and biomedical sciences.[4]

Michael reactions are manifested by the addition of a C-H fragment (also known as a Michael donor) across an alkene moiety (also known as a Michael acceptor) resulting in the net formation of C-C and C-H bonds. In a vast number of Michael reactions, the donor (usually a compound that contains a C(sp^3)-H fragment and neighboring electron withdrawing group(s) such as acyl and cyano) is activated by a base followed by a nucleophilic attack on the acceptor (usually an *α,β*-unsaturated carbonyl compound). Compounds bearing C(sp^2)-H fragments have also being used as nucleophiles in Lewis acid- and iminium-catalyzed electrophilic aromatic substitutions/conjugate additions but these transformations were limited to exclusively heteroaromatic substrates such as indoles and 4-hydroxy substituted coumarin-like compounds.[5,6] In recent years, groups of Franzén,[7] Bertrand[8] and Werner[9] showed that electron rich aromatic compounds (e.g. N,N-dimethylaniline) could act as Michael donors for Lewis-acid catalyzed Michael additions (Scheme 1). However, trityl-catalyzed additions were limited only to a very activated Michael acceptor (i.e. ethyl-4-oxo-2-butenoate) and sometimes required prolonged reaction times (72 h).[7] Additionally, gold- and borane-catalyzed reactions were performed under extensive (24 h) heating (≥ 120 and 80°C, respectively), with the former system generating only moderate product yields, while the latter transformations suffering from poor product selectivity.[8,9]

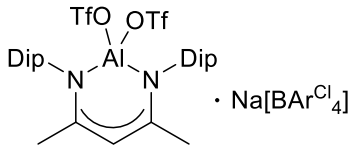
In our recent work, we have reported that well-defined and well-characterized Al-based complexes could serve as quite reactive Lewis acid catalysts for various Diels-Alder transformations.[10,11] In particular, *β*-diketiminate-supported aluminum bis(triflate) compound ^{Dip}LAl(OTf)$_2$ (^{Dip}L = CH(CMe)$_2$(N-C$_6$H$_3$-^{i}Pr$_2$)$_2$; Tf = O$_2$SCF$_3$), when combined with Na[BAr$^{Cl}_4$] (Ar^{Cl} = 3,5-Cl$_2$-C$_6$H$_3$), was a very active catalyst for a wide variety of these cycloadditions (**1**, Figure 1).[10] Additionally, we have shown that the activity of **1** was solely due to its Lewis acid properties and that this complex did not act as sources of a Brønsted acid.[10] Herein, we report that

Scheme 1. Comparative reaction conditions for Michael additions involving N,N-dimethylaniline and either ethyl-4-oxo-2-butenoate or 3-buten-2-one as catalyzed by trityl cation (Franzén), gold-based complex (Bertrand), tris(pentafluorophenyl)borane (Werner) and our β-diketiminate-stabilized aluminum complex 1.



system **1** is capable of catalyzing Michael additions between a diverse range of electron rich (hetero)arenes and several dienophiles exhibiting, in a vast majority of cases, dramatic improvements with respect to the catalyst loading, reaction times and/or temperature as well as product yields and selectivity in comparison to the published methods for the same transformations.[8,9]

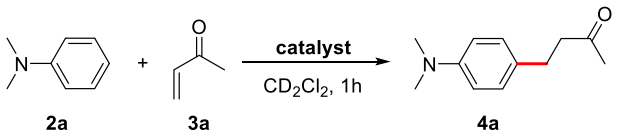
After establishing that complex **1** was a very active Lewis acid catalyst for numerous Diels-Alder cycloadditions,[10] we aimed to extend its activity to Michael reactions. Our initial examination showed that hydroarylation between methyl vinyl ketone (**2a**) and N,N-dimethylanaline (**3a**), using a 1:1 mole ratio, proceeded within 1 h at room temperature using 2.5 mol% of **1** to give the target product **4a** in 87 % yield (entry 1, Table1). This was a quite significant result considering that substantially harsher reaction conditions (i.e. elevated temperatures to 80 or 120°C), higher catalyst loadings (5 mol%) and noticeably longer reaction times (24 h) were needed for the same transformation using gold-[8] and borane-based[9] catalysts. (Scheme 1). With this encouraging observation in hand, we optimized this particular reaction with respect to the reactant ration (entries 2 and 3) and the catalyst loading (entry 4). Our best results were obtained using a 2:1 mole ratio of the aniline to the dienophile and 2.5 mol% of **1** at room temperature for 1h. These initial experiments immediately hinted that **1** was a fairly superior catalyst in comparison to the gold- and borane-based compounds (Scheme 1) because, as mentioned, the target transformation catalyzed by the competitive systems not only required twice as much the catalyst loading but was also left for considerably longer reaction times (24 h) at significantly higher reaction temperatures (80 or 120°C) to form the desired product.[8,9] In fact, remarkable activity of **1** was also evident from the fact that lowering the reaction temperature to 0°C had no observable impact on the reaction rate or the isolated yield of **4a** (entry 5, Table 1). It should be emphasized that the absence of catalytic system **1** (entry 6) did not result in any detectable formation of the desired product **4a** as observed by ^{1}H NMR spectroscopy. The catalytic system's individual components (entries 7 and 8) also showed no activity with respect to the investigated transformation. Lastly, as there is a growing concern that the presence of hidden Brønsted acids might interfere or completely be responsible for the observed product formations,[10-12] we also examined the target reaction in the presence of a soluble source of triflic acid (HOTf), generated by mixing ^{t}BuCl (^{t}Bu = *tert*-butyl) and AgOTf (entry 9), and by addition of 2,6-^{t}Bu$_2$-pyridine in the reaction mixture containing **1** (entry 10).[12e] Triflic acid was not an adequate catalyst for the investigated reaction while the presence of a bulky base had no influence on the reaction rate or the isolated yield of **4a**. These control experiments are consistent with system **1** acting as a Lewis acid and not a source of a Brønsted acid.



Dip = 2,6-^{i}Pr$_2$-C$_6$H$_3$
Tf = O$_2$SCF$_3$
Ar^{Cl} = 3,5-Cl$_2$-C$_6$H$_3$

Figure 1. General structure for complex **1**.

Table 1. Michael addition of N,N-dimethylanaline (2a)



2a **3a** **4a**

and methyl vinyl ketone (3a).[a]

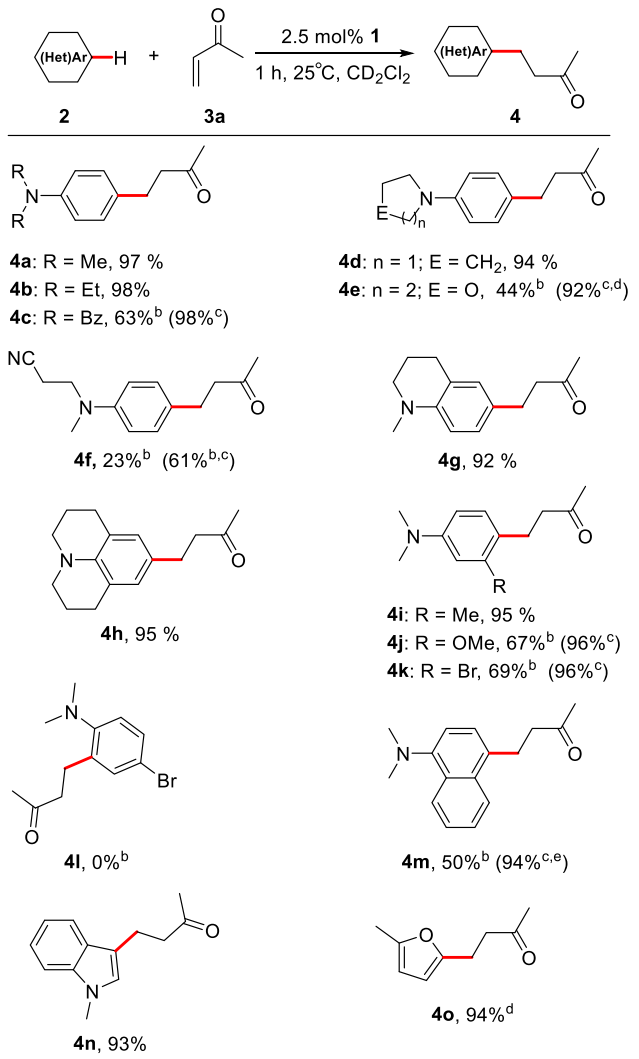
#	Catalyst	Catalyst loading (%)	**2a**:**3a**	temp (°C)	yield (%)[b]
1	**1**	2.5	1:1	25	87
2	**1**	2.5	1:2	25	43
3	**1**	2.5	2:1	25	> 99
4	**1**	1.5	2:1	25	57
5	**1**	2.5	2:1	0	> 99
6	None	-	2:1	25	0
7	^{Dip}LAl(OTf)$_2$	2.5	2:1	25	0
8	Na[BAr$^{Cl}_4$]	2.5	2:1	25	0
9	^{t}BuCl/AgOTf	1	2:1	25	0
10[c]	**1**	2.5	2:1	25	> 99

[a]Standard reaction conditions: **2a** (1.0-2.0 mmol), **3a** (1.0-2.0 mmol), cat., CD_2Cl_2, 0 or 25°C for 1h, unless otherwise noted. [b]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as standard. [c]In the presence of 2,6-^{t}Bu$_2$-pyridine (0.025 mmol i.e. 1:1 mol equiv with respect to **1**).

Having optimized the reaction conditions, we aimed to expand the substrate scope using a diverse range of electron rich aromatic and heteroaromatic reactants (Scheme 2). Unsurprisingly, apart from 4-bromo-N,N-dimethylaniline (**4l**),[9] all other target products (**4a**-**4o**) were obtained in moderate to excellent yields. The use of N,N-diethylaniline (**2b**), N,N-dibenzylaniline (**2c**) and their cyclic analogue (**2d**) generated the corresponding products (**4b**-**4d**) in excellent yields. The formation of morpholine- and cyano-containing products (**4e** and **4f**) were sluggish with the established reaction conditions but the yields (92 and 61%, respectively) were dramatically improved with the use of 5 mol% of **1** and after allowing the reaction to proceed for 12 and 24 h, respectively (Scheme 2)**.** It should be noted that the yield of 61% for the formation of **4f** was still twice as high as the value of 30% reported by Werner *et al.* for the same transformation even though this particular transformation was performed at room temperature instead of 80°C required when the borane-containing system was used.[9] Similarly, excellent isolated yields of 92 and 95%, respectively, were obtained for **4g** and **4h** representing a dramatic improvement over the yields of 39 and 57%, respectively, observed when these particular reactions were catalyzed by B(C$_6$F$_5$)$_3$ at 80 and 130°C, respectively.[9]

Substitution at a *meta* position of N,N-dimethylaniline (**2i**-**2k**) did not prevent the formation of the target products but the isolated yields for **4j** and **4k** were moderate (67 and 69%, respectively) even after the reaction was allowed to run for 24 h (Scheme 2). However, excellent product yields for **4j** (96%) and **4k** (96%) were generated once the catalyst loading was increased to 5 mol%. It is also noteworthy that only the desired product was obtained when 3-methoxy-N,N-dimethylaniline (**2j**) was used as Michael donor which was not the case with the B(C$_6$F$_5$)$_3$ catalyzed reaction that yielded a mixture of two products.[7] The use of the borane similarly generated two products when N-methylindole (**2n**) was reacted with **3a**,[9]

Scheme 2. Substrate scope of electron-rich aromatic and heteroaromatic compounds 2 with methyl vinyl ketone (3a).[a]



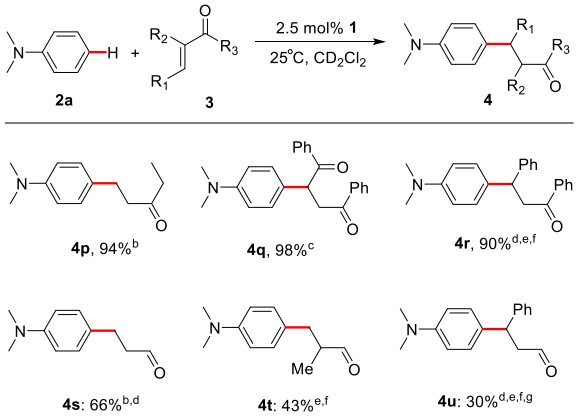
[a]Standard reaction conditions: **2** (2.0 mmol), **3a** (1.0 mmol), **1** (0.025 mmol), CD_2Cl_2 (1.5 mL), 25°C for 1h, unless otherwise noted. Isolated yields are reported. [b]24 h. [c]5 mol% (0.050 mmol) of **1**. [d]12 h. [e]2 h.

while our catalytic system exhibited perfect selectivity control producing only **4n** in excellent yields (93%). Extensive (24 h) heating (80°C) might have been the main cause for the selectivity issues with these borane catalyzed reactions as the same reaction catalyzed by **1** were completed at room temperature within 1h.

Furthermore, increasing the catalyst loading to 5 mol% and extending the reaction time to 2h was needed to generate **4m** in excellent yields (94%). Lastly, reaction time of 12 h was required to obtain excellent product yields (94%) between 2-methylfuran (**2o**) and **3a.** It should be emphasized that all reactions summarized in Scheme 2 that generated excellent reaction yields (> 90%) exhibited complete conversion (> 99%) of **3a** to only the desired products. Therefore, our catalytic system **1** showed superior overall activity in comparison to gold- and borane-based catalysts as it generated higher product yields under perfect selectivity control while, in most cases, requiring much shorter reaction time (1 vs 24 h) under ambient reaction conditions as well as using 50% less of the catalyst loading.[8,9]

Our next aim was to investigate the scope of the Michael acceptor and the main results are summarized in Scheme 3. Ethyl vinyl ketone (**3b**) and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**3c**) were quite adequate substrates when reacted with N,N-dimethylanaline producing excellent isolated yields of **4p** (94%) and **4q** (98%), respectively, under standard reaction conditions. Even though it required a larger excess of the aniline (4 equiv with respect to the dienophile), prolonged reaction times (24 h) as well as 5 mol% of **1,** the reaction involving chalcone (**3d**) resulted in an excellent isolated yield of **4r** (90%) at ambient temperature, which was significantly better than the product yield of 62% obtained by a gold-based catalytic system at 135°C.[8] It should be also mentioned that Werner *et al.* did not report the use of **3d** in this particular transformation. Furthermore, a few aldehydes were also successfully converted to their respective products **4s**-**4u**, albeit in moderate yields (30-66%), but the formation of the last product required the reaction mixture to be heated to 60°C. It is noteworthy that in the reaction mixture involving acrolein and methacrolein (yielding **4s** and **4t**, respectively) significant amounts of unidentified side-products were detected, even after the reaction temperature was lowered to 0°C. This observation might suggest that our system is not as compatible with α,β-unsaturated aldehydes as it is with the ketone analogues because, as indicated, there were no observable side products when **3a**-**3d** were used as Michael acceptors.

Scheme 3. Substrate scope of various Michael acceptors.[a]



[a]Reaction conditions: **2a** (2.0 mmol), **3** (1.0 mmol), **1** (0.025 mmol), CH_2Cl_2 (1.0 mL) at 25°C unless otherwise noted. [b]1h. [c]12h. [d]**2a** (4.0 mmol). [e]5 mol% (0.050 mmol) of **1**. [f]24 h. [g]60°C.

In conclusion, $Na[BAr^{Cl}{}_4]$-activated β-diketiminate-supported aluminum bistriflate complex **1** showed exceptional activity regarding Michael addition between a wide range of electron-rich aromatic/heteroaromatic substrates and several dienophiles. In a vast majority of cases the reaction conditions, such as catalyst loadings, reaction time and/or temperature, were significantly favorable when **1** was used in comparison to the use of the gold- and borane-based catalysts.[8,9] Also, for a vast majority of explored Michael additions considerably better isolated product yields were generated with **1** than with the competitive catalytic systems. Lastly, a perfect selectivity control was achieved using **1** for the preparation of **4j** and **4n** (i.e. only the desired products were obtained), which was not the case with the use of $B(C_6F_5)_3$ that yielded a mixture of two products.[9]

EXPERIMENTAL SECTION.

General Considerations: All manipulations were carried out using standard Schlenk techniques and a dry-box. $CDCl_3$ and CD_2Cl_2 were distilled over CaH_2. Catalytic system **1** has been prepared and used according to a published report.[10] All other chemicals were purchased from commercial sources and used without further purification. NMR spectra were received using Bruker AV 300 or JEOL ECA400 SL spectrometers. Mass spectrometry was performed by Waters Q-Tof Premier Micromass instrument, using the electrospray ionization (ESI) mode.

General Procedures - Coupling reaction of aromatic and hetro-aromatic compounds with α, β-unsaturated carbonyl-containing compounds: **1** (formed by mixing its components $^{Dip}La(OTf)_2$ (19 mg, 0.025 mmol, 2.5 mol%) and $NaBAr^{Cl}{}_4$ (16 mg, 0.025 mmol, 2.5 mol%) was dissolved dissolved in 1.5 mL CD_2Cl_2 in a J. Young NMR tube. Subsequently 1 equiv of the α,β-unsaturated carbonyl-containing compounds (1.0 mmol) and 2 equiv of the aromatic or hetro-aromatic compounds (2.0 mmol) were added. The reaction mixture was left for the time indicated in Table 1 and Scheme 2 - 3 in the main text. After reaction completion, the corresponding products were purified by flash column chromatography on silica gel using hexane/ethyl acetate mixtures. The formation of **4a** and **4n** was also achieved by reacting 1.0g (8.2 mmol) of **2a** and 1.07 g (8.2 mmol) of **2n**, respectively, with 0.29g (4.1 mmol) of **3a** in the presence of 78 mg (0.10 mmol) of $^{Dip}La(OTf)_2$ and 66 mg (0.10 mmol) of $NaBAr^{Cl}{}_4$ in about 10 ml of CH_2Cl_2 for 1h at room temperature. These products were also isolated by the established procedure.

Characterization of the synthesized compounds:

4-(4-(dimethylamino)phenyl)butan-2-one (**4a**): 185 mg, 97% (for the NMR scale reaction) and 760 mg, 97% (for the gram scale reaction). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 2.91 (s, 6H), 2.88 - 2.77 (m, 2H), 2.76 - 2.65 (m, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 149.2, 129.0, 128.9, 113.2, 45.7, 41.0, 30.2, 28.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{18}NO$ 192.1388; Found 192.1382.

4-(4-(diethylamino)phenyl)butan-2-one (**4b**): 215 mg, 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J* = 6.8 Hz, 2H), 6.64 (d, *J* = 6.8 Hz, 2H), 3.35 (q, *J* = 5.6 Hz, 4H), 2.81 - 2.77 (m, 2H), 2.76 - 2.65 (m, 2H), 2.14(s, 3H), 1.16 (t, *J* = 5.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 146.3, 129.0, 127.6, 112.2, 45.7, 44.4, 30.1, 28.8, 12.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{22}NO$ 220.1701; Found 220.1721.

4-(4-(dibenzylamino)phenyl)butan-2-one (**4c**): 336 mg, 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 - 7.23 (m, 10H), 6.99 (m, 2H), 6.67 (m, 2H), 4.62 (s, 4H), 2.91 (s, 6H), 2.80 - 2.76 (m, 2H), 2.75 - 2.65 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 147.7, 138.1, 129.0, 128.9, 128.7, 126.9, 126.7, 112.7, 54.4, 45.6, 30.1, 28.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}NO$ 344.2014; Found 344.2012.

4-(4-(pyrrolidin-1-yl)phenyl)butan-2-one (**4d**): 204 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 6.51 Hz, 2H), 6.51 (d, *J* = 6.51 Hz, 2H), 3.39 - 3.23 (m, 4H), 2.80 - 2.78 (m, 2H), 2.72 - 2.70 (m, 2H), 2.13 (s, 3H), 2.00 - 1.97 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 146.7, 129.0, 127.5, 111.8, 47.8, 45.9, 30.2, 29.0, 25.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{21}NO$ 218.1545; Found 218.1548.

4-(4-morpholinophenyl)butan-2-one (**4e**): 214 mg, 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 - 7.08 (m, 2H), 6.85 - 6.83 (m, 2H), 3.83 - 3.86 (m, 4H), 3.12 - 3.10 (m, 4H), 2.84 - 2.80 (m, 2H), 2.73 - 2.69 (m, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 149.7, 132.6, 129.0, 116.0, 67.0, 49.7, 45.4, 30.2, 28.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO_2$ 234.1494; Found $C_{14}H_{20}NO_2$ 234.1502.

3-(methyl(4-(3-oxobutyl)phenyl)amino)propanenitrile (**4f**): 140 mg, 61%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 4.8 Hz, 2H), 6.85 (d, *J* = 4.8 Hz, 2H), 3.69(t, *J* = 5.52 Hz, 2H), 2.98 (s, 3H), 2.82 - 2.80 (m, 2H), 2.79 - 2.68 (m, 2H), 2.56 (t, *J* = 5.52 Hz, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 146.1, 130.2, 129.4, 118.6, 113.0, 49.2, 45.5, 38.8, 30.1, 28.8, 15.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{19}N_2O$ 231.1497; Found 231.1495.

4-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)butan-2-one (**4g**): 200 mg, 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, *J* = 6.2 Hz, 1H), 6.78 (m, 1H), 6.53 (d, *J* = 6.2 Hz, 1H), 3.19 - 3.16 (m, 2H), 2.85 (s, 3H), 2.75 - 2.70 (m, 6H), 2.13 (s, 3H), 1.98-1.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 145.3, 128.9, 128.5, 126.7, 123.1, 111.3, 51.4, 45.8. 39.3, 30.1, 28.9, 27.8, 22.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO$ 218.1545; Found 218.1544.

4-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)butan-2-one (**4h**): 231 mg, 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (s, 2H), 3.11 - 3.07 (m, 4H), 2.75 - 2.70 (m, 8H), 2.15 (s, 3H), 2.00 - 1.92 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 141.3, 128.1, 126.7, 121.8, 50.1, 45.8, 30.0, 28.9, 27.5, 22.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{22}NO$ 244.1701; Found 244.1699.

4-(4-(dimethylamino)-2-methylphenyl)butan-2-one (**4i**): 195 mg, 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 - 6.97 (m, 1H), 6.56 - 6.53 (m, 2H), 2.90 (s, 6H), 2.80 - 2.77 (m, 2H), 2.68 - 2.66 (m, 2H), 2.28 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 149.4, 136.4, 129.3, 127.3, 114.9, 110.8, 44.5, 40.8, 30.0, 26.3, 19.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{20}NO$ 206.1545; Found 206.1548.

4-(4-(dimethylamino)-2-methoxyphenyl)butan-2-one (**4j**): 222 mg, 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 - 6.95 (m, 1H), 6.26 - 6.24 (m, 2H), 3.82 (s, 3H), 2.92 (s, 6H), 2.70 - 2.75 (m, 2H), 2.73 - 2.67 (m, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 158.1, 150.8, 130.2, 117.5, 104.8, 96.5, 55.0, 44.3, 40.9, 29.9, 24.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{20}NO_2$ 222.1494; Found 222.1499.

4-(2-bromo-4-(dimethylamino)phenyl)butan-2-one (**4k**): 259 mg, 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.7 Hz, 1H), 2.92 (m, 8H), 2.73 (m, 2H), 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 150.1, 130.6, 127.3, 124.9, 116.3, 111.9, 44.0, 40.5, 30.0, 29.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{17}NOBr$ 270.0494; Found 270.0506.

4-(4-(dimethylamino)naphthalen-1-yl)butan-2-one (**4m**): 227 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 - 8.29 (m, 1H), 7.96 - 7.94 (m, 1H), 7.51 -7.49 (m, 2H), 7.25 - 7.23 (m, 1H), 7.01 (d, *J* = 5.9 Hz, 1H), 3.31 - 3.27 (m, 2H), 2.90 m,8H), 2.16 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 149.9, 132.7, 131.5, 129.3, 125.9, 125.0, 124.9, 123.9, 113.8, 45.4, 44.6, 30.1, 26.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}NO$ 242.1545; Found 242.1544.

4-(1-methyl-1H-indol-3-yl)butan-2-one (**4n**): 187 mg, 93% (for the NMR scale reaction) and 780 mg, 95% (for the gram scale reaction). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 - 7.62 (m, 1H), 7.33-7.21 (m, 2H), 7.17 - 7.16 (m, 1H), 6.88 (s, 1H), 3.76 (s, 3H), 3.10 - 3.07 (m, 2H), 2.89 - 2.86 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 137.0, 127.5, 126.4, 121.6, 118.7, 118.7, 113.6, 109.2, 44.3, 32.5, 30.0, 19.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{16}NO$ 202.1232; Found 202.1225.

4-(5-methylfuran-2-yl)butan-2-one (**4o**):143 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 - 5.82 (m, 2H), 2.85 - 2.83 (m, 2H), 2.77 - 2.75 (m, 2H), 2.23 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 152.7, 150.6, 105.9, 105.8, 42.0, 29.9, 22.3, 13.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{13}O_2$ 153.0916; Found 153.0916.

1-(4-(dimethylamino)phenyl)pentan-3-one (**4p**): 193 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 6.5 Hz, 2H), 6.70 (d, *J* = 6.5 Hz, 2H), 2.91 (s, 6H), 2.81 - 2.77 (m, 2H), 2.70 - 2.65 (m, 2H), 2.41 (q, *J* = 5.5 Hz, 2H), 2.41 (t, *J* = 5.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 149.2, 129.2, 128.9, 113.1, 44.4, 40.9, 36.2, 29.0, 7.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{20}NO$ 206.1545; Found 206.1550.

2-(4-(dimethylamino)phenyl)-1,4-diphenylbutane-1,4-dione (**4q**): 350 mg, 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 - 7.98 (m, 4H), 7.57 - 7.39 (m, 6H), 7.32 - 7.19 (m, 2H), 6.68 - 6.64 (m, 2H), 5.25 - 5.20 (m, 1H), 4.23 (dd, *J* = 18.0, 9.9 Hz, 1H), 3.30 (dd, *J* = 18.0, 3.6Hz, 1H), 2.90 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 198.5, 149.7, 136.7, 136.6, 133.1, 132.6, 128.9, 128.5, 128.4, 128.1, 125.8, 113.0, 47.7, 43.8, 40.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}NO_2$ 358.1807; Found 358.1806.

3-(4-(dimethylamino)phenyl)-1,3-diphenylpropan-1-one (**4r**): 296 mg, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4.2 Hz, 2H), 7.53 - 7.52 (m, 1H), 7.45 - 7.41 (m, 2H), 7.26 - 7.24 (m, 4H), 7.15 - 7.13 (m, 3H), 6.67 (d, *J* = 5.1 Hz, 2H), 4.75 (t, *J* = 4.2 Hz, 1H), 3.71 (d, *J* = 4.2 Hz, 2H), 2.89 (s, 6H). ^{13}C NMR (75 MHz, CDCl3) δ 198.5, 149.2, 144.9, 137.2, 132.9, 132.2, 128.5, 128.4, 128.1, 127.7, 126.1, 112.8, 45.1, 45.0, 40.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{24}NO$ 330.1858; Found 330.1847.

3-(4-(dimethylamino)phenyl)propanal (**4s**): 117 mg, 66%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.5 Hz, 1H), 7.10 - 7.06 (m, 2H), 6.71 - 6.69 (m, 2H), 2.92 (s, 6H), 2.92 - 2.85 (m, 2H), 2.75 - 2.69 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 149.4, 128.9, 128.2, 113.1, 45.7, 40.8, 27.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{16}NO$178.1232; Found 178.1224.

3-(4-(dimethylamino)phenyl)-2-methylpropanal (**4t**): 82 mg, 43%. ^{1}H NMR (300 MHz, CDCl3) δ 9.22 (s, 1H), 7.05 - 7.02 (m, 2H), 6.71 - 6.67 (m, 2H), 3.01 - 2.92 (m, 7H), 2.65 - 2.50 (m, 2H), 1.08 - 1.06 (m, 2H). 13C NMR (75 MHz, CDCl3) δ 204.9, 149.3, 129.6, 126.5, 112.8, 48.3, 40.7, 35.8, 13.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{18}NO$ 192.1388; Found 192.1384.

3-(4-(dimethylamino)phenyl)propanal (**4u**): 75 mg, 30%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (m, 1H), 7.30 - 7.23 (m, 5H), 7.10 - 7.08 (m, 2H), 6.68 - 6.61 (m, 2H), 4.59 (t, *J* = 7.8 Hz, 1H), 3.12 - 3.08 (m, 2H), 3.07 - 2.90 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 149.4, 144.0, 131.0, 128.7, 128.4, 127.7, 126.4, 112.8, 49.6, 44.3, 40.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}NO$ 254.1545; Found 254.1546.

ASSOCIATED CONTENT

Supporting Information

Copies of multinuclear NMR spectra. The Supporting Information is available free of charge on the ACS Publications website.

Conflicts of Interest

Authors declare no competing financial interests.

AUTHOR INFORMATION

Corresponding Author

*Email: drasko.vidovic@monash.edu

ACKNOWLEDGMENT

We thank Monash University (DV) and South University of Science and Technology of China (ZL) for the financial support.

REFERENCES

(1) See, for example: Brown, W. H.; Foote, C. S.; Iverson, B. L.; Anslyn, E. V. Carbon-carbon bond formation and synthesis (Ch 24.). In *Organic Chemistry*, 5th edition, Brooks/Cole Cengage Learning, 2009.

(2) (a) Grubbs, R. H. Olefin-metathesis catalysts for the preparation of molecules and materials (Nobel Lecture). *Angew. Chem. Int. Ed.* **2006**, *45*, 3760-3765. (b) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. From noble metal to Nobel Prize: palladium-catalyzed coupling reactions as key methods in organic synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 9047-9050.

(3) (a) Michael, A. Über die Addition von Natriumacetessig- und Natriummalonsaureather zu den Athern ungesättigter Säuren. *J. Prakt. Chem.* **1887**, *35*, 349-356. (b) Tokoroyama, T. Discovery of the Michael Reaction. *Eur. J. Org. Chem.* **2010**, 2009-2016.

(4) See, for example: (a) d'Angelo, J.; Revial, G.; Costa, P. R. R.; Castro, R. N.; Antunes, O. A. C. Asymmetric Michael addition of chiral imines to phenylvinylsulfone: Preparation of key chiral building blocks for the synthesis of Aspidosperma and Hunteria alkaloids. *Tetrahedron: Asymmetry* **1991**, *2*, 199-202. (b) Richardson, S. C. W.; Pattrick, N. G.; Stella Man, Y. K.; Ferruti, P.; Duncan, R. Poly(Amidoamine)s as Potential Nonviral Vectors: Ability to Form Interpolyelectrolyte Complexes and to Mediate Transfection in Vitro. *Biomacromolecules* **2001**, *2*, 1023-1028. (c) Vázquez, E.; Dewitt, D. M.; Hammond, P. T.; Lynn, D. M. Construction of Hydrolytically-Degradable Thin Films via Layer-by-Layer Deposition of Degradable Polyelectrolytes *J. Am. Chem. Soc.* **2002**, *124*, 13992-13993. (d) Akinc, A.; Lynn, D. M.; Anderson, D. G.; Langer, R. Parallel Synthesis and Biophysical Characterization of a Degradable Polymer Library for Gene Delivery *J. Am. Chem. Soc.* **2003**, *125*, 5316-5323. (e) Vernon, B.; Tirelli, N.; Bachi, T.; Haldimann, D.; Hubbell, J. A. Water-borne, *in situ* crosslinked biomaterials from phase-segregated precursors. *J. Biomed. Mater. Res., Part A* **2003**, *64A*, 447-456. (f) Ferruti, P.; Bianchi, S.; Ranucci, E.; Chiellini, F.; Caruso, V. Novel poly(amido-amine)-based hydrogels as scaffolds for tissue engineering. *Macromol. Biosci.* **2005**, 5, 613-622.

(5) See, for example: (a) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. $InCl_3$-Catalysed Conjugate Addition of Indoles with Electron-Deficient Olefins. *Synthesis* **2001**, 2165-2169. (b) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. Sequential One-Pot $InBr_3$-Catalyzed 1,4- then 1,2-Nucleophilic Addition to Enones. *J. Org. Chem.* **2002**, *67*, 3700-3704. (c) Ji, S.-J.; Wang, S.-Y. Ultrasound-accelerated Michael Addition of Indole to α,β-Unsaturated Ketones Catalyzed by Ceric Ammonium Nitrate (CAN). *Synlett* **2003**, 2074-2076. (d) Shi, M.; Cui, S.-C.; Li, Q.-J. Zirconium triflate-catalyzed reactions of indole, 1-methylindole, and pyrrole with α,β-unsaturated ketone. *Tetrahedron* **2004**, *60*, 6679-6684. (e) Zhan, Z.-P.; Yang, R.-F.; Lang, K. Samarium triiodide-catalyzed conjugate addition of indoles with electron-deficient olefins. *Tetrahedron Lett.* **2005**, *46*, 3859-3862. (f) Austn, J. F.; MacMillian, D. W. C. Enantioselective Organocatalytic Indole Alkylations. Design of a New and Highly Effective Chiral Amine for Iminium Catalysis. *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173. (g) Paras, N. A.; MacMillian, D. W. C. New Strategies in Organic Catalysis: The First Enantioselective Organocatalytic Friedel−Crafts Alkylation. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371. (h) Fadeev, A. A.; Uchuskin, M. G.; Trushkov, I. V.; Makarov, A. S. Copper(II) bromide-catalyzed conjugate addition of furans to α,β-unsaturated carbonyl compounds. *Chem. Heterocycl. Compd.* **2017**, *53*, 1286-1293.

(6) See, for example: (a) Halland, N.; Hansen, T.; Jørgensen, K. A. Organocatalytic Asymmetric Michael Reaction of Cyclic 1,3-Dicarbonyl Compounds and α,β-Unsaturated Ketones—A Highly Atom-Economic Catalytic One-Step Formation of Optically Active Warfarin Anticoagulant. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955-4957. (b) Kim, H.; Yen, C.; Preston, P.; Chin, J. Substrate-Directed Stereoselectivity in Vicinal Diamine-Catalyzed Synthesis of Warfarin. *Org. Lett.* **2006**, *8*, 5239-5242. (c) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis *Chem. Rev.* **2007**, *107*, 5416-5470.

(7) Bah, J.; Franzén, J. Carbocations as Lewis Acid Catalysts in Diels–Alder and Michael Addition Reactions. *Chem. Eur. J.* **2014**, *20*, 1066.

(8) (a) Hu, X.; Martin, D.; Melaimi, M.; Bertrand, G. Gold-Catalyzed Hydroarylation of Alkenes with Dialkylanilines. *J. Am. Chem. Soc.* **2014**, *136*, 13594-13597. (b) The exact mechanism for hydroarylation of enones as reported by Bertrand and co-workers (ref. 8a) is not discussed so it is assumed that the gold complex was acting as a Lewis acid to activate various enones.

(9) Li, W.; Werner, T. $B(C_6F_5)_3$-Catalyzed Michael Reactions: Aromatic C–H as Nucleophiles *Org. Lett.* **2017**, *19*, 2568-2571.

(10) Liu, Z.; Lee, J. H. Q.; Ganguly, R.; Vidović, D. A Well-Defined Aluminum-Based Lewis Acid as an Effective Catalyst for Diels–Alder Transformations *Chem. Eur. J.* **2015**, *21*, 11344-11348.

(11) Liu, Z.; Ganguly, R.; Vidović, D. Pursuing the active species in an aluminium-based Lewis acid system for catalytic Diels-Alder cycloadditions. *Dalton Trans.* **2017**, *46*, 753-759.

(12) (a) Dang,T. T.; Boeck,F.; Hintermann, L. Hidden Brønsted Acid Catalysis: Pathways of Accidental or Deliberate Generation of Triflic Acid from Metal Triflates. *J. Org. Chem.* **2011**, *76*, 9353-9361. (b) Tschan, M. J.-L.; Thomas, C. M.; Strub, H.; Carpentier, J.-F. Copper(II) Triflate as a Source of Triflic Acid: Effective, Green Catalysis of Hydroalkoxylation Reactions. *Adv. Synth. Catal.* **2009**, *351*, 2496-2504. (c) Mathia, F.; Szolcsányi, P. Bismuth(III) triflate promoted intramolecular hydroamination of unactivated alkenyl sulfonamides in the preparation of pyrrolidines. *Org. Biomol. Chem.* **2012**, *10*, 2830-2839. (d) Jiang, X.; Pan, Z.; Douglas, C. J. Cyclization of an alkene-bearing cyclopentanone: The role of rhodium and Brønsted acid. *Tetrahedron Lett.* **2015**, *56*, 5324-5327.

Table of Contents Image