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Enantioselective Radical Reactions. Formation of Chiral Quaternary Centers

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Abstract

A novel addition/trapping radical reaction to establish all carbon chiral quaternary centers has been developed.

Keywords

Radical Reactions; Chiral Lewis acid; Quaternary Centers; Conjugate additions; Imides

Construction of all carbon chiral quaternary centers still remains a challenge.¹ Radical chemistry, which was once considered to be an underdeveloped field, has seen tremendous progress in the past two decades, and has emerged as a powerful branch in synthetic organic chemistry.² Radical chemistry is well suited for the formation of quaternary carbon centers.³ Although there are a fair number of reports which demonstrate installation of quaternary centers diastereoselectively, enantioselective methods have only begun to emerge recently.⁴

There are only a few examples that demonstrate enantioselective C-C bond formation leading to quaternary centers using free radical intermediates. One of the earliest examples of quaternary center formation with high enantioselectivity was a report by Hoshino and coworkers wherein the allylation of α -alkyl- α -iodolactone was accomplished by the use of catalytic and stoichiometric amounts of a chiral Lewis acid.⁵ Highly enantioselective atom-transfer cyclization mediated by chiral Lewis acids has been reported by Yang and coworkers. The same group reported an example of enantioselective tandem atom-transfer cyclization. Installation of four stereocenters in a single step was the highlight of this work.⁶ We have been interested in evaluating an enantioselective tandem addition/trapping strategy for the formation of quaternary centers (Scheme 1). The process involves the conjugate addition of a nucleophilic radical to **A** mediated by a chiral Lewis acid. The intermediate radical **B** is then trapped by allylstannane to provide the product **C**. We have previously shown that templates play a crucial role in determining reactivity and selectivity in reactions with α -substituted and α,β -disubstituted acyclic systems.⁷ In prior work we have also established that imides are excellent templates for other enantioselective transformations.⁸ These templates offer handles for tuning reactivity and selectivity. In this study we detail the use of imide templates for establishing chiral quaternary centers using a tandem radical process.

Conjugate addition of isopropyl radical to **1–3** followed by trapping with allyltributyl stannane under previously established reaction conditions from our laboratory was used to carry out preliminary studies.^{9,10} A chiral Lewis acid derived from lanthanide triflates and the pybox ligand **10** was used. Experiments were designed to understand the role of the imide substituent on the efficiency of the reaction as well as the level of enantioselectivity. Results from these experiments are tabulated in table 1. Tandem addition-trapping experiments with **1** and stoichiometric amounts of ytterbium triflate as a Lewis acid gave the addition product in good yield and selectivity (entry 1).¹¹ Lowering the catalytic loading to either 50% (entry 2) or 30%

(entry 3) gave product **4** with lower ee. In an effort to improve efficiency and selectivity, reactions with alternate Lewis acids were investigated next. Of the other Lewis acids investigated, only yttrium triflate gave product **5** with good to modest selectivity (entries 4–6). The effect of the imide substituent on reaction efficiency and selectivity was investigated next. Changing the substituent from tert-butyl (**1**) to isopropyl (**2**) or phenyl (**3**) did not improve the level of selectivity (entries 7–8). These reactions demonstrated that one could establish an all carbon chiral quaternary center in good yield and selectivity if one chooses the appropriate Lewis acid and template.

The next set of experiments was designed to evaluate the role of the chiral Lewis acid by changing the ligand and results from these experiments are tabulated in Table 2. For these experiments we used substrate **1**. Of the different pybox ligands investigated in combination with ytterbium triflate as a Lewis acid (entries 1–5), ligand **10** was still optimal (entry 1). In reaction using ligand **14**, a byproduct arising from ethyl radical addition was also observed (entry 5). Changing the Lewis acid from ytterbium to yttrium triflate in combination with **14** did not lead to any improvement (entry 6). Kanemasa has shown that ligand **15**, the so-called DBFOX ligand, is excellent in many enantioselective transformations.¹² Addition/trapping experiments to **1** using ligand **15** and three different Lewis acids were examined next (entries 7–9). Of these three, only ytterbium triflate showed modest reaction efficiency and selectivity (entry 7). Our laboratory has shown that bisoxazoline ligand **16** derived from amino indanol provides very high levels of selectivity in a variety of enantioselective experiments.¹³ Radical addition/trapping reactions using three different Lewis acids and **16** were investigated (entries 10–12). All the three experiments proved disappointing giving the product **4** in poor yield and selectivity. The above experiments demonstrated that a combination of ytterbium (or yttrium) triflate and ligand **10** is optimal for the addition/trapping experiments with **1**.

The breadth of the radical fragment in addition/trapping experiments to **1** was investigated next using ytterbium and yttrium triflates and ligand **10** as the chiral Lewis acid. These results are presented in Table 3. Reaction with ethyl iodide/tributyl allyl stannane was chemically efficient (entries 1–2). Of the two Lewis acids examined, reaction with yttrium triflate was more chemically efficient (entry 2). However, the enantioselectivities were very low with both Lewis acids. Similar results were obtained when n-butyl radical was used as the reagent (entries 3–4). Isopropyl radical, an acyclic secondary radical, gave much higher levels of enantioselectivity for the addition/trapping product (entries 5–6). The highest level of enantioselectivity for the addition/trapping product was achieved when the bulky tert-butyl radical was used (entry 8). Of the two cyclic radicals examined (entries 9–10), cyclohexyl radical gave good enantioselectivity (entry 10). Overall, a variety of radicals differing in nucleophilicity and steric size participate in addition/trapping experiments to afford products with chiral quaternary centers with varying degrees of selectivity.

In conclusion, we have developed a novel addition/trapping radical reaction to establish all carbon chiral quaternary centers. A variety of radicals can be used in these experiments. Experiments to further improve the level of enantioselectivity to install chiral quaternary centers and to arrive at a model for the observed selectivity are underway. Work is also underway to increase the scope of the radicals and trapping reagents in these experiments.

General procedure for the addition trapping reaction

To a suspension of Lewis acid (0.2 mmol) in 1.5 mL of CH₂Cl₂ was added the chiral ligand (0.2 mmol) and stirred at room temperature for 2 hrs resulting in a clear solution. Substrate (0.2 mmol) in CH₂Cl₂ was added to above chiral Lewis acid and the reaction cooled to –78 °C and stirred for 1 hour. The radical precursor (6 mmol) was added, followed by addition of allyltributyltin (0.62 mL, 2 mmol), Et₃B (1 mL, 1 mmol) and 10 mL of O₂. The reaction was

allowed to reach room temperature over 12 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and silica gel (4g) was added. After removal of the solvent, the silica gel was washed with hexane (30 mL), followed by hexane/ethyl acetate (1:1, 30 mL). The hexane/ethyl acetate solution was concentrated to give the crude, which was purified by flash chromatography to give pure product. The enantiomeric purity was determined by chiral GC. Conditions for GC analyses: Supelco β -Dex 225 column, 30 m in length, 0.25 mm inner diameter, isotherm temperature program, and He as carrier gas (1 mL/min)

2-Isobutyl-2-methyl-pent-4-enoic acid (2,2-dimethyl-propionyl)-amide (5)

Mp 67-68°C; Rf 0.3 (hexane: ethyl acetate = 4:1); 70% ee (1 mL/min, T = 80 °C, R_{t1} = 42 min, R_{t2} = 43.6 min); IR (film) 1758, 1478, 1453 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.25 (br.s, 1H), 5.76 (m, 1H), 5.15-5.10 (m, 2H), 2.39 (dd, J = 14.0, 7.0 Hz, 1H), 2.18 (dd, J = 14.5, 7.5 Hz, 1H), 1.72 (m, 1H), 1.62 (dd, J = 14.5, 7.0 Hz, 1H), 1.41 (dd, J = 14.5, 5.5 Hz, 1H), 1.24 (s, 9H), 1.21 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.0, 174.3, 133.1, 119.3, 48.5, 47.5, 44.7, 40.5, 27.1, 24.7, 24.5, 23.5, 21.3; HRMS Calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_2\text{Na}^+$: 276.1933, Found: 276.1932.

2-(2,2-Dimethyl-propyl)-2-methyl-pent-4-enoic acid (2, 2-dimethyl-propionyl)-amide (6)

Mp 73-74 °C; Rf 0.33 (hexane: ethyl acetate = 4:1); 73% ee (1 mL/min, T = 75 °C, R_{t1} = 91.3 min, R_{t2} = 93.1 min); IR (film) 3054, 1758, 1478 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.29 (br.s, 1H), 5.73 (m, 1H), 5.15-5.08 (m, 2H), 2.39 (dd, J = 14.0, 6.5 Hz, 1H), 2.13 (dd, J = 13.5, 8.0 Hz, 1H), 1.87 (d, J = 14.5 Hz, 1H), 1.45 (d, J = 15.0 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.9, 174.3, 132.8, 119.5, 52.7, 47.9, 47.1, 40.5, 31.7, 31.2, 27.1, 21.7; HRMS Calcd for $\text{C}_{16}\text{H}_{29}\text{NO}_2\text{Na}^+$: 290.2090, Found: 290.2080.

2-Cyclohexylmethyl-2-methyl-pent-4-enoic acid (2,2-dimethyl-propionyl)-amide (12)

Mp 90-91°C; Rf 0.33 (hexane: ethyl acetate = 4:1); 64% ee (1.6 mL/min, T = 123 °C, R_{t1} = 46.3 min, R_{t2} = 46.9 min); IR (film) 3054, 1758, 1479 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.24 (br s, 1H), 5.75 (m, 1H), 5.16-5.08 (m, 2H), 2.38 (dd, J = 14.0, 6.8 Hz, 1H), 2.18 (ddt, J_d = 14.0, 8.0 Hz, J_t = 1.2 Hz, 1H), 1.69-1.56 (m, 7H), 1.40-1.35 (m, 2H), 1.25 (s, 9H), 1.20 (s, 3H), 1.18-1.06 (m, 2H), 0.99-0.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.0, 174.3, 133.1, 119.2, 47.38, 47.35, 44.7, 35.1, 34.3, 34.2, 27.1, 26.31, 26.27, 26.1, 21.5; HRMS Calcd for $\text{C}_{18}\text{H}_{31}\text{NO}_2\text{Na}^+$: 316.2246, Found: 316.2256.

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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Table 1
Optimization of Chiral Lewis Acids for Addition/trapping Experiments.

Entry	Sub.	Lewis Acid (loading)	Yield, % ^a	Ee, % ^b
1	1	Yb(OTf) ₃ (100 mol%)	64	70
2	1	Yb(OTf) ₃ (50 mol%)	62	63
3	1	Yb(OTf) ₃ (30 mol%)	59	52
4	1	Y(OTf) ₃ (100 mol%)	72	57
5	1	Sm(OTf) ₃ (100 mol%)	52	12
6	1	Sc(OTf) ₃ (100 mol%)	37	25
7	2	Yb(OTf) ₃ (100 mol%)	46	10
8	3	Yb(OTf) ₃ (100 mol%)	42	9

^aFor typical reaction conditions see footnote.

^bIsolated yield after column chromatography.

^cDetermined by chiral GC.

Table 2
Evaluation of Different Chiral Lewis Acids in Addition/trapping Experiments

Entry	Lewis Acid ^a	Subs	Yield, % ^b	Ee, % ^c
1	Yb(OTf) ₃	10	64	70
2	Yb(OTf) ₃	11	63	19
3	Yb(OTf) ₃	12	51	1
4	Yb(OTf) ₃	13	34	1
5	Yb(OTf) ₃	14	55 (17) ^d	19
6	Y(OTf) ₃	14	54 (17) ^d	27
7	Yb(OTf) ₃	15	50	39
8	Mg(ClO ₄) ₂	15	84	8
9	Ni(ClO ₄) ₂	15	35	8
10	MgI ₂	16	22 (16) ^d	41
11	Mg(ClO ₄) ₂	16	32 (14) ^d	10
12	Ni(ClO ₄) ₂	16	36 (4) ^d	41

^a 100 mol% of the catalyst was used.

^b Yields are for chromatographically pure and isolated product.

^c Chiral GC analysis.

^d Yield in parenthesis is for the ethyl addition product **7**.

Table 3Evaluation of different radical precursors in addition/trapping experiments ^a

Entry	Radical	Lewis Acid	Yield, % ^b	ee, % ^c
1	Et (7)	Yb(OTf) ₃	55	15
2	Et (7)	Y(OTf) ₃	64	22
3	n-Bu (17)	Yb(OTf) ₃	38	18
4	n-Bu (17)	Y(OTf) ₃	55	20
5	i-Pr (4)	Yb(OTf) ₃	64	70
6	i-Pr (4)	Y(OTf) ₃	72	57
7	t-Bu (18)	Yb(OTf) ₃	46	64
8	t-Bu (18)	Y(OTf) ₃	64	73
9	Cyclopentyl (19)	Y(OTf) ₃	58	24
10	Cyclohexyl (20)	Y(OTf) ₃	63	64

^aFor typical reaction conditions see footnote.^bIsolated yield after column chromatography.^cDetermined by chiral GC.