DECARBOXYLATIVE CROSS-COUPLING AND APPLICATIONS THEREOF

STATEMENT OF GOVERNMENT RIGHTS

This invention was made with government support under Grant No. GM103558 and GM100985 awarded by the National Institutes of Health (NIGMS). The government has certain rights in the invention.

RELATED APPLICATION DATA

The present application claims priority pursuant to 35 U.S.C. § 119(e) to United States Provisional Patent Application Serial Number 61/975,667 filed April 4, 2014 and United States Provisional Patent Application Serial Number 62/020,165 filed July 2, 2014, each of which is incorporated herein by reference in its entirety.

FIELD

The present invention relates to decarboxylative cross-coupling and, in particular, to decarboxylative cross-coupling via use of photoredox and transition metal catalysts.

BACKGROUND

Molecular synthesis plays a critical role in a significant number of industries including the pharmaceutical, biological, biochemical and materials industries. Substantial resources and time are invested in the construction and development of molecular libraries for the characterization and identification of molecular species having promise for a particular application. Such libraries, however, are often rendered incomplete by the inability to efficiently synthesize a wide variety of chemical species. Many classes of chemical species, for example, require expensive reagents, complex and time consuming synthetic pathways and/or result in the production of hazardous by-products.

SUMMARY

~~In one aspect, s~~Synthetic methods are described herein operable to efficiently produce a wide variety of molecular species. For example, methods described herein enable the production of numerous molecular species through decarboxylative cross-coupling via use of photoredox and transition metal catalysts.

In one aspect, there is provided a method of cross-coupling comprising: providing a reaction mixture comprising a coupling partner and a substrate having a carboxyl group; and cross-coupling the substrate and the coupling partner via a mechanism including formation of a substrate radical via a single electron transfer process followed by decarboxylation to a secondary substrate radical, wherein the secondary substrate radical is collected by an intermediate transition metal complex of the reaction mixture for bond formation with the coupling partner. A method described herein, in some ~~embodiments~~examples, comprises

providing a reaction mixture including a photoredox catalyst, a transition metal catalyst, a coupling partner and a substrate having a carboxyl group. The reaction mixture is irradiated with a radiation source resulting in cross-coupling of the substrate and coupling partner via a mechanism including decarboxylation, wherein the coupling partner is selected from the group consisting of a substituted aromatic compound and a substituted aliphatic compound. In some ~~embodiments~~examples, the substrate of the reaction mixture is an aliphatic carboxylic acid or a keto acid. Additionally, in some ~~embodiments~~examples, the reaction mixture further comprises a ligand component.

In another ~~aspect~~example, acylation methods are described herein employing decarboxylative pathways. For example, a method of acylation comprises providing a reaction mixture including an acylating agent, a photoredox catalyst, a transition metal catalyst and a substrate having a carboxyl group. The reaction mixture is irradiated with a radiation source resulting in acylation of the substrate via a mechanism including decarboxylation. In some ~~embodiments~~examples, substrate of the reaction mixture is aliphatic carboxylic acid, and the acylating agent is acyl halide. Moreover, the reaction mixture, in some ~~embodiments~~examples, further comprises a ligand component.

In a further ~~aspect~~example, methods of fluorination via decarboxylative pathways are described herein. A method of fluorination comprises providing a reaction mixture comprising a fluorination reagent, a photoredox catalyst and an aliphatic carboxylic acid. The reaction mixture is irradiated with a radiation source yielding fluoroalkane via a mechanism including decarboxylation of the aliphatic carboxylic acid and fluorination by the fluorinating reagent. In some ~~embodiments~~examples, the reaction mixture further comprises base.

These and other embodiments are described further in the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates various ligand species of the ligand component of a decarboxylative cross-coupling reaction mixture according to some embodiments described herein.

Figure 2 illustrates a mechanistic pathway of decarboxylative arylation according to one example of a method described herein.

Figure 3 illustrates a mechanistic pathway of decarboxylative arylation according to one example of a method described herein.

Figure 4 illustrates a mechanistic pathway of decarboxylative fluorination according to one example of a method described herein.

CLAIMS

1. A method of cross-coupling comprising:

providing a reaction mixture including a photoredox catalyst, a transition metal catalyst, a coupling partner and a substrate having a carboxyl group; and

irradiating the reaction mixture with a radiation source resulting in cross-coupling of the substrate and coupling partner via a mechanism including decarboxylation, wherein the coupling partner is selected from the group consisting of a substituted aromatic compound and substituted aliphatic compound.

2. The method of claim 1, wherein the substrate is an aliphatic carboxylic acid.

3. The method of claim 2, wherein the aliphatic carboxylic acid is an amino acid.

4. The method of claim 2, wherein the aliphatic carboxylic acid is a fatty acid.

5. The method of claim 2, wherein the aliphatic carboxylic acid is of formula R^1-CO_2H, wherein R^1 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -alkynyl, -alkyl-aryl, -alkyl-heteroaryl, -alkyl-alkoxy, -alkenyl-aryl, -alkenyl-heteroaryl, -cycloalkyl-aryl, -cycloalkyl-heteroaryl, -cycloalkenyl-aryl, -heterocycloalkenyl-aryl, and -alkenyl-alkoxy.

6. The method of claim 1, wherein the substrate is a keto acid.

7. The method of claim 6, wherein the keto acid is an aliphatic keto acid.

8. The method of claim 6, wherein the keto acid is an aryl keto acid or heteroaryl keto acid.

9. The method of claim 6, wherein the keto acid is of the formula R^2-C(O)-CO_2H, wherein R^2 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -alkynyl,

-aryl, -heteroaryl, -alkyl-aryl, -alkyl-heteroaryl, -alkyl-alkoxy, -alkenyl-aryl, -alkenyl-heteroaryl and -alkenyl-alkoxy.

10. The method of claim 1, wherein the cross-coupling is a sp^3–sp^2 cross-coupling.

11. The method of claim 1, wherein the cross-coupling is a sp^3–sp^3 cross-coupling.

12. The method of claim 1, wherein the substituted aromatic compound is a substituted aryl or substituted heteroaryl.

13. The method of claim 12, wherein the substituted aryl or substituted heteroaryl comprises a halide leaving group.

14. The method of claim 1, wherein the substituted aliphatic compound comprises one or more points of unsaturation.

15. The method of claim 14, wherein the substituted aliphatic compound is an allyl carbonate.

16. The method of claim 1, wherein the substituted aliphatic compound is saturated.

17. The method of claim 16, wherein the substituted aliphatic compound comprises a halide leaving group.

18. The method of claim 17, wherein the substituted aliphatic compound is of the formula R^3-X, wherein X is the halide leaving group and R^3 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -alkynyl, -alkyl-aryl, -alkyl-heteroaryl, -alkyl-alkoxy, -alkenyl-aryl, -alkenyl-heteroaryl and -alkenyl-alkoxy.

19. The method of claim 1, wherein the photoredox catalyst is an iridium complex or ruthenium complex.

20. The method of claim 19, wherein the photoredox catalyst is a heteroleptic iridium complex.

21. The method of claim 20, wherein the heteroleptic iridium complex is selected from the group consisting of $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$, $Ir(ppy)_2(dtbbpy)^+$ and $Ir[dF(5\text{-}Me)ppy]_2(tetraMePhen)^+$.

22. The method of claim 19, wherein the photoredox catalyst is present in the reaction mixture in an amount of 0.1 to 5 mol.%.

23. The method of claim 1, wherein the transition metal catalyst is selected from the group consisting of nickel catalyst, copper catalyst and palladium catalyst.

24. The method of claim 23, wherein the transition metal catalyst is present in the reaction mixture in an amount of 1 to 15 mol.%.

25. The method of claim 23, wherein the transition metal catalyst is selected from the group consisting of $NiCl_2$·dimethoxyethane and $NiCl_2$·dtbbpy.

26. The method of claim 1, wherein the reaction mixture further comprises a ligand component.

27. The method of claim 26, wherein the ligand component comprises one or more pyridine moieties.

28. The method of claim 26, wherein the ligand component is present in the reaction mixture in an amount of 5 to 50 mol%.

29. A method of acylation comprising:

providing a reaction mixture including an acylating agent, a photoredox catalyst, a transition metal catalyst and a substrate having a carboxyl group; and

irradiating the reaction mixture with a radiation source resulting in acylation of the substrate via a mechanism inlcuding decarboxylation.

30. The method of claim 29, wherein the substrate is an aliphatic carboxylic acid.

31. The method of claim 30, wherein the aliphatic carboxylic acid is an amino acid.

32. The method of claim 30, wherein the aliphatic carboxylic acid is an α-oxy acid.

33. The method of claim 29, wherein the acylating agent is an acyl halide.

34. The method of claim 33, wherein the acylating agent is of the formula X-C(O)R^4, wherein X is a halide leaving group and R^4 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -aryl, -heteroaryl, -alkyl-aryl, -alkyl-heteroaryl, -cycloalkyl-aryl, -cycloalkyl-heteroaryl, -aryl-alkyl and -aryl-alkoxy.

35. The method of claim 29, wherein the photoredox catalyst is a heteroleptic iridium complex.

36. The method of claim 35, wherein the heteroleptic iridium complex is selected from the group consisting of $Ir(4',6'\text{-dF-5-}CF_3\text{-ppy})_2(4,4'\text{-dtbbpy})^+$ and $Ir(4',6'\text{-dF-5-OMe-ppy})_2(4,4'\text{-dtbbpy})^+$.

37. The method of claim 29, wherein the transition metal catalyst is selected from the group consisting of nickel catalyst, copper catalyst and palladium catalyst.

38. A method of fluorination comprising:

providing a reaction mixture comprising a fluorination reagent, a photoredox catalyst and an aliphatic carboxylic acid; and

irradiating the reaction mixture with a radiation source yielding fluoroalkane via a mechanism including decarboxylation of the aliphatic carboxylic acid and fluorination by the fluorinating reagent.

39. The method of claim 38, wherein the aliphatic carboxylic acid is of the formula R^5CO_2H, wherein R^5 is selected from the group consisting of -alkyl, -heteroalkyl, -cycloalkyl, -heterocycloalkyl, -alkyl-aryl, -heteroalkyl-aryl, -alkyl-heteroaryl, -alkyl-cycloalkyl, -alkyl-hetercycloalkyl, -heteroalkyl-heteroaryl, -cycloalkyl-aryl, -cycloalkyl-heteroaryl, -heterocycloalkyl-aryl, -heterocycloalkyl-heteroaryl, -cycloalkyl-alkyl, -heterocycloalkyl-alkyl, -cycloalkyl-heteroalkyl, and -heterocycloalkyl-heteroalkyl.

40. The method of claim 38, wherein the photoredox catalyst is a heteroleptic iridium complex or homoleptic ruthenium complex.

41. The method of claim 40, wherein the photoredox catalyst is selected from the group consisting of $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$, $Ru(bpz)_3^{2+}$ and $Ru(phen)_3^{2+}$.

42. The method of claim 38, wherein the fluorinating reagent comprises 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate.

43. The method of claim 38, wherein the reaction mixture further comprises a base.

44. The method of claim 38, wherein the reaction mixture is a homogeneous solution of the aliphatic carboxylic acid, photoredox catalyst and fluorinating reagent.

45. The method of claim 44, where solvent of the reaction mixture is CH_3CN/H_2O.

CLAIMS

1. A method of cross-coupling comprising:

providing a reaction mixture comprising a coupling partner and a substrate having a carboxyl group; and

cross-coupling the substrate and the coupling partner via a mechanism including formation of a substrate radical via a single electron transfer process followed by decarboxylation to a secondary substrate radical, wherein the secondary substrate radical is collected by an intermediate transition metal complex of the reaction mixture for bond formation with the coupling partner.

2. The method of claim 1, wherein the substrate radical is a carboxyl radical.

3. The method of claim 1, wherein the intermediate transition metal complex is a nickel complex.

4. The method of claim 1, wherein the single electron transfer process involves single electron transfer between a transition metal and the substrate.

5. The method of claim 1, wherein the single electron transfer process involves single electron transfer between photoredox catalyst and the substrate.

6. The method of claim 5, wherein the photoredox catalyst is a transition metal complex.

7. The method of claim 6, wherein the transition metal complex is an iridium complex or a ruthenium complex.

8. The method of claim 6, wherein the transition metal complex is a heteroleptic iridium complex.

9. The method of claim 8, wherein the heteroleptic iridium complex is selected from the group consisting of $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$, $Ir(ppy)_2(dtbbpy)^+$ and $Ir[dF(5\text{-}Me)ppy]_2(tetraMePhen)^+$.

10. The method of claim 1, wherein the secondary substrate radical is an alkyl radical.

11. The method of claim 1, wherein the substrate is an aliphatic carboxylic acid.

12. The method of claim 11, wherein the aliphatic carboxylic acid is an amino acid.

13. The method of claim 11, wherein the aliphatic carboxylic acid is a fatty acid.

14. The method of claim 11, wherein the aliphatic carboxylic acid is of formula R^1-CO_2H, wherein R^1 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -alkynyl, -alkyl-aryl, -alkyl-heteroaryl, -alkyl-alkoxy, -alkenyl-aryl, -alkenyl-heteroaryl, -cycloalkyl-aryl, -cycloalkyl-heteroaryl, -cycloalkenyl-aryl, -heterocycloalkenyl-aryl, and -alkenyl-alkoxy.

15. The method of claim 1, wherein the substrate is a keto acid.

16. The method of claim 15, wherein the keto acid is an aliphatic keto acid.

17. The method of claim 15, wherein the keto acid is an aryl keto acid or heteroaryl keto acid.

18. The method of claim 15, wherein the keto acid is of the formula R^2-C(O)-CO_2H, wherein R^2 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -alkynyl, -aryl, -heteroaryl, -alkyl-aryl, -alkyl-heteroaryl, -alkyl-alkoxy, -alkenyl-aryl, -alkenyl-heteroaryl and -alkenyl-alkoxy.

19. The method of claim 1, wherein the cross-coupling is a sp^3–sp^2 cross-coupling.

20. The method of claim 1, wherein the cross-coupling is a sp^3–sp^3 cross-coupling.

21. The method of claim 1, wherein the substituted aromatic compound is a substituted aryl or substituted heteroaryl.

22. The method of claim 21, wherein the substituted aryl or substituted heteroaryl comprises a halide leaving group.

23. The method of claim 1, wherein the substituted aliphatic compound comprises one or more points of unsaturation.

24. The method of claim 1, wherein the substituted aliphatic compound is saturated.

25. The method of claim 24, wherein the substituted aliphatic compound comprises a halide leaving group.

26. The method of claim 25, wherein the substituted aliphatic compound is of the formula R^3-X, wherein X is the halide leaving group and R^3 is selected from the group consisting of -alkyl, -cycloalkyl, -heteroalkyl, -heterocycloalkyl, -alkenyl, -cycloalkenyl, -heteroalkenyl, -heterocycloalkenyl, -alkynyl, -alkyl-aryl, -alkyl-heteroaryl, -alkyl-alkoxy, -alkenyl-aryl, -alkenyl-heteroaryl and -alkenyl-alkoxy.

27. The method of claim 1, wherein the carboxyl group of the substrate is in protonated form, deprotonated form, salt form or a carboxylate ester.

28. The method of claim 1, wherein the bond formation occurs by reductive elimination.

29. The method of claim 1, wherein the secondary substrate radical is an acyl radical.