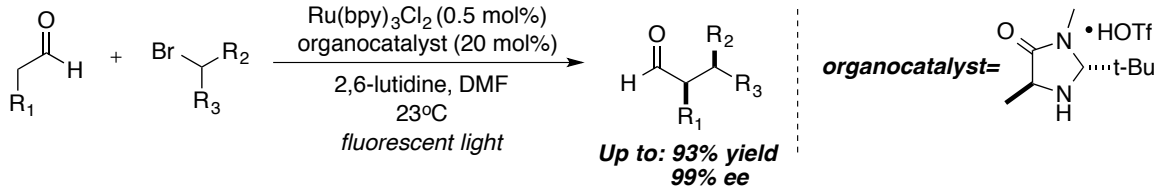
ASYMMETRIC PHOTOREDOX DUAL-CATALYSIS

Reported by Christopher C. Pattillo April 28th, 2015

COMBINING PHOTOREDOX AND ORGANOCATALYSIS

In 2008, MacMillan and coworkers reported the combination of photoredox and chiral enamine catalysis to allow for the first catalytic asymmetric, intermolecular α-alkylation of aldehydes (Scheme 1).[1] The proposed mechanism for this reaction involves the addition of an electrophilic radical species to a chiral, electron rich enamine in a highly enantioselective fashion, allowing for the preparation of α-alkylated aldehydes in good to outstanding enantiomeric excess (88-99%). This reaction has also been extended to the asymmetric α-trifluoromethylation, benzylation, and amination of aldehydes.[2] In 2014, Luo and co-workers reported an elegant asymmetric alkylation of β-ketoester and β-ketoamide substrates in excellent yields and enantioselectivities via photoredox/chiral enamine dual catalysis, further demonstrating the adaptability of this reaction platform.[2]

Scheme 1. Asymmetric alkylation *via* combined photoredox and enamine catalysis

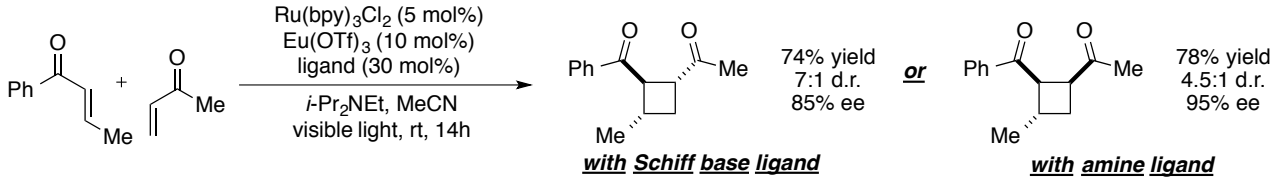


Rovis and co-workers have recently disclosed an asymmetric α-acylation of tertiary amines through the combination of N-heterocyclic carbene catalysis with a photoredox catalytic cycle.[2] Photoredox catalysis has also been combined with anion-binding catalysis for the enantioselective preparation of β-amino esters, as well as chiral Brønsted acid catalysis in an elegant aza-pinacol cyclization.[2] While these examples demonstrate the utility of tandem photoredox/organocatalysis, each requires the use of a *specifically* designed organic catalyst. In recent years, the use of chiral Lewis acid catalysis has emerged as a potentially more general solution to asymmetric C-C bond formation promoted by a photoredox catalytic cycle.

PHOTOREDOX/CHIRAL LEWIS ACID DUAL CATALYSIS

Yoon and coworkers have recently demonstrated that chiral Lewis acid catalysis can be successfully paired with a photoredox cycle for asymmetric [2+2] photocycloadditions (Scheme 2).[3] In this example, the ruthenium photoredox catalyst effects single electron reduction of the enone substrate, which is activated by a chiral scandium Schiff base complex. This radical anion intermediate is then positioned to undergo an enantioselective [2+2] cycloaddition with high stereocontrol (from 84-97% ee) and generally good yields (from 80% yield).

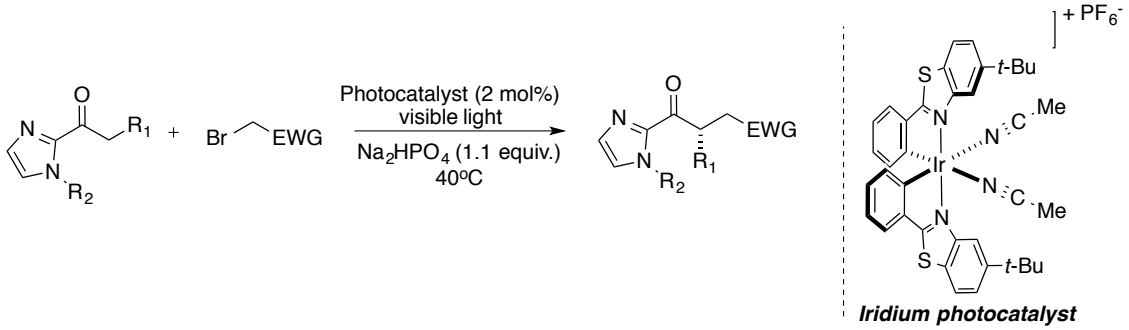
Scheme 2. Enantioselective [2+2] Photocycloadditions Promoted by Chiral Lewis Acids.



This dual catalysis mode was later applied to the asymmetric conjugate addition of α-amino radicals. Chiral Lewis acid activation of enone acceptors allowed for the conjugate addition of photoredox generated α-amino radicals in up to 96% ee and 96% yield.[4]

Meggers and coworkers have recently demonstrated that a *chiral-at-metal* iridium photocatalyst is capable of acting as both a photoredox catalyst *and* a chiral Lewis acid for the alkylation of 2-acyl imidazoles in outstanding yields (84-100%) and selectivities (90-99% ee).[5] While the use of chiral-at-metal complexes in this area of catalysis is still underdeveloped, catalysts of this type will likely be readily applied to a variety of other transformations, providing for highly enantioenriched products with a single metal catalyst.

Scheme 3. Asymmetric Photoredox Catalysis *via* a Chiral-at-Metal Iridium Complex.



OUTLOOK

The last decade has seen exciting new trends emerging in the field of asymmetric photoredox dual catalysis. Recent developments in chiral Lewis acid co-catalysis, specifically using chiral-at-metal catalysts, appear as a promising direction for expanding the scope of reactions amenable to this methodology. While a demonstration of the applicability of these methods in the context of complex molecule synthesis remain to be seen, it is clear that photoredox dual catalysis offers a unique and complementary method to traditional asymmetric C-C bond forming processes.

REFERENCES

[1]MacMillan, D.W.C. et al. *Science*. **2008**, *322*, 77-80
[2]Meggers, E. *Chem. Commun.* **2015**, *51*, 3290-3301
[3]Yoon, T.P. et al. *Science*. **2014**, *344*, 392-396
[4]Yoon, T.P. et al. *J. Am. Chem. Soc.* **2015**, *137*, 2452-2455
[5]Meggers, E. et al. *Nature*. **2014**, *515*, 100-103