



Dual Nickel- and Photoredox-Catalyzed Enantioselective Desymmetrization of Cyclic *meso*-Anhydrides

Erin E. Stache, Tomislav Rovis,* and Abigail G. Doyle*

Abstract: The enantioselective desymmetrization of cyclic *meso*-anhydrides with benzyl trifluoroborates under nickel-photoredox catalysis is described. The reaction tolerates a variety of sterically and electronically different trifluoroborates, as well as structurally unique cyclic anhydrides. The *trans* isomer of the keto-acid products is also observed at varying levels dependent on the trifluoroborate identity and relative catalyst loading. A mechanism involving decarbonylation and Ni–C bond homolysis of a Ni^{II} adduct is proposed. This feature allows access to a *trans* keto-acid as the major product in high enantioselectivity from a *cis* *meso* anhydride.

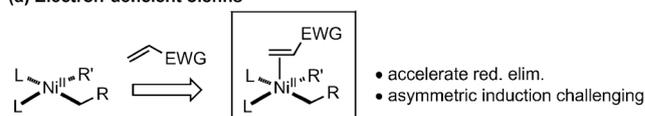
Application of photoredox catalysis to transition metal-catalyzed cross-coupling has rapidly gained prominence as a strategy that enables a broad range of novel bond-forming reactions.^[1] In this approach, a photoredox catalyst is used to modulate the oxidation state of the transition metal catalyst by single-electron transfer and/or generate a radical coupling partner that engages the transition metal in fragment coupling. By re-directing the elementary steps of cross-coupling away from traditional two-electron processes, this reaction manifold can overcome difficult oxidative additions, transmetalations, and reductive eliminations.^[2] Recently, our two labs questioned whether the combination of photoredox and transition metal catalysis could also offer solutions to challenges in stereoselective cross-coupling.

Beginning in 2002, the Rovis group developed a collection of transition metal-catalyzed cross-coupling methods for the ring opening of cyclic carboxylic anhydrides.^[3] A primary attribute of this methodology is the capacity to convert simple synthetic building blocks to complex keto-acids possessing a stereodefined backbone through desymmetrization of *meso* precursors. Nickel catalysts were found to impart broad scope and good reactivity. Mechanistic studies with a Ni bipyridine catalyst system were most consistent with rate-limiting reductive elimination from a nickel(II) species.^[4] Efforts to

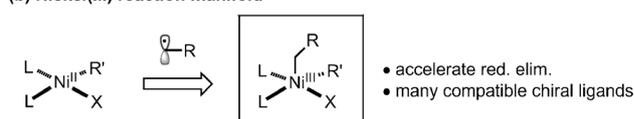
achieve a highly enantioselective methodology using Ni catalysts were unsuccessful.

Knochel first introduced electron-deficient olefins as ligands in alkyl cross-coupling reactions, and proposed that they accelerate reductive elimination by withdrawing electron density from the metal center.^[5,6] Previous studies from the Rovis group had identified a qualitative acceleration effect of electron-deficient olefin additives (Figure 1).^[3b] We hypothe-

(a) Electron-deficient olefins



(b) Nickel(III) reaction manifold



Can these two strategies be functionally equivalent?

(c) This work

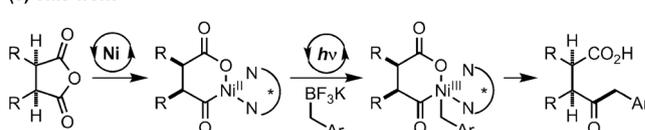


Figure 1. a) Use of electron-deficient olefins as ligands in nickel catalysis. b) Alternative nickel(III) reaction manifold. c) Nickel-photoredox for the desymmetrization of *meso* anhydrides.

sized that single-electron oxidation of a Ni^{II} to a Ni^{III} species could mimic, and perhaps accentuate, the effect of the electron-deficient olefin on the rate and selectivity of this C–C bond-forming reaction. Such a nickel and photoredox-catalyzed desymmetrization of *meso* anhydrides would provide an attractive complement to the precious-metal alternatives utilizing Pd and Rh catalysis that the Rovis group ultimately developed in its stead.^[7] Nickel catalysts are inexpensive and abundant, and most chiral ligand frameworks for Ni feature similar attributes, as they are diamine or diimine derivatives of amino acids. Furthermore, the original chemistry with Ni, Pd, and Rh catalysis was limited to relatively harsh organometallic nucleophiles, such as aryl and alkyl zinc reagents. In a dual catalysis manifold, a broad range of air-stable, easily accessible, and functional group tolerant coupling partners have been shown to deliver fragments to Ni.^[8]

[*] E. E. Stache, Prof. A. G. Doyle

Department of Chemistry, Princeton University
120 Washington Road, Princeton, NJ 08544 (USA)
E-mail: adoyle@princeton.edu

E. E. Stache, Prof. T. Rovis
Department of Chemistry, Colorado State University
Fort Collins, CO 80523 (USA)
E-mail: tr2504@columbia.edu

Prof. T. Rovis
Department of Chemistry, Columbia University
New York, NY 10027 (USA)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<http://dx.doi.org/10.1002/anie.201700097>.

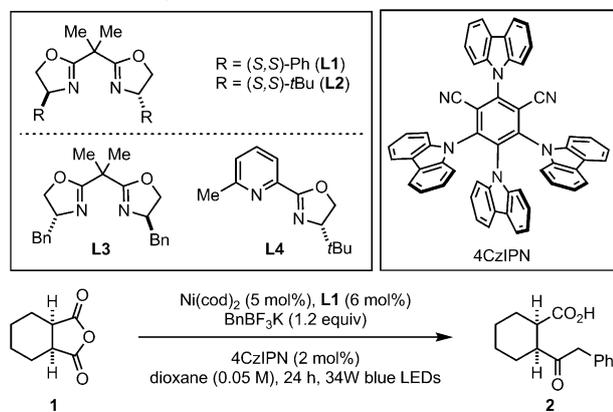
We report here an enantioselective Ni and photoredox-catalyzed desymmetrization of *meso*-succinic anhydrides with C(sp³)-organotrifluoroborates. Notably, enantioselective metalphotoredox reactions have remained largely elusive.^[9] To date, only a single example of a highly enantioselective method has been reported.^[2a,10] The MacMillan and Fu groups described a synthesis of enantioenriched benzylic amines by stereoconvergent decarboxylative coupling of amino acids with aryl iodides. In their reaction, the radical intermediate is the prochiral component. The reaction reported herein demonstrates that a chiral Ni catalyst is also capable of inducing asymmetry on the electrophilic coupling partner.

We chose to examine benzyl trifluoroborates as a radical source due to their ready availability and precedent for coupling in the Ni/photoredox manifold, as introduced by the Molander group.^[2a] After an exploration of conditions using carboxylic anhydride **1** as a model substrate, we found that Ni(cod)₂, (*S,S*)-PhBox (**L1**), and the organophotocatalyst 4CzIPN^[11] gave the product in 85 % yield and 90 % *ee* after 24 h at room temperature under irradiation with 34 W blue LEDs (Table 1, entry 1). In the absence of ligand, a modest amount of racemic product is formed, suggesting a possible route for erosion of enantioselectivity (see below) (entry 2).^[12] In screening other ligands, we observed intermediate levels of selectivity when using either (*S,S*)-*t*-BuBox (**L2**) or (*R,R*)-BnBox (**L3**), whereas distinct ligand frameworks, such as (*S*)-*t*-BuPyrOx **L4**, delivered inferior results (entries 3–5). Employment of a nickel(II) pre-catalyst that

benefits from air/moisture stability and low cost compared to Ni(cod)₂ provides product in good yield albeit low asymmetric induction (entry 6).^[13] An attractive feature of this method is that the optimal photocatalyst is an inexpensive organic photocatalyst, recently introduced by the Zhang group for Ni/photoredox cross-coupling.^[11] Under the optimized conditions, use of [Ir(dFCF₃ppy)₂dtbbpy]PF₆ instead of 4CzIPN affords **2** in modest yield and slightly reduced selectivity (entry 7). Excellent enantioselectivity can be obtained with the Ir photocatalyst using THF as solvent, although the yield of the transformation remains low (entry 8). In the absence of nickel, light or photocatalyst, no product is observed (entries 9–11).

With optimized conditions in hand, we explored the scope and limitations of the method. As can be seen in Table 2, the desymmetrization of anhydride **1** proceeds smoothly on larger

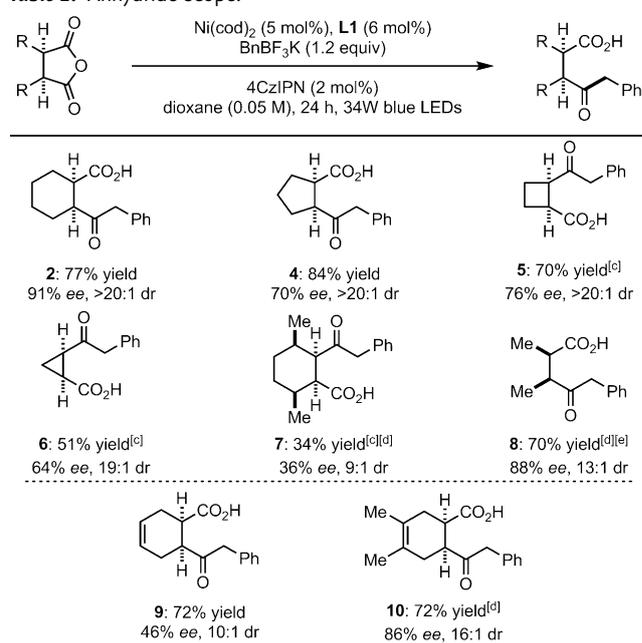
Table 1: Reaction optimization.



Entry	Deviation from standard conditions	Yield ^[a] [%]	<i>ee</i> ^[b] [%]
1	none	85	90
2	no ligand	7	nd
3	L2 (6 mol%)	25	45
4	L3 (6 mol%)	71	–43
5	L4 (6 mol%)	65	40
6	NiCl ₂ ·glyme (5 mol%)	64	32
7	[Ir(dFCF ₃ ppy) ₂ dtbbpy]PF ₆ 3 (2 mol%)	43	78
8	3 (2 mol%), THF (0.05 M)	45	94
9	no nickel	0	nd
10	no light	0	nd
11	no photocatalyst	0	nd

[a] Yield determined by ¹H NMR on 0.1 mmol scale using benzoic acid as a standard. [b] *ee* determined by HPLC using a chiral stationary phase.

Table 2: Anhydride scope.^[a,b]



[a] Yields and selectivities are an average of two runs, 0.25 mmol scale. [b] *ee* and d.r. determined by HPLC using a chiral stationary phase. [c] **L3** used (6 mol%). [d] d.r. determined by ¹H NMR. [e] Reaction time 48 h.

scale to yield keto-acid **2** in 77 % yield, 91 % *ee* and >20:1 d.r. favoring the *cis* isomer (see below).^[14,15] Notably, cyclopentyl, cyclobutyl and cyclopropyl succinic anhydrides are all suitable electrophiles. However, anhydrides bearing β-substitution undergo coupling in more modest yield and enantioselectivity (**7**). Although these conditions were optimized for bicyclic anhydrides, they can be applied successfully to monocyclic succinic anhydrides; acyclic keto-acid **8** was isolated in 70 % yield and 88 % *ee*. Interestingly, benzylation of tetrahydrophthalic anhydride occurs in good yield but with reduced enantioselectivity compared with the parent cyclohexane carboxylic anhydride (**9**). We attribute this loss of selectivity to the ability of the backbone alkene to coordinate to the nickel center. Indeed, in the formation of product **10**, the

selectivity was nearly restored, presumably because the more substituted alkene discourages coordination to nickel.^[3b]

A wide array of trifluoroborates are also well tolerated in the reaction. Electron-deficient and electron-neutral trifluoroborates react smoothly with anhydride **1** in good yield and high enantio- and diastereoselectivity (**11–13**)

Table 3: Trifluoroborate scope.^[a,b,c]

11: 77% yield 89% ee, 13:1 dr	12: 72% yield 81% ee, 11.5:1 dr ^[d]	13: 90% yield 88% ee, 16:1 dr	14: 53% yield 79% ee, 9.5:1 dr ^[d]
15: 85% yield 85% ee, >20:1 dr	16: 84% yield 82% ee, >20:1 dr ^[d]	17: 86% yield 89% ee, 11.5:1 dr	18: 84% yield 86% ee, 11.5:1 dr
19: 77% yield 85% ee, 8:1 dr	20: 83% yield 75% ee, 6:1 dr	21: 89% yield 70% ee, >20:1 dr	22: 90% yield ^[d] 94% ee, >20:1 dr ^[e]

[a] Yields and selectivities are an average of two runs, 0.25 mmol scale.

[b] ee determined by HPLC on a chiral stationary phase. [c] d.r.

determined by ¹H NMR. [d] d.r. determined by HPLC on a chiral

stationary phase. [e] Et₂O/THF (10:1) used instead of dioxane.

(Table 3). Gratifyingly, cross-coupling proceeds chemoselectively with a *para*-chloro-substituted benzyl trifluoroborate, leaving behind a functional group for further derivatization. Trifluoroborates with *meta* or *ortho* substituents also react in high yield and enantioselectivity; however, *ortho*-substituted nucleophiles deliver keto-acids **19** and **20** with significantly eroded diastereoselectivity (see below). Benzyl trifluoroborates possessing electron-donating substituents are suitable reaction partners, affording **21** and **22** in good yield and diastereoselectivity and good to excellent enantioselectivity. The attenuated enantioselectivity obtained in the case of **21** is likely due to a more prolific racemic background reaction with the nucleophilic trifluoroborate;^[16] indeed, for **22**, switching from dioxane to the less polar solvent diethyl ether suppressed the racemic background reaction and raised the enantioselectivity from 48 to 94% ee.^[17]

Based on a computational investigation, Molander and Kozlowski have put forward a Ni^{0/III} mechanism for related Ni/photoredox cross couplings wherein the C-centered radical generated from an organotrifluoroborate reacts with Ni⁰ prior to oxidative addition of aryl halide, and reductive elimination serves as the stereodetermining step.^[9] In our system, UV studies support oxidative addition of Ni⁰ to anhydride **1**.^[18] As such, a mechanism proceeding first via *ee*-determining Ni⁰ oxidative addition to the anhydride, followed by interception of the benzylic radical on a Ni^{II} species is more likely.

Formation of the *trans* keto-acid products in Tables 2 and 3 is also noteworthy from a mechanistic perspective.^[19] Control experiments show that the product is configurationally stable under the reaction conditions.^[20] Further, the nearly identical enantioselectivity of the *cis* and *trans* products suggests that no significant epimerization is occurring on the anhydride substrate, rather that epimerization occurs on the catalytic cycle after the *ee*-determining step.^[21] A mechanism wherein the Ni^{II} adduct, generated upon *ee*-determining oxidative addition of Ni⁰ to the anhydride, can undergo decarbonylation followed by Ni–C bond homolysis could account for this observation (Figure 2).^[22,23] Recombi-

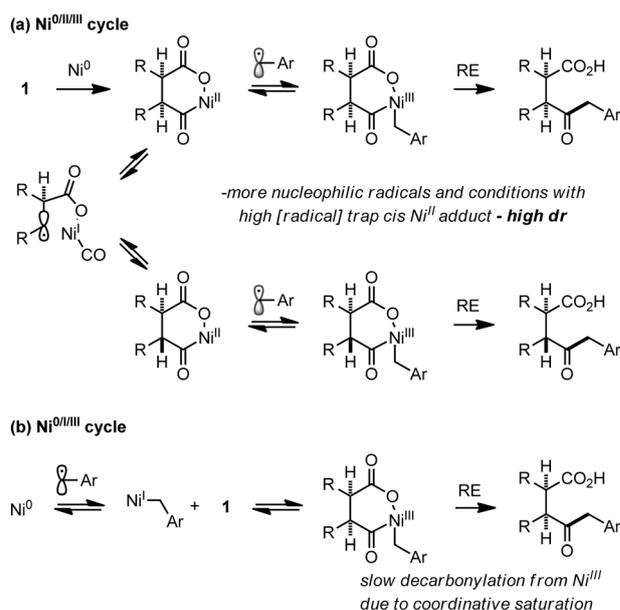


Figure 2. a) Proposed mechanism and plausible pathway for epimerization observations. b) Alternative mechanism inconsistent with observations.

nation and carbonyl insertion from the planar radical intermediate would regenerate both the *cis* and *trans* diastereomers without erosion in enantioselectivity. Decarbonylation, and thus epimerization, should be slow from a Ni^{III} intermediate due to coordinative saturation, lending additional support for the involvement of a Ni^{0/III} pathway.

Further study into the mechanism of epimerization showcased a significant correlation between nickel loading and the degree of epimerization (Table 4). At 2.5 mol% Ni loading, the *cis*-**2** product was formed exclusively. Simply increasing the Ni loading to 15 mol% led to the formation of the *trans*-**2** isomer in nearly 1:1 d.r. with 88% ee. We propose that at high relative concentrations of the radical (low Ni loading relative to photocatalyst) high diastereoselectivity is observed due to efficient trapping of the Ni^{II} adduct in the Ni^{0/III} cycle prior to epimerization. The relationship of diastereoselectivity to the identity of the trifluoroborate, with more nucleophilic radicals providing high levels of diastereoselectivity is further support for this hypothesis (Table 3). According to this proposal, manipulation of the photocatalyst

Table 4: Epimerization investigation.

Entry	Nickel (mol %)	4CzIPN (mol %)	Yield ^[a] [%]	d.r. ^[b]	ee cis ^[c] [%]	ee trans ^[d] [%]
1	2.5	2	91	99:1	79	nd
2	5	2	72	24:1	87	nd
3	10	2	62	3.8:1	90	83
4	15	2	56	1.4:1	81	88
5	15	4	78	2.1:1	90	85
6	15	1	49	1:1.2	86	82

[a] Yield determined by ¹H NMR on 0.1 mmol scale using benzoic acid as a standard. [b] d.r. determined by HPLC on the acid on a chiral stationary phase. [c] ee of *cis-2* determined by HPLC on the methyl ester on a chiral stationary phase. [d] ee of *trans-2* determined by HPLC on the acid on a chiral stationary phase. [e] Performed on 0.25 mmol scale using benzoic acid as a standard.

loading should also impact the diastereoselectivity by changing the relative concentration of radical to Ni. Indeed, by lowering the photocatalyst loading and maintaining the Ni loading at 15 mol%, *trans-2* could be favored in a modest 1.2:1 ratio. This result demonstrates the attractive possibility of forming either the *cis* or *trans* keto-acid products in high enantioselectivity from a *cis-meso* anhydride solely through changes to catalyst loading.

In summary, we report a nickel/photoredox catalyzed desymmetrization of *meso* anhydrides affording enantio-enriched keto-acids.^[24] We have identified an epimerization event on an intermediate in the catalytic cycle that provides access to *trans* keto-acid products from *cis* anhydrides in modest selectivity.

Acknowledgements

We thank NIGMS (GM100985 to A.G.D.) and Princeton University (to E.E.S.) for support and Phil Jeffrey of Princeton University for X-ray crystallographic structure determination.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · cross-coupling · desymmetrization · nickel · photoredox catalysis

- [1] a) J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel, G. A. Molander, *Acc. Chem. Res.* **2016**, *49*, 1429–1439; b) M. D. Levin, S. Kim, F. D. Toste, *ACS Cent. Sci.* **2016**, *2*, 293–301; c) M. N. Hopkinson, A. Tiahuext-Aca, F. Glorius, *Acc. Chem.*

- Res.* **2016**, *49*, 2261–2272; d) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926.
- [2] a) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433–436; b) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437–440; c) J. A. Terrett, J. D. Cuthbertson, V. W. Shurtliff, D. W. C. MacMillan, *Nature* **2015**, *524*, 330–334; d) E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald, D. W. C. MacMillan, *Science* **2016**, *353*, 279–283.
- [3] a) E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 174–175; b) E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 247–254.
- [4] J. B. Johnson, E. A. Bercot, J. M. Rowley, G. W. Coates, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 2718–2725.
- [5] A possible coordination number and geometry change at the metal cannot be discounted; see: a) R. Giovannini, T. Stüdemann, G. Dussin, P. Knochel, *Angew. Chem. Int. Ed.* **1998**, *37*, 2387–2390; *Angew. Chem.* **1998**, *110*, 2512–2515; b) R. Giovannini, T. Stüdemann, A. Devasagayaraj, G. Dussin, P. Knochel, *J. Org. Chem.* **1999**, *64*, 3544–3553.
- [6] a) J. B. Johnson, T. Rovis, *Angew. Chem. Int. Ed.* **2008**, *47*, 840–871; *Angew. Chem.* **2008**, *120*, 852–884.
- [7] a) E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 10248–10249; b) M. J. Cook, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 9302–9303; c) J. B. Johnson, E. A. Bercot, C. M. Williams, T. Rovis, *Angew. Chem. Int. Ed.* **2007**, *46*, 4514–4518; *Angew. Chem.* **2007**, *119*, 4598–4602.
- [8] We recently reported the coupling of acyclic anhydrides with tertiary amines under a nickel/photoredox manifold: C. L. Joe, A. G. Doyle, *Angew. Chem. Int. Ed.* **2016**, *55*, 4040–4043; *Angew. Chem.* **2016**, *128*, 4108–4111.
- [9] O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896–4899.
- [10] Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832–1835.
- [11] J. Luo, J. Zhang, *ACS Catal.* **2016**, *6*, 873–877.
- [12] A racemic background reaction is not detected under identical conditions using Ir (**3**). This suggests 4CzIPN is promoting the racemic background. See the Supporting Information (SI) for more details.
- [13] Control experiments suggest COD or DME are not responsible for this difference in enantioselectivity. We propose the possibility of a competitive Ni^{0/III} pathway. See Scheme S1 in SI for a proposed catalytic cycle.
- [14] Epimerization was never observed in previous nickel-, palladium- or rhodium-catalyzed anhydride desymmetrizations. See Ref. [3] and [7].
- [15] Products **4** and **5** will epimerize to the *trans* product under extended work-up conditions. See SI for more details.
- [16] Hammett analysis shows no correlation between enantiomeric ratio and σ values.
- [17] A significant racemic background was observed for more nucleophilic trifluoroborates under standard reaction conditions. High enantioselectivity could be obtained for product **21** by employing Et₂O; however, reduced yield was obtained due to solubility issues. See SI (Section VII) for full details.
- [18] Oxidative addition was observed via UV/Vis using Ni(cod)₂, **L1** and 20 equiv of anhydride. See SI for ligand comparisons and more details. Also see Ref. [6] for previous demonstrations of oxidative addition studies.
- [19] Derivatization reactions provided evidence that the ketone stereocenter is being epimerized, as opposed to the carboxylate center. See SI for full experimental details.
- [20] Extended reaction times or subjecting the product to the reaction conditions did not result in a significant increase in the formation of the *trans* product.
- [21] For a related example of decarbonylation under nickel cross-coupling conditions, see: E. M. O'Brien, E. A. Bercot, T. Rovis,

- J. Am. Chem. Soc.* **2003**, *125*, 10498–10499. For an example of decarboxylation and recombination under photoredox conditions, see C. Le, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 11938–11941.
- [22] A small amount (<2%) of racemic *trans* anhydride is present in the *cis* anhydride, which accounts for the difference in *ee* between the *cis* and *trans* products.
- [23] C. J. Cordier, R. J. Lundgren, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10946–10949.
- [24] The reaction was scaled using the Merck photoreactor to 0.5 mmol for derivatization reactions, providing keto-acid **2** in 75% yield, 90% *ee* and 19:1 d.r.. The product was purified further to yield the *cis* isomer in >99% *ee*. See SI for more details.

Manuscript received: January 4, 2017

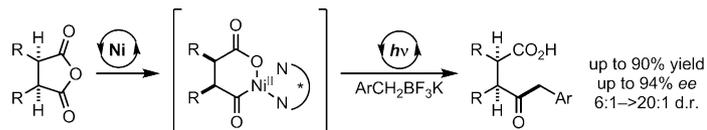
Final Article published: ■ ■ ■ ■, ■ ■ ■ ■ ■

Communications



Asymmetric Synthesis

E. E. Stache, T. Rovis,*

A. G. Doyle*   Dual Nickel- and Photoredox-Catalyzed
Enantioselective Desymmetrization of
Cyclic *meso*-Anhydrides

Catalytic teamwork: Cyclic anhydrides are efficiently desymmetrized through dual nickel- and photoredox-catalyzed alkylation using benzylic trifluoroborate salts as pronucleophiles. A mechanistic

nuance illustrates that an intermediate in the catalytic cycle undergoes epimerization leading to *trans* keto-acid products from *cis* anhydrides under modified reaction conditions.